Assessment of Evidence for COVID-19-Related Treatments: Updated 02/11/2021

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility’s approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

ASHP’s patient medication information is available at [http://www.safemedication.com/](http://www.safemedication.com/). Visit our [website](http://www.ashp.org) for the latest information on current drug shortages.

Selected entries were updated 02/11/2021; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by **.

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### Antiviral Agents

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<td>Baloxavir&lt;br&gt;Updated 1/14/21</td>
<td>8:18.92 Antiviral</td>
<td>Antiviral active against influenza viruses&lt;br&gt;Conflicting data regarding possible in vitro antiviral activity against SARS-CoV-2</td>
<td>Only very limited data available regarding use of baloxavir for treatment of COVID-19&lt;br&gt;Exploratory, open-label, randomized controlled study at a single center in China (ChiCTR2000029544): 29 adults hospitalized with COVID-19 receiving antiviral treatment with lopinavir/ritonavir, darunavir/cobicistat, or umifenovir (Arbidol®), in combination with inhaled interferon-α, were randomized to treatment with baloxavir marboxil (80 mg orally on day 1 and on day 4, and 80 mg orally on day 7 as needed) (n=10), favipiravir (1600 or 2200 mg orally on day 1, followed by 600 mg three times daily for up to 14 days) (n=9), or control (standard antiviral treatment) (n=10). Results did not indicate a benefit of adding baloxavir to the treatment regimen. Percentage of pts with viral conversion (2 consecutive tests with undetectable viral RNA results) after 14 days of treatment was 70, 77, and 100% in the baloxavir, favipiravir, and control groups, respectively, with median time to clinical improvement of 14, 14, and 15 days, respectively.</td>
<td>A baloxavir marboxil dosage of 80 mg on day 1 and on day 4, and another dose of 80 mg on day 7 (as needed; not to exceed 3 total doses) was used in one open-label COVID-19 study in adults in China.</td>
<td>Although investigated as a potential treatment during the early stages of the COVID-19 pandemic, in vitro antiviral activity against SARS-CoV-2 was not confirmed and there are no data to support the use of baloxavir in the treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel states that treatment of influenza is the same in all pts regardless of SARS-CoV-2 coinfection. (See Neuraminidase Inhibitors in this Evidence Table.) Significant drug interactions not expected with baloxavir and remdesivir. CDC states that baloxavir may be used for the treatment of suspected or confirmed uncomplicated influenza in outpatients; the drug is not recommended for use in pregnant or nursing women, as monotherapy in severely immunosuppressed pts, or for the treatment of severe influenza.</td>
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<td>Chloroquine Phosphate&lt;br&gt;Updated 12/17/20</td>
<td>8:30.08 Antimalarial (4-aminoquinoline derivative)</td>
<td>In vitro activity against various viruses, including coronaviruses&lt;br&gt;In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; some evidence it may block infection in Vero E6 cells exposed to SARS-CoV-2&lt;br&gt;Active in vitro against SARS-CoV-1 and MERS-CoV&lt;br&gt;Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in inflammatory response in</td>
<td>Only limited clinical trial data available to date to evaluate use of chloroquine for treatment or prevention of COVID-19&lt;br&gt;Small, randomized study in hospitalized adults in China compared chloroquine with LPV/RTV (Huang et al): 10 pts (7 with moderate and 3 with severe COVID-19) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate and 5 with severe COVID-19) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR results for SARS-CoV-2 by day 13 and were discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from hospital by day 14; 50% improvement of 14, 14, and 15 days, respectively.</td>
<td>Consider: 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base</td>
<td>Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established. No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19. Data from various published randomized, controlled clinical trials and retrospective, cohort studies have not substantiated initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19. (See Hydroxychloroquine in this Evidence Table.) NIH COVID-19 Treatment Guidelines Panel recommends against use of chloroquine for treatment of COVID-19.</td>
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<td>patients with viral infections 1-3, 13, 15-16</td>
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<td>Known pharmacokinetics and toxicity profile based on use for other indications 13, 17</td>
<td>The hospital by day 14. <strong>Note:</strong> Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively). 20</td>
<td><strong>Oral chloroquine phosphate dosage in Chinese guidelines:</strong> 500 mg twice daily for 7 days (adults 18-65 years weighing &gt;50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing &lt;50 kg) 11</td>
<td>Chloroquine (with or without azithromycin) for the treatment of COVID-19 in hospitalized pts and <strong>recommends against</strong> use of chloroquine (with or without azithromycin) for the treatment of COVID-19 in nonhospitalized patients, except in a clinical trial. The panel also <strong>recommends against</strong> use of high-dose chloroquine (i.e., 600 mg twice daily for 10 days) for the treatment of COVID-19 because such dosage has been associated with more severe toxicities compared with lower-dose chloroquine. 25</td>
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<td><strong>Double-blind, randomized, phase 2b study in Brazil (Borbà et al; NCT04323527):</strong> Efficacy and safety of two different chloroquine dosages were evaluated for adjunctive therapy in hospitalized adults with severe COVID-19. According to the initial study protocol, pts were randomized 1:1 to receive high-dose chloroquine (600 mg twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. Analysis of data available for the first 81 enrolled pts indicated that, by day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QTc &gt;500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). <strong>Note:</strong> The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data at the time of the interim analysis were insufficient to evaluate efficacy. 25</td>
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<td>See Hydroxychloroquine in this Evidence Table for additional information on clinical trials and experience with 4-aminoquinoline antimalarials in the management of COVID-19.</td>
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<td>Several clinical trials evaluating chloroquine for treatment of COVID-19 are registered at clinicaltrials.gov, including the following: 10 NCT04345419</td>
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**NIH COVID-19 Treatment Guidelines Panel** **recommends against** the use of any agents, including chloroquine, for preexposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection, except in a clinical trial. The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure. 35 Because 4-aminoquinolines (chloroquine, hydroxychloroquine) are associated with QT prolongation, caution is advised if considering use of the drugs in pts with COVID-19 at risk for QT prolongation or receiving other drugs associated with arrhythmias; 11, 17, 36, 39 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 35, 36, 37 (See Hydroxychloroquine in this Evidence Table.) | | |
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| NCT04353336  
NCT04420247  
NCT04447534       |             |           |                              |         |fluoroquinolones, macrolides [including azithromycin] only if necessary. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving chloroquine (or hydroxychloroquine). |
| Several clinical trials evaluating chloroquine for prevention of COVID-19 in the healthcare setting are registered at clinical-trials.gov, including the following:  
NCT04303507  
NCT04433732 |             |           |                              |         | FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. |
|           |             |           |                              |         | Emergency use authorization (EUA) for chloroquine (now revoked): Effective June 15, 2020, FDA has revoked the EUA for chloroquine and hydroxychloroquine previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible. Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met. Based on the totality of scientific evidence available, FDA concluded that it is unlikely that chloroquine and hydroxychloroquine may be effective in treating COVID-19 and, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of chloroquine and hydroxychloroquine do not outweigh the known and |

Updated 02-11-2021. The current version of this document can be found on the ASHP COVID-19 Resource Center.
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<td>Favipiravir (Avigan®, Avifavir®, Favilavir)</td>
<td>8:18.32 Antiviral</td>
<td>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses</td>
<td>Some data regarding use of favipiravir for the treatment of COVID-19 are available from open-label, randomized or nonrandomized studies and prospective or retrospective observational studies performed in various countries. <strong>Open-label, prospective, randomized, multicenter study</strong> in 786 adults with COVID-19 pneumonia in China (ChiCTR20000300245): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir. Licensed in Japan and China for treatment of influenza.</td>
<td>A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days was used in several open-label COVID-19 studies in adults and adolescents ≥16 years of age in other countries. Protocols in many registered trials generally specify a favipiravir dosage of 1600 or 1800 mg twice daily on day 1, then a total daily dosage of 1200–2000 mg in 2, 3, or 4 divided doses for 4–13 days for treatment of COVID-19 in adults. Protocol in one trial (NCT04448119) specifies a prophylactic favipiravir dosage of 1600 mg twice daily on day 1, then 800 mg twice daily on days 2–25 and a treatment favipiravir dosage of 2000 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 in older adults in long-term care homes experiencing COVID-19 outbreaks. The prophylactic regimen is considered pre-exposure prophylaxis, post-exposure prophylaxis, or preemptive therapy in this setting; those diagnosed with COVID-19 will be offered the treatment regimen. Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2, it has been suggested that high favipiravir dosages, like those used in the treatment of Ebola virus disease, should be considered for the treatment of COVID-19. One such favipiravir regimen used in the treatment of Ebola virus disease includes a loading dosage of 6000 mg (doses of 2400 mg, 2400 mg, and 1200 mg given 8 hours apart on day 1), then a maintenance dosage of 1200 mg every 12 hours on days 2–10.</td>
<td>Not commercially available in the US. Efficacy and safety of favipiravir for treatment of COVID-19 not established. Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dosage and treatment duration. Given the lack of pharmacokinetic and safety data for the high favipiravir dosages proposed for treatment of COVID-19, the drug should be used with caution at such dosages. There is conflicting evidence as to whether favipiravir is associated with QT prolongation. Some have suggested close cardiac and hepatic monitoring during treatment, as well as monitoring of plasma and tissue concentrations of the drug and, if possible, the active metabolite. Some data suggest that favipiravir exposure may be greater in Asian populations. Early embryonic deaths and teratogenicity observed in animal studies. Favipiravir is contraindicated in women with known or suspected pregnancy and precautions should be taken to avoid pregnancy during treatment with the drug. Based on a pharmacokinetic interaction, if favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g. Note that favipiravir-induced fever has been described in several COVID-19 pts receiving the drug.</td>
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### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage* | Comments
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with asymptomatic or mild COVID-19 in Japan (jRCTs041190120): Early treatment (beginning on day of hospital admission) with favipiravir (two 1800-mg doses given orally at least 4 hours apart on day 1, then 800 mg orally twice daily for a total of up to 19 doses over 10 days) (n=36) was not associated with significant improvement in viral clearance compared with late treatment with favipiravir (same regimen beginning day 6 after admission) (n=33). Viral clearance occurred by day 6 in 66.7 and 56.1% of patients in the early and late treatment groups, respectively. Viral clearance was assessed by RT-PCR of nasopharyngeal specimens. Most common adverse effect was transient hyperuricemia (84.1% of patients).

In an open-label, randomized controlled trial in Oman in 89 adults (≤75 years of age) hospitalized with moderate to severe COVID-19 pneumonia (NCT04385095), pts received favipiravir (1600 mg on day 1, then 600 mg twice daily for a maximum of 10 days) in combination with inhaled interferon β-1b (n=44) or standard of care (which included hydroxychloroquine) (n=45). At interim analysis, there were no differences between the groups in improvement in inflammatory markers or other clinical outcomes (e.g., hospital length of stay, hospital discharge, 14-day mortality); however, the study lacked sufficient power to detect such differences.

In a small, open-label, nonrandomized study in patients with non-severe COVID-19 in China (ChiCTR2000029600), favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (n=35) was associated with decreased median time to viral clearance (4 vs 11 days) and higher improvement rate on chest CT imaging on day 14 (91 vs 62%) compared with the control group receiving lopinavir/ritonavir (n=45); both groups also received aerosolized interferon α-1b.

In a prospective, observational, single-center study in 174 adults in Turkey with probable or confirmed COVID-19 (20.1% with mild disease, 61.5% with moderate disease), for the treatment of COVID-19, one pharmacokinetic simulation model suggested that a dosage of 2400 mg twice daily on day 1, followed by 1600 mg twice daily on days 2–10 should achieve adequate favipiravir trough plasma concentrations and may be more pharmacologically relevant than lower dosages.

Another pharmacokinetic simulation model suggested that, despite rapid clearance of the parent drug from plasma, a favipiravir dosage of 1600 mg twice daily on day 1 followed by maintenance doses of 800 or 1200 mg twice daily may be sufficient to provide therapeutic intracellular concentrations of the favipiravir metabolite across the dosing interval, owing to its long intracellular half life. Pharmacokinetic data are available from a study in critically ill pts with COVID-19 requiring mechanical ventilation who received a favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–5 (or longer if needed) via NG tube. Trough serum concentrations of the drug in most samples were lower than the lower limit of quantification and lower than the in vitro EC$_{50}$ of the drug reported for SARS-CoV-2; trough concentrations in these critically ill pts also were much lower than those previously reported in healthy individuals who received the same dosage.

While its molecular weight, protein binding rate, and volume of distribution suggest that favipiravir would be eliminated by dialysis, data from a COVID-19 pt treated with favipiravir (1800 mg twice daily on day 1, then 800 mg twice daily) who was undergoing hemodialysis (2 or 3 times weekly) indicated that blood concentrations of the drug were similar to those reported in nondialysis pts.
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<td>disease, 18.4% with severe pneumonia) admitted to the hospital within a median of 3 days after symptom onset, 32 pts received a regimen that included favipiravir. Most pts who received favipiravir (93.8%) received the drug either in combination with, or as sequential therapy to, hydroxychloroquine with or without azithromycin. In pts who received a favipiravir-containing regimen, the median time to defervescence and to clinical improvement on therapy was 3 and 6 days, respectively. Critically ill pts with sepsis and/or ARDS at the time of admission were excluded.</td>
<td>Data from 4 critically ill pts with COVID-19 who received favipiravir 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–7 (a dosage considered to be &quot;low dose&quot;) indicate that the drug was well-tolerated in these pts.</td>
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In a small, observational study in Turkey in 107 critically ill adults with COVID-19 pneumonia, 65 pts received favipiravir (1600 mg twice daily on day 1, then 600 mg daily for 4 days) and 42 pts received lopinavir/ritonavir. While length of hospital stay in the favipiravir group was decreased (6.6 vs 9 days), mortality in the favipiravir group was increased (66.2 vs 54.8%).

In an open-label, prospective, nonrandomized, observational, single-center sequential cohort study in Hungary, 150 hospitalized adults with moderate to severe COVID-19 received treatment with favipiravir (n=75) or other antivirals (n=75). Disease progression, 14-day all cause mortality, requirement for mechanical ventilation, and PCR negativity rate were unaffected in pts receiving favipiravir (1600 mg twice daily on day 1, then 600 mg twice daily for a total course of at least 10 days) compared with those receiving other antivirals (i.e., chloroquine/hydroxychloroquine, oseltamivir, or LPV/RTV).

In a prospective, single-center study in 13 pts requiring mechanical ventilation for severe COVID-19 in Japan, pts received favipiravir (3600 mg orally on day 1, then 1600 mg orally on days 2–14), along with methylprednisolone, and low molecular weight heparin (LMWH) or unfractionated heparin. Improvements in PaO$_2$/FiO$_2$ (P/F ratio), interleukin-6 concentration, and prepsespin concentration suggested that favipiravir may have some effect on inflammatory mediators, but could not.
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<td>completely control inflammatory mediators or respiratory status.</td>
<td><strong>In a retrospective, observational, multi-center study</strong> in 63 adults with COVID-19 in Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and median maintenance doses of 17.9 mg/kg per day for a median total duration of 12 days), clinical improvement at day 7 was reported in 66.7% of patients (92.5% in patients not requiring oxygen supplementation, 47.2% in patients requiring oxygen supplementation) and clinical improvement at day 14 was reported in 85.7% of patients (100% in patients not requiring oxygen supplementation, 75% in patients requiring oxygen supplementation). Overall mortality at day 28 was 4.8%. Nearly all patients also received a chloroquine-based therapy and an HIV protease inhibitor. Multivariate analysis revealed that older age, higher baseline disease severity, and loading doses &lt;45 mg/kg per day were negative predictors of early clinical improvement.</td>
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<td>In a retrospective cohort study of 26 pts with COVID-19 who received various antiviral regimens in Japan, 3 pts ≥74 years of age received treatment that included favipiravir; 2 of these pts demonstrated improvement and 1 pt died.</td>
<td><strong>Comments</strong></td>
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<td>In a meta-analysis of 13 studies assessing the efficacy and safety of favipiravir in the treatment of COVID-19, clinical deterioration was less likely with favipiravir than with other antiviral agents, although the difference was not statistically significant, and those treated with favipiravir had substantial clinical and radiological improvements compared with those treated with standard of care. Viral clearance, requirement for oxygen or noninvasive ventilation, and adverse effects were similar between the favipiravir and standard of care treatment groups.</td>
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<td><strong>US</strong>: Randomized, controlled open-label proof-of-concept trial (NCT04358549) of favipiravir for the treatment of COVID-19.</td>
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<sup>a</sup>Dosage details not provided in the text.
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<tr>
<th>Drug(s)</th>
<th>AHFS Class</th>
<th>Rationale</th>
<th>Trials or Clinical Experience</th>
<th>Dosage*</th>
<th>Comments</th>
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<tbody>
<tr>
<td>HIV Protease Inhibitors</td>
<td>8:18 08.08</td>
<td>HIV Protease Inhibitors</td>
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<td>Updated 12/17/20</td>
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<td>Darunavir (DRV):</td>
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<td>In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 in Vero E6 cells; in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells</td>
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<td>Atazanavir (ATV):</td>
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<td>Some evidence that ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells and human epithelial pulmonary cells (AS49), and human monocytes.</td>
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<td>Lopinavir (LPV):</td>
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<td>Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells; in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group.</td>
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<td>Nelfinavir (NFV), Ritonavir (RTV), Saquinavir (SQV), and Tipranavir (TPV):</td>
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<td>Some evidence of in vitro activity against SARS-CoV-2 in Vero cells</td>
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<tr>
<td>LPV/RTV:</td>
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<td>Some evidence of clinical benefit when used in conjunction with ribavirin and/or interferon in pts with SARS or MERS.</td>
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<td>US: Randomized, double-blind, placebo-controlled trial (NCT04346628) to evaluate efficacy of favipiravir in pts with mild or asymptomatic COVID-19</td>
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<td>Multiple clinical trials initiated in pts with COVID-19 in China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents.</td>
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<td>LPV/RTV (COVID-19):</td>
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<td>LPV 400 mg/RTV 100 mg orally twice daily for up to 14 days with or without other antivirals (e.g., interferon, umifenovir) has been used.</td>
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<td>LPV/RTV (SARS):</td>
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<td>LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours)</td>
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<td>LPV/RTV (MERS):</td>
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<td>LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α; LPV 400 mg/RTV 100 mg orally twice daily with interferon β-1b (0.25 mg/mL sub-Q on alternate days) for 14 days</td>
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<tr>
<td>LPV/RTV:</td>
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<td>Efficacy for the treatment of COVID-19, with or without other antivirals, not established.</td>
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<td>Darunavir: Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/c for treatment of COVID-19. Results of an open-label, controlled study in China indicated that a 5-day regimen of DRV/c was not effective for treatment of COVID-19 and there are no published clinical studies that have evaluated efficacy and safety of DRV/RTV or the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide for treatment of COVID-19.</td>
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<td>discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from the hospital by day 14. <strong>Note:</strong> Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively).</td>
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<td>LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone in open-label, randomized trial in adults with mild to moderate COVID-19 in Hong Kong (Hung et al; NCT04276688): 127 pts were randomized 2:1 to receive LPV/RTV (LPV 400 mg/RTV 100 mg) twice daily for 14 days) with ribavirin (400 mg twice daily) and interferon β-1b (8 million IU sub-Q on alternate days for up to 3 doses depending on how soon treatment initiated after symptom onset) or a 14-day regimen of LPV/RTV alone. Median time to negative RT-PCR results for SARS-CoV-2 in nasopharyngeal samples was 7 days in pts treated with the 3-drug regimen vs 12 days in those treated with LPV/RTV alone; median duration of hospitalization was 9 or 14.5 days, respectively. Adverse effects reported in 48% of those treated with the 3-drug regimen and in 49% of those treated with LPV/RTV alone. <strong>Note:</strong> Results indicate a 3-drug regimen that included LPV/RTV, ribavirin, and interferon β-1b was more effective than LPV/RTV alone in pts with mild to moderate COVID-19, especially when treatment was initiated within 7 days of symptom onset.</td>
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<td>LPV/RTV retrospective cohort study in China (Deng et al) evaluated use of LPV/RTV with or without umifenovir (Arbidol®) in adults. Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 6/17 pts (35%) treated with LPV/RTV alone vs 12/16 (75%) treated with both drugs; chest CT</td>
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**IDSA recommends against** use of LPV/RTV for the treatment of COVID-19 in hospitalized pts. \(^23\)
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<td>scans were improving in 29% of pts treated with LPV/RTV alone vs 69% of pts treated with both drugs. (^{(6)}) (See Umifenovir in this Evidence Table.)</td>
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<td><strong>LPV/RTV in randomized, controlled, open-label, platform trial (NCT04381936; RECOVERY):</strong> This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the LPV/RTV arm (now terminated), 1616 pts were randomized to receive LPV/RTV (LPV 400 mg/RTV 100 mg every 12 hours for 10 days or until discharge, whichever came first) plus standard of care and 3424 pts were randomized to standard of care alone. At the time of study enrollment, 26% of pts did not require oxygen support, 70% required oxygen support, and only 4% were on mechanical ventilation. The primary outcome was all-cause mortality at day 28. <strong>Results of this study indicated that LPV/RTV is not an effective treatment for COVID-19 in hospitalized pts.</strong> Mortality rate at 28 days was 23% in those treated with LPV/RTV plus standard of care vs 22% in those treated with standard of care alone. In addition, LPV/RTV did not reduce the time to hospital discharge (median length of stay was 11 days in both groups) and, in those not requiring mechanical ventilation at baseline, LPV/RTV did not decrease the risk of progression to mechanical ventilation (10% in the LPV/RTV group vs 9% in standard of care alone group). Results were consistent across all prespecified pt subgroups (age, sex, ethnicity, level of respiratory support, time since symptom onset, and predicted 28-day mortality risk at time of randomization). (^{(27)})</td>
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<td><strong>Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY):</strong> The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. (^{(29,30)}) From March 22 to July</td>
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| Trials or Clinical Experience: 1411 pts were randomized to receive LPV/RTV (two tablets containing LPV 200 mg/RTV 50 mg orally twice daily for 14 days) with local standard of care and 1380 pts were randomized to LPV/RTV control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (1399 pts in LPV/RTV group and 1372 pts in standard of care group) indicated that **LPV/RTV did not reduce in-hospital mortality** (either overall or in any subgroup defined by age or ventilation status at study entry) and **did not reduce the need for initiation of ventilation or the duration of hospitalization**. The log-rank death rate ratio for LPV/RTV in the ITT population was 1.00; 148/1399 pts treated with LPV/RTV (9.7%) and 146/1372 pts treated with standard of care (10.3%) died. Ventilation was initiated after randomization in 126 pts receiving LPV/RTV and 121 pts receiving standard of care.  

Daranavir and cobicistat (DRV/c) randomized, open-label trial in China (Chen et al; NCT04252274): A total of 30 adults with mild, laboratory-confirmed COVID-19 were randomized 1:1 to receive DRV/c (fixed combination darunavir 800 mg/cobicistat 150 mg once daily for 5 days) or no DRV/c (control group); all pts received interferon alfa-2b and standard of care. The primary end point was viral clearance rate at day 7 (defined as RT-PCR negative for SARS-CoV-2 in at least 2 consecutive oropharyngeal swabs collected at least 1-2 days apart). At day 7, viral clearance rate in the intention-to-treat (ITT) population was 47% in those treated with DRV/c and 60% in the control group. In the per-protocol (PP) population, viral clearance rate at day 7 was 50% in those treated with DRV/c and 60% in the control group. The median time from randomization to negative RT-PCR result was 8 and 7 days, respectively. This study indicated that a 5-day regimen of DRV/c in pts with mild COVID-19 did not provide clinical benefits compared with use of standard care alone. |
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<tr>
<td>Hydroxychloroquine (Plaquenil®)</td>
<td>8:30.08 Antimalarial (4-aminoquinoline derivative)</td>
<td>Updated 12/17/20</td>
<td><strong>In vitro activity against various viruses, including coronaviruses</strong>&lt;sup&gt;1, 8, 12-14&lt;/sup&gt;</td>
<td><strong>Clinical experience in treating pts with COVID-19:</strong> Majority of data to date involves use in pts with mild or moderate COVID-19; only limited clinical data on use in pts with severe and critical disease.</td>
<td><strong>LPV/RTV COVID-19 Clinical Trials:</strong> Some clinical trials registered at clinicaltrials.gov listed below:</td>
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<td>In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed.</td>
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<td><strong>Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established</strong>&lt;sup&gt;10, 24, 39&lt;/sup&gt;</td>
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<td>Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections&lt;sup&gt;3, 8, 13, 15, 16&lt;/sup&gt;.</td>
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<td>Data from various published randomized, controlled clinical trials and retrospective, cohort studies have not substantiated initial reports of efficacy of 4-aminoquinoline antimalarials (with or without azithromycin) for the treatment of COVID-19. A few studies reported benefits when hydroxychloroquine was used in pts with COVID-19. There has been concern about limitations related to trial design of some studies evaluating efficacy of hydroxychloroquine (e.g., lack of blinding and/or randomization, retrospective and/or observational nature, insufficient statistical power, inconsistency regarding concomitant therapy), and there are some ongoing studies.</td>
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<td>Known pharmacokinetics and toxicity profile based on use for other indications.</td>
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<td>NIH COVID-19 Treatment Guidelines Panel recommends against use of hydroxychloroquine (with or without azithromycin) for the treatment of COVID-19.</td>
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<td>Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects; may have more favorable dose-related toxicity profile than chloroquine, but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs.</td>
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<td>Hydroxychloroquine randomized, parallel-group study in adults in China (ChiCTR2000029559): 31 pts with COVID-19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 26 days) followed by conventional therapy (all pts showed improvement at discharge); median duration from hospitalization to negative conversion of SARS-CoV-2 in infected Vero E6 cells was 12 days.</td>
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<td>Vero E6 cells reported; In vitro activity against various coronaviruses</td>
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<td>Known pharmacokinetics and toxicity profile based on use for other indications.</td>
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<td>Hydroxychloroquine small pilot study conducted in China: 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV. Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).</td>
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5 days) and standard treatment \( (O_2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids) \) and 31 other pts received standard treatment alone (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group). \(^{31}\) Note: This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, \(^{32}\) data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported. \(^{31}\)

Hydroxychloroquine randomized, parallel-group, open-label study in hospitalized adults with mild to moderate COVID-19 in China (ChiCTR2000029868): 150 pts (148 with mild to moderate disease and 2 with severe disease) were randomized 1:1 to receive hydroxychloroquine (1200 mg daily for 3 days, then 800 mg daily for total treatment duration of 2-3 weeks) with standard of care or standard of care alone. Mean time from onset of symptoms to randomization was 16.6 days (range: 3-41 days).

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<td>COVID-19 in hospitalized pts and recommends against use of hydroxychloroquine (with or without azithromycin) for the treatment of COVID-19 in nonhospitalized pts, except in a clinical trial. (^{35}) IDSA recommends against use of hydroxychloroquine for the treatment of COVID-19 in hospitalized pts and also recommends against use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19 in hospitalized pts. (^{38}) NIH COVID-19 Treatment Guidelines Panel recommends against the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection, except in a clinical trial. (^{35}) The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure. (^{35}) Because 4-aminoquinolines (hydroxychloroquine, chloroquine) and azithromycin are independently associated with QT prolongation and because concomitant use of the drugs may further increase the risk of QT prolongation, caution is advised if considering use of hydroxychloroquine (with or without azithromycin) in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. (^{35, 36, 38, 39, 41-44}) NIH panel states that 4-aminoquinolines (hydroxychloroquine, chloroquine) should be used concomitantly with drugs that pose a moderate to high risk for QT prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, fluoroquinolones, macrolides [including azithromycin]) only if necessary. In addition, because of the long half-lives of both hydroxychloroquine (up to 40 days) and azithromycin (up to 72 hours), caution is warranted even when these drugs are used sequentially. The panel</td>
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<td>Standard of care included IV fluids, O₂, various antivirals (e.g., umifenovir, LPV/RTV), antibiotics, and/or glucocorticoid therapy. By day 28, 73% of pts (53 treated with hydroxychloroquine with standard of care and 56 treated with standard of care alone) had converted to negative for SARS-CoV-2. The probability of negative conversion by day 28 in those treated with hydroxychloroquine was similar to that in those treated with standard of care alone; the median time to negative seroconversion (6 and 7 days) also was similar in both groups. Adverse effects reported in 30% of those treated with hydroxychloroquine and 9% of those treated with standard of care alone. <strong>Note</strong>: Results indicate that use of hydroxychloroquine in pts with mild to moderate COVID-19 did not provide additional benefits compared with use of standard of care alone.</td>
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**Hydroxychloroquine with azithromycin open-label, nonrandomized study in France (Gautret et al):** Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6. **Note**: This was a small nonrandomized study that didn’t appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity were unclear (some asymptomatic pts were included when study initiated). states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving hydroxychloroquine (or chloroquine). 

The benefits and risks of hydroxychloroquine (with or without azithromycin) should be carefully assessed; diagnostic testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 

FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA **cautions against** use of chloroquine or hydroxychloroquine for treatment or prevention of COVID-19 outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to **FDA MedWatch**.

**Emergency use authorization (EUA) for hydroxychloroquine (now revoked):** Effective June 15, 2020, FDA has revoked the EUA for hydroxychloroquine and chloroquine previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible. Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met. Based on the totality of scientific evidence available, FDA concluded that it is unlikely that hydroxychloroquine and chloroquine may be effective in treating COVID-19 and, in light of
and information on disease progression and clinical outcomes was not presented.

**Hydroxychloroquine with azithromycin open-label, uncontrolled study in France (Molina et al):** 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O₂. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen was discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. **Note:** In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.

**Hydroxychloroquine with azithromycin uncontrolled, retrospective, observational study in France (Gautret et al):** 80 adults with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O₂ saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O₂; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. **Note:** Almost all pts were considered low risk for clinical

ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of hydroxychloroquine and chloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA. **57**

The basis for the FDA decision to revoke the EUA for hydroxychloroquine and chloroquine is summarized below:

1) Suggested hydroxychloroquine and chloroquine dosage regimens as detailed in the EUA fact sheets for healthcare providers are unlikely to produce an antiviral effect. **52**

2) Earlier observations of decreased viral shedding with hydroxychloroquine or chloroquine treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between hydroxychloroquine and standard of care alone. **57**

3) Current US treatment guidelines do not recommend the use of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19 outside of a clinical trial and the NIH guidelines now recommend against such use outside of a clinical trial. **57**

4) Recent data from a large, randomized, controlled trial showed no evidence of benefit in mortality or other outcomes such as hospital length of stay or need for mechanical ventilation for hydroxychloroquine treatment in hospitalized patients with COVID-19. **57**

Consult the FDA letter regarding the revocation of the EUA for hydroxychloroquine and chloroquine and the FDA memorandum explaining the basis for the revocation for additional information. **57**
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<td>Hydroxychloroquine with azithromycin</td>
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- **uncontrolled, observational, retrospective analysis in France (Million et al):** Data for 1061 pts with PCR-documented SARS-CoV-2 RNA who were treated with a regimen of hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) were analyzed for clinical outcomes and persistence of viral shedding. Pts were included in the analysis if they received the combined regimen for at least 3 days and were clinically assessable at day 9. There were 56 asymptomatic and 1005 symptomatic pts; the majority (95%) had relatively mild disease and were considered low risk for clinical deterioration; median age was 43.6 years (range: 14-95 years) and mean time between onset of symptoms and initiation of treatment was 6.4 days. Within 10 days of treatment, good clinical outcome reported in 973 pts (91.7%) and poor clinical outcome reported in 46 pts (4.3%). Persistent nasal carriage of SARS-CoV-2 reported at completion of treatment in 47 pts (4.4%); 8 pts died.

- **Hydroxychloroquine (with or without azithromycin) in a retrospective analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers (Magagnoli et al):** Data for 368 males (median age >65 years) treated with hydroxychloroquine in addition to standard supportive management were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in
those treated with hydroxychloroquine, 22.1% (25/113) in those treated with hydroxychloroquine and azithromycin, and 11.4% (18/158) in those not treated with hydroxychloroquine; rate of ventilation was 13.3, 6.9, and 14.1%, respectively. Use of hydroxychloroquine alone (but not use of hydroxychloroquine and azithromycin) was associated with increased overall mortality compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation. \(^{43}\) \(\text{Note:}\) The pt population included only elderly males 59-75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures.

Two different retrospective studies analyzed outcome data for hospitalized pts with confirmed COVID-19 in New York to assess the effects of treatment with hydroxychloroquine with or without azithromycin (Rosenberg et al, Geleris et al): Results of these studies suggest that use of hydroxychloroquine with or without azithromycin is not associated with decreased in-hospital mortality. \(^{44,45}\)

Rosenberg et al analyzed data for 1438 hospitalized pts (735 received hydroxychloroquine with azithromycin, 271 received hydroxychloroquine alone, 211 received azithromycin alone, 221 received neither drug) and assessed in-hospital mortality (primary outcome). Overall, in-hospital mortality was 20.3%; in-hospital mortality was 25.7, 19.9, 10, or 12.7% in those treated with hydroxychloroquine with azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug, respectively. \(^{45}\)

Geleris et al analyzed data for 1376 hospitalized pts (811 received hydroxychloroquine [486 of these also received azithromycin] and 565 did not receive hydroxychloroquine [127 of these received azithromycin]) and assessed the primary end point of time from study baseline to intubation or death. Overall, 346 pts (25.1%) progressed to a primary end point of intubation and/or death and the

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<td>composite end point of intubation or death was not affected by hydroxychloroquine treatment (intubation or death reported in 32.3% of pts treated with hydroxychloroquine and 14.9% of pts not treated with the drug).</td>
<td>Large, randomized, controlled, open-label, platform trial evaluating efficacy of various treatments in hospitalized pts with COVID-19 (NCT04381936; RECOVERY): This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. The protocol-specified primary outcome is all-cause mortality at day 28; secondary outcomes include duration of hospitalization and composite of initiation of invasive mechanical ventilation (including ECMO) or death among those not receiving invasive mechanical ventilation at time of randomization. In the hydroxychloroquine sulfate arm (now terminated), 1561 adults were randomized to receive hydroxychloroquine sulfate (two 800-mg doses given 6 hours apart followed by two 400-mg doses given 12 and 24 hours after the initial dose on day 1, then 400 mg every 12 hours thereafter for 9 days or until hospital discharge, whichever came first) plus standard of care and 3155 were randomized to standard of care alone. Data analyses for this intention-to-treat (ITT) population indicated that hydroxychloroquine did not reduce mortality and did not provide other benefits in pts hospitalized with COVID-19. The 28-day mortality rate was 27% in those treated with hydroxychloroquine plus standard care vs 25% in those treated with standard care alone (death rate ratio 1.09); results were consistent across all subgroups defined at the time of randomization (age, sex, race, time since illness onset, level of respiratory support, predicted 28-day risk of death). In addition, pts in the hydroxychloroquine group had a longer duration of hospitalization than those in the standard care alone group (median time to discharge 16 vs 13 days) and a lower probability of discharge alive within 28 days. Among those not receiving invasive mechanical ventilation at baseline, the number of pts who progressed to invasive...</td>
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<td>mechanical ventilation or death was higher in the hydroxychloroquine group than the standard care alone group (risk ratio 1.14). 53</td>
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<td>Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY): The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. 54, 65</td>
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<td>From March 22 to June 19, 2020, 954 pts were randomized to receive hydroxychloroquine sulfate (two 800-mg doses given 6 hours apart followed by a 400-mg dose given 12 hours after the initial dose on day 1, then 400 mg twice daily for 10 days) with local standard of care and 909 pts were randomized to hydroxychloroquine control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (947 pts in hydroxychloroquine group and 906 pts in standard of care only group) indicated that hydroxychloroquine did not reduce in-hospital mortality (either overall or in any subgroup defined by age or ventilation status at study entry) and did not reduce the need for initiation of ventilation or the duration of hospitalization. The log-rank death rate ratio for hydroxychloroquine in the ITT population was 1.19; 104/947 pts treated with hydroxychloroquine (10.2%) and 84/906 pts treated with standard of care (8.9%) died. Ventilation was initiated after randomization in 75 pts receiving hydroxychloroquine and 66 pts receiving standard of care. 64</td>
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<td>Multicenter, randomized, blinded, placebo-controlled trial evaluating hydroxychloroquine in adults hospitalized with COVID-19 (Self et al): A total of 479 adults with laboratory-confirmed SARS-CoV-2 infection were randomized 1:1 to receive hydroxychloroquine sulfate (400 mg twice daily on day 1, then 200 mg twice daily on days 2-5) or placebo. Baseline</td>
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a Doses are taken on an empty stomach.
characteristics were similar between both groups; median age was 57 years and median duration of symptoms prior to randomization was 5 days. The primary outcome was clinical status at 14 days after randomization and clinical status was assessed using a 7-category ordinal scale (COVID outcomes scale); secondary outcomes included all-cause all-location mortality at 14 and 28 days after randomization, time to recovery, composite of death or need for ECMO, and support-free days through 28 days (e.g., no need for hospitalization, oxygen, intensive care, ventilator, vasopressors). At day 14, there was no difference in clinical status between the hydroxychloroquine group (242 pts) and placebo group (237 pts); median score (interquartile range) on the COVID outcomes scale was 6 (4-7) in both groups (score of 6 was defined as not hospitalized and unable to perform normal activities). There also was no difference in clinical status at day 14 between the hydroxychloroquine and placebo groups in any of the prespecified subgroups (e.g., based on age, sex, race/ethnicity, baseline illness severity, duration of symptoms). In addition, there were no differences in any of the secondary outcomes between the treatment groups. Data for pts with confirmed vital status at day 28 indicated that 10.4% of those in the hydroxychloroquine group and 10.6% of those in the placebo group had died.

Retrospective, comparative cohort study evaluating clinical outcomes in hospitalized COVID-19 pts treated with hydroxychloroquine vs hydroxychloroquine with azithromycin vs azithromycin alone (Arshad et al): Data for 2541 consecutive pts with laboratory-confirmed COVID-19 who were admitted to hospitals within the Henry Ford Health System in Michigan and received hydroxychloroquine and/or azithromycin or did not receive these drugs were analyzed. Median age of patients was 64 years; the majority had BMI of 30 or greater and many had various other comorbidities; 68% received corticosteroid treatment and 4.5% received tocilizumab; mSOFA scores were not available for 25% of pts and data were not available.
regarding duration of symptoms prior to hospitalization; and the median length of hospitalization was 6 days. The primary end point was inpatient mortality; median follow-up was 28.5 days. Results indicated that crude mortality rates were 18.1% in the entire group, 13.5% in the hydroxychloroquine group, 20.1% in the hydroxychloroquine with azithromycin group, 22.4% in the azithromycin group, and 26.4% in those not treated with hydroxychloroquine and/or azithromycin. The primary causes of mortality were respiratory failure (88%), cardiac arrest (4%), and cardiopulmonary arrest and multi-organ failure (8%).

**Note:** Only selected pts with minimal cardiac risk factors received hydroxychloroquine with azithromycin and all pts treated with hydroxychloroquine were monitored closely with telemetry and serial QTc evaluations.

Open-label, randomized study in hospitalized pts with mild to moderate COVID-19 (Cavalcanti et al; Brazil; NCT04322123): Adults hospitalized with COVID-19 were randomized 1:1:1 to receive standard care (control group), hydroxychloroquine (400 mg twice daily for 7 days) with standard care, or hydroxychloroquine (same dosage) plus azithromycin (500 mg once daily for 7 days) with standard care. Pts not requiring supplemental oxygen or only requiring supplemental oxygen at a rate of 4 L/min or less at baseline were enrolled; pts with a history of severe ventricular tachycardia or with QTc of 480 msec or greater at baseline were excluded. The median time from onset of symptoms to randomization was 7 days. The primary outcome was clinical status at day 15 evaluated using a 7-point ordinal scale. Data for the 504 pts in the modified intention-to-treat population with laboratory-confirmed COVID-19 (173 pts in the control group, 159 pts in the hydroxychloroquine group, 172 pts in the hydroxychloroquine and azithromycin group) indicated there was no significant difference in clinical status at day 15 in those treated with hydroxychloroquine with or without azithromycin compared with the control group. There also were no significant differences in secondary outcomes (e.g., need for mechanical
ventilation, duration of hospitalization, in-hospital death) among the groups.  

**Open-label, randomized study in outpatients with mild COVID-19 (Mitja et al; Spain):** Total of 293 adults with laboratory-confirmed COVID-19 who did not require hospitalization and had mild symptoms (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, influenza-like illness) for less than 5 days before study enrollment were randomized 1:1 to receive hydroxychloroquine (800 mg on day 1, then 400 mg once daily for 6 days) or usual care only. The primary outcome was reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment initiation. Median age of pts was 41.6 years, 53% reported chronic health conditions, and 87% were healthcare workers. The median time from symptom onset to randomization was 3 days, and the mean viral load at baseline was 7.9 log_{10} copies/mL. Results indicated that a 7-day hydroxychloroquine regimen did not provide any clinical benefits compared with usual care alone in these outpatients with mild COVID-19. There was no significant reduction in viral load at day 3 or 7 in those treated with hydroxychloroquine vs those treated with usual care only and there was no decrease in median time to resolution of COVID-19 symptoms (10 and 12 days, respectively) and no decrease in risk of hospitalization (7 and 6%, respectively).  

**Double-blind, randomized, placebo-controlled study in outpatients with confirmed or probable early COVID-19 (Skipper et al; US and Canada; NCT04308668):** A total of 423 symptomatic adults with laboratory-confirmed COVID-19 or with symptoms compatible with COVID-19 and a high-risk exposure to a contact with laboratory-confirmed COVID-19 were randomized 1:1 to receive hydroxychloroquine (initial dose of 800 mg, 600 mg given 6-8 hours later, then 600 mg once daily for the next 4 days) or placebo. Enrolled pts had been symptomatic for no more than 4 days and did not require hospitalization at the time of enrollment. The primary efficacy end point specified in

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|         |            |           | the initial study protocol was subsequently changed to overall symptom severity over 14 days; symptoms and severity were self-reported by the pts at days 3, 5, 10, and 14 using a survey with a 10-point visual analog scale. Median age of pts was 40 years, 68% reported no chronic medical conditions, 57% were healthcare workers, 25% had been exposed to COVID-19 through household contacts, and 56% of pts had enrolled within 1 day of symptom onset. **Results indicated that a 5-day hydroxychloroquine regimen did not provide any substantial improvement in symptom severity in these outpatients with confirmed or probable COVID-19.** At day 5, 54% of pts in the hydroxychloroquine group and 56% in the placebo group reported symptoms. At day 14, 24% of those treated with hydroxychloroquine had ongoing symptoms compared with 30% of those treated with placebo. Overall, the decrease in prevalence of symptoms and the reduction in symptom severity score over 14 days were not significantly different between the two groups (symptom severity in the 10-point scale decreased 2.6 points in those treated with hydroxychloroquine and 2.3 points in those treated with placebo). In addition, there was no difference between the groups in the incidence of hospitalization or death.  

**Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to assess the effects of hydroxychloroquine or chloroquine used with or without a macrolide (Mehra et al; now retracted):** Original publication included data obtained worldwide for 96,032 pts hospitalized with COVID-19 between Dec 20, 2019 and Apr 14, 2020, including 14,888 pts who received chloroquine or hydroxychloroquine with or without a macrolide (azithromycin or clarithromycin) initiated within 48 hours of diagnosis (treatment group) and 81,144 pts who did not receive these drugs (control group). Based on those data, in-hospital mortality rate in the control group was 9.3% compared with 18% in those treated with hydroxychloroquine alone (n=3016), 23.8% in those treated with hydroxychloroquine and a macrolide. |
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<td>Hydroxychloroquine for postexposure prophylaxis of COVID-19 randomized, placebo-controlled trial in the US and Canada (NCT04308668): Asymptomatic adults with occupational or household exposure to an individual with COVID-19 were randomly assigned 1:1 to receive postexposure prophylaxis with a 5-day regimen of hydroxychloroquine sulfate (initial 800-mg dose followed by a 600-mg dose given 6-8 hours after first dose on day 1, then 600 mg once daily for 4 additional days) or placebo (folate tablets). A total of 821 asymptomatic adults were enrolled within 4 days after COVID-19 exposure (414 randomized to hydroxychloroquine and 407 randomized to hydroxychloroquine and 407 randomized to placebo); 66% were healthcare workers. Overall, 88% of participants reported high-risk exposures (occurred at a distance of &lt;6 feet for &gt;10 minutes while not wearing a face mask or eye shield) and the others reported moderate-risk exposures (occurred at a distance of &lt;6 feet for &gt;10 minutes while wearing a face mask but no eye shield). Note: Participants were recruited primarily through social media outreach and traditional media platforms and were enrolled using an internet-based survey. The exposure event and subsequent onset of new symptoms and illness compatible with COVID-19 after enrollment were self-reported using email surveys on days 1, 5, 10, and 14 and at 4-6 weeks. Results of these surveys and information obtained using additional forms of follow-up indicated that confirmed or probable COVID-19 (based on self-reported symptoms or PCR testing) developed in 13% of participants overall (107/821) and did not differ significantly between those who received hydroxychloroquine prophylaxis (11.8%) and those who received...</td>
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<td>placebo (14.3%) (^{35}) Note: The various limitations of the trial design should be considered when interpreting the results. Exposure to someone with confirmed COVID-19, time from the exposure event to initiation of prophylaxis, and all outcome data (including possible COVID-19 symptoms and PCR test results) were self-reported by study participants. COVID-19 was confirmed with PCR testing in only a small percentage (&lt;3%) of participants who self-reported COVID-19 symptoms. Survey results indicated that full adherence to the 5-day prophylaxis regimen was reported by only 75% of patients randomized to hydroxychloroquine and 83% of those randomized to placebo. In addition, a total of 52 participants did not complete any surveys after study enrollment. (^{35,36})</td>
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<td>Double-blind, placebo-controlled, randomized trial in the US to evaluate hydroxychloroquine for preexposure prophylaxis of COVID-19 (Abella et al; NCT04329923): Healthcare personnel working ≥20 hours per week in hospital-based units (nurses, physicians, certified nursing assistants, emergency technicians, respiratory therapists) who had no known history of SARS-CoV-2 infection and no symptoms suggestive of COVID-19 within 2 weeks prior to trial enrollment were randomized 1:1 to receive hydroxychloroquine (600 mg daily) or placebo for preexposure prophylaxis of COVID-19. Nasopharyngeal swab tests for SARS-CoV-2 and serologic tests for anti-nucleocapsid IgG, anti-spike protein receptor-binding domain (RBD) IgM, and anti-RBD IgG were performed at the time of randomization (baseline) and at 4 and 8 weeks; participants also were surveyed weekly for adherence and adverse events. The primary outcome was rate of conversion to SARS-CoV-2-positive status based on nasopharyngeal swab testing at 8 weeks. A total of 125 participants were evaluable for the primary outcome (64 in the hydroxychloroquine arm and 61 in the placebo arm); 22 of the evaluable participants (17.6%) discontinued study treatment early. Results indicate that preexposure prophylaxis with hydroxychloroquine did not provide clinical benefits in</td>
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hospital-based healthcare personnel. The rate of COVID-19 positivity was similar in the hydroxychloroquine group (6.3%) and placebo group (6.6%); cases of infection occurred throughout the 8-week study period. All 8 individuals who became infected (4 in each group) were either asymptomatic or had mild disease with full recovery; none required hospitalization. After reviewing data at the time of a second planned interim analysis, the data safety and monitoring board recommended that the trial be terminated early. Grade 3 or 4 adverse events were not reported in any participants; the incidence of adverse events was significantly higher in the hydroxychloroquine group than the placebo group (45 vs 26%). **Note:** Limitations of this trial include the possibility that it was insufficiently powered because of low enrollment, data are not available to quantify the frequency of participant exposures to the virus or specific timing of such exposures, and most participants were young and healthy.

**Retrospective cohort study in the US to evaluate possible SARS-CoV-2 preventive benefits of hydroxychloroquine therapy used in pts with rheumatic conditions** (Gentry et al): Possible benefit of long-term hydroxychloroquine therapy used for management of rheumatic conditions for prevention of SARS-CoV-2 infection in such pts was investigated retrospectively using data obtained from the US Veterans Affairs Medical Centers (VAMCs) database. Adults in the database with ICD-10 diagnostic code entries for rheumatoid arthritis, systemic lupus erythematosus, and associated rheumatologic conditions were identified and each such pt receiving hydroxychloroquine was matched to 2 such pts not receiving hydroxychloroquine (controls). The primary end point was the proportion of pts with PCR-confirmed SARS-CoV-2 infection between March 1 and June 30, 2020 among those receiving long-term hydroxychloroquine therapy versus the propensity-matched patients not receiving hydroxychloroquine. Data analyses indicated that long-term hydroxychloroquine therapy in patients receiving the drug for

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Note: Limitations of this trial include the possibility that it was insufficiently powered because of low enrollment, data are not available to quantify the frequency of participant exposures to the virus or specific timing of such exposures, and most participants were young and healthy.
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<td>Neuraminidase inhibitors (e.g., oseltamivir)</td>
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<td>Antivirals active against influenza viruses</td>
<td>Oseltamivir has been included as a component of various antiviral regimens used for the treatment of COVID-19.5,6,7 While oseltamivir is noted to have been widely used for confirmed or suspected COVID-19 cases in hospitals in China in the early stages of the pandemic, there has been no evidence that oseltamivir is effective in the treatment of COVID-19.2 In a retrospective case series of 99 adults with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of pts received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died.1</td>
<td>Dosage of oseltamivir in the case series of 99 COVID-19 patients was 75 mg orally every 12 hours.1 Dosages of oseltamivir from registered COVID-19 trials have included 75 mg orally twice daily or 300 mg (or 4-6 mg/kg) orally daily.3 Although oseltamivir was suggested as a potential treatment and included in various antiviral regimens used during the early stages of the COVID-19 pandemic,5,6,7,11 the drug does not appear to have in vitro activity against SARS-CoV-2 and there are no data to support the use of oseltamivir or other neuraminidase inhibitors in the treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel states that, when SARS-CoV-2 and influenza are cocirculating, testing for both viruses is recommended in all hospitalized pts with acute respiratory illness and also recommended in outpatients with acute respiratory illness if</td>
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rheumatic conditions was not associated with a preventive effect against SARS-CoV-2 infection. The incidence of SARS-CoV-2 infection was similar in pts receiving hydroxychloroquine (0.3%; 31 of 10,703 pts) and those not receiving the drug (0.4%; 78 of 21,406 pts). In those who developed active SARS-CoV-2 infection, there were no significant differences in secondary outcomes between the hydroxychloroquine group and control group.63

Multiple clinical trials evaluating hydroxychloroquine for treatment of COVID-19 are registered at clinicaltrials.gov, including the following: 
10 NCT04395768 NCT04342169 NCT04342221 NCT04344457 NCT04353336 NCT04447534 NCT04605588

Multiple clinical trials evaluating hydroxychloroquine for prevention of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov, including the following: 
10 NCT04303507 NCT04334148 NCT04335084 NCT04363450 NCT04384458

Neuraminidase inhibitors (e.g., oseltamivir) Updated 1/14/21

Antivirals active against influenza viruses
Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV-1 in vitro cell culture.4 Oseltamivir did not demonstrate in vitro antiviral activity against SARS-CoV-2 in Vero E6 cells5,9 Data are not available on in vitro antiviral activity of peramivir or zanamivir against SARS-CoV-23
In a retrospective case series of 79 adults with COVID-19 who were negative for influenza A and B, early use of oseltamivir had no effect on COVID-19 and did not effectively slow the progression of the disease.  

In a retrospective cohort study of 1190 adults with COVID-19 at a single center in Wuhan from 12/29/19 to 2/28/20, 61.6% of pts received antiviral therapy (e.g., oseltamivir, ganciclovir, lopinavir/ritonavir, interferon, umifenovir). A survival analysis indicated that administration of oseltamivir appeared to have reduced the risk of death in pts with severe disease and seemed to have been associated with less deterioration (i.e., progression from nonsevere to severe disease or severe disease to death).  

**Note:** Limitations of this study include missing laboratory data because of retrospective data extraction, lack of information on possible mixed viral infections, and inability to analyze possible reasons for mortality benefit.

Oseltamivir may be included in some COVID-19 clinical trials registered at clinicaltrials.gov

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<td>Remdesivir (Veklury®)</td>
<td>8:18.32 Antiviral</td>
<td>Nucleotide analog prodrug; RNA polymerase inhibitor</td>
<td>Randomized, double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al): Pts were randomized 2:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10) or placebo initiated within 12 days of symptom onset. Primary outcome was time to clinical improvement within 28 days after randomization or hospital discharge, whichever came first. ITT population included 158 pts treated with remdesivir and 78 pts treated with placebo; 32% of pts also received interferon α-2b, 28% also received LPV/RTV, and 66% also received</td>
<td>Remdesivir dosage for FDA-labeled indication for treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing at least 40 kg (lyophilized powder formulation or solution concentrate formulation): Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts not requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment results will change clinical management of the pt. Testing is the only way to distinguish between influenza and SARS-CoV-2 and identify coinfection. Treatment of influenza is the same in all pts regardless of SARS-CoV-2 coinfection. If SARS-CoV-2 and influenza are cocirculating, the panel recommends that hospitalized pts suspected of having one or both viral infections should receive oseltamivir for empiric influenza treatment as soon as possible without waiting for influenza testing results; empiric influenza treatment can be de-escalated based on results of testing and intubation status. Significant drug interactions not expected with oseltamivir and remdesivir.</td>
<td>The only direct-acting antiviral (DAA) currently approved by FDA for treatment of COVID-19 in certain populations. Received FDA approval on October 22, 2020 for treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing at least 40 kg who are hospitalized or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Safety and effectiveness have not been established in pediatric patients &lt;12 years of age or weighing &lt;40 kg.</td>
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<td>Remdesivir</td>
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<td>In Rhesus macaques infected with SARS-CoV-2, treatment with a 6-day regimen of IV remdesivir initiated 12 hours after virus inoculation was associated with some benefits (lower disease severity scores, fewer pulmonary infiltrates, lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control. In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected. Corticosteroids during hospitalization. Median time to clinical improvement was not significantly different in remdesivir group (21 days) vs placebo group (23 days); 28-day mortality rate was similar in both groups (14 vs 13%). When remdesivir was initiated within 10 days of symptom onset, median time to clinical improvement was numerically shorter (but not statistically significant) compared with placebo group (18 vs 23 days). Duration of invasive mechanical ventilation was numerically shorter (but not statistically significant) in remdesivir group; only a small percentage of pts (0.4%) were on invasive mechanical ventilation at time of enrollment. Remdesivir did not result in significant reduction in SARS-CoV-2 viral load in nasopharyngeal, oropharyngeal, and sputum samples. Remdesivir was discontinued in 18 pts (12%) because of adverse effects. Not: Enrollment was terminated before the pre-specified number of pts was attained (lack of available pts); trial was insufficiently powered to detect assumed differences in clinical outcome. Phase 3 randomized, open-label trial in hospitalized pts with severe COVID-19 (NCT04292899; GS-US-540-5773: SIMPLE-Severe) sponsored by the manufacturer (Gilead): Initial study protocol was designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care in adults with severe COVID-19 not receiving mechanical ventilation at study entry. Protocol was subsequently modified to include pts 12 years of age or older, add an extension phase, and include a cohort of pts receiving mechanical ventilation. Data for the initial 267 pts not requiring mechanical ventilation at study entry (200 received a 5-day regimen and 197 received a 10-day regimen) indicate similar clinical improvement with both treatment durations after adjusting for baseline clinical status. Pt demographics and clinical characteristics at baseline generally were similar in both groups, although the 10-day group included a higher percentage of pts in the most may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. Emergency use authorization (EUA) remdesivir dosage for treatment of COVID-19 in pediatric patients weighing 3.5 to &lt;40 kg (lyophilized powder formulation only): Loading dose of 5 mg/kg by IV infusion on day 1, followed by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2. For pts not requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. Emergency use authorization (EUA) remdesivir dosage for treatment of COVID-19 in pediatric patients &lt;12 years of age weighing ≥40 kg (lyophilized powder formulation only): Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts not requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. NIH COVID-19 Treatment Guidelines Panel-recommended duration of remdesivir treatment: The NIH panel recommends that hospitalized patients may be discharged from the hospital after demonstrating clinical improvement and no longer requiring supplemental oxygen, mechanical ventilation, and/or ECMO. Available under an emergency use authorization (EUA) for treatment of suspected or laboratory-confirmed COVID-19 in pediatric patients weighing 3.5 to &lt;40 kg and pediatric patients &lt;12 years of age weighing at least 3.5 kg who are hospitalized or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Emergency use authorization (EUA) for remdesivir: The original EUA issued by FDA on May 1, 2020 permitted use of remdesivir for treatment of COVID-19 in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 and severe disease (defined as oxygen saturation [SpO2] ≤94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO); on August 28, 2020, FDA broadened the EUA to allow use of the drug in hospitalized patients irrespective of disease severity. In response to FDA approval of remdesivir for use in adults and pediatric patients ≥12 years of age weighing at least 40 kg, the EUA was reissued on October 22, 2020 to allow continued authorization of the drug (lyophilized powder formulation only) for emergency use in pediatric patients weighing 3.5 to &lt;40 kg and pediatric patients &lt;12 years of age weighing at least 3.5 kg with suspected or laboratory-confirmed COVID-19. The EUA for remdesivir requires that the drug be administered by a healthcare provider in an inpatient hospital setting (or alternative care site capable of providing acute care comparable to general inpatient hospital care) via IV injection at dosages recommended in the EUA. The EUA also requires that healthcare facilities and healthcare providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). Although distribution of remdesivir under the EUA was previously directed by the HHS Office of Public Health Preparedness and Response (OPHP), the Office of Biomedical Advanced Research and Development (BARDA), or the Biomedical Advanced Research and Development Authority (BARDA), the Health Resources and Services Administration (HRSA) may continue to provide drug under the EUA. Pharmacokinetic data available from studies in healthy adults.</td>
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<td>severe disease categories and a higher proportion of men (who are known to have worse COVID-19 outcomes than women); median duration of symptoms before first dose of remdesivir was similar in both groups [8 or 9 days]. At day 14, 129/200 pts (65%) in the 5-day group and 106/197 pts (54%) in the 10-day group achieved clinical improvement [defined as an improvement of at least 2 points from baseline on a 7-point ordinal scale]. After adjusting for baseline imbalances in disease severity, data indicate that clinical status at day 14, time to clinical improvement, recovery, and death (from any cause) were similar in both groups. Although eligibility criteria according to the initial study protocol excluded pts receiving invasive mechanical ventilation, 4 pts in the 5-day group and 9 pts in the 10-day group were receiving invasive mechanical ventilation or ECMO (need identified after initial screening and before treatment initiation or pts were accepted as protocol deviations). There also were more pts in the 10-day group (30%) who required high-flow oxygen support at baseline compared with the 5-day group (24%). Post-hoc analysis among pts receiving mechanical ventilation or ECMO at day 5 indicate that, by day 14, 40% of such individuals who had received the 5-day regimen had died compared with 17% of those who had received the 10-day regimen. Treatment with remdesivir beyond 5 days did not appear to improve outcomes among pts who were receiving noninvasive positive-pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air. Note: Results for the initial 397 study pts with severe COVID-19 not requiring mechanical ventilation at study entry cannot be extrapolated to critically ill pts receiving mechanical ventilation. 23 Comparative analysis of data from phase 3 SIMPLE-Severe trial and real-world retrospective cohort of patients: The manufacturer announced results of an analysis that compared data for 312 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial with a retrospective cohort of 818 pts with similar baseline characteristics and pts who require supplemental oxygen but do not require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, should receive remdesivir for a duration of 5 days or until hospital discharge, whichever comes first. If such pts progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO during such treatment, the panel recommends that the remdesivir course be completed. The panel states that there are insufficient data on the optimal duration of remdesivir treatment for pts who have not shown clinical improvement after a 5-day regimen; some experts would extend the total duration of remdesivir treatment to up to 10 days in these patients. 20</td>
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<td>the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state health departments, 25, 38 the EUA now designates the manufacturer (Gilead) and its authorized distributor(s) as the parties responsible for distribution of the drug. 39 For additional information about the remdesivir EUA, consult the EUA letter of authorization, 40 EUA fact sheet for healthcare providers, 26 and EUA fact sheet for parents and caregivers. 27 Healthcare providers should contact Gilead’s sole US distributor (AmerisourceBergen at 800-746-6273) to purchase remdesivir for age-appropriate use under the FDA-approved indication (lyophilized powder formulation or solution concentrate formulation) or the EUA (lyophilized powder formulation only). 47 Concerns regarding variations in remdesivir packaging: The manufacturer is alerting healthcare providers that there are variations in remdesivir packaging and labeling (e.g., use of the tradename Veklury®, expiration dates) depending on whether the drug was originally manufactured for use under the EUA or for commercial use. 49 FDA states that, if patient safety can be assured, they do not intend to object to remdesivir supplies that have labels specifying “for use under Emergency Use Authorization” being distributed for appropriate use under the FDA-labeled indication during the first six months after the drug received this approval. 48 Questions related to carton or vial labeling or expiration dates should be directed to Gilead at 866-633-4474 or <a href="http://www.askgileadmedical.com">www.askgileadmedical.com</a>. 49 The NIH COVID-19 Treatment Guidelines Panel issued the following recommendations for use of remdesivir (with or without dexamethasone) for the management of COVID-19 based on disease severity:</td>
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Subgroup analyses of data from Phase 3 SIMPLE-Severe trial: The manufacturer announced results of subgroup analyses of 229 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial and were enrolled at US trial sites. Clinical improvement was defined as a 2-point or greater improvement on a 7-point ordinal scale. At day 14, the rate of clinical improvement was 84% in black pts (n=43), 76% in Hispanic white pts (n=17), 67% in Asian pts (n=18), 67% in non-Hispanic white pts (n=119), and 63% in pts who did not identify with any of these groups (n=32). An analysis of 397 pts who were enrolled globally indicated that black race, age less than 65 years, treatment outside of Italy, and requirement of only low-flow oxygen support or room air at baseline were factors significantly associated with clinical improvement at least 2 points on day 14. Another subgroup analysis was performed to evaluate outcomes in pts who received concomitant therapy with remdesivir and hydroxychloroquine vs those who received only remdesivir. At a median follow-up of 14 days, the rates and likelihood of recovery were lower in those treated with both drugs (57%) compared with those treated with remdesivir alone (69%). Although concomitant hydroxychloroquine was not associated with increased mortality at 14 days, the overall rate of adverse effects was higher and, after adjusting for baseline variables, the incidence of grade 3-4 adverse events was significantly higher in those treated with both drugs.

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<td>1) Hospitalized not requiring supplemental oxygen: The panel states that data are insufficient to recommend either for or against routine use of remdesivir. For pts at high risk of disease progression, use of remdesivir may be appropriate. 20</td>
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<td>2) Hospitalized requiring supplemental oxygen but not requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO: The panel recommends remdesivir (e.g., for pts requiring minimal supplemental oxygen) or remdesivir plus dexamethasone (e.g., for pts requiring increasing amounts of supplemental oxygen) or dexamethasone alone (e.g., when remdesivir in unavailable or cannot be used). In rare circumstances when corticosteroids cannot be used, the panel states that remdesivir plus baricitinib can be used instead of remdesivir plus dexamethasone. 20 (See Baricitinib entry in this table.)</td>
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<td>3) Hospitalized requiring high-flow oxygen or noninvasive ventilation: The panel recommends dexamethasone alone or dexamethasone plus remdesivir. In rare circumstances when corticosteroids cannot be used, the panel states that baricitinib plus remdesivir can be used. 20</td>
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<td>4) Hospitalized requiring invasive mechanical ventilation or ECMO: The panel recommends dexamethasone. Dexamethasone plus remdesivir may be considered for pts who were recently intubated. The panel does not recommend use of remdesivir alone. 20</td>
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<td>5) Not hospitalized, mild to moderate disease: The panel states that data are insufficient to recommend either for or against any specific antiviral or antibody therapy. The panel states that dexamethasone should not be used. 20 (See Corticosteroids [Systemic] in this Evidence Table.)</td>
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Phase 3 randomized, open-label trial in hospitalized pts with moderate COVID-19 (NCT04292730; GS-US-540-5774; SIMPLE-Moderate) sponsored by the manufacturer (Gilead): Initial study protocol was designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care compared with standard care alone in adults with moderate COVID-19 (i.e., hospitalized with evidence of pulmonary infiltrates and SpO$_2$ >94% on room air); protocol was subsequently modified to change the primary end point to clinical status on day 11 based on a 7-point ordinal scale, include pts 12 years of age or older, and add an extension phase to include additional pts. Data for the initial group of adults who received a 5-day regimen of remdesivir with standard care (n=191), 10-day regimen of the drug with standard care (n=193), or standard care alone (n=200) have been published. At day 11, 70, 65, or 61% of pts in the 5-day, 10-day, or standard care alone group, respectively, had clinical improvement based on at least a 2-point improvement from baseline on a 7-point ordinal scale. Pts in the 5-day remdesivir group had statistically significant higher odds of a better clinical status distribution on the 7-point scale on day 11 than those receiving standard care (odds ratio: 1.65) but the difference was of uncertain clinical importance; the difference in clinical status distribution between pts in the 10-day remdesivir group and the standard care group was not statistically significant. At day 11, 4 deaths were reported in the standard care alone group compared with none in the 5-day group and 2 in the 10-day group. There were no significant differences between the 5- or 10-day remdesivir groups and standard care group for any of the exploratory end points at day 11 (time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, time to discontinuation of oxygen support). At day 14, the clinical status of pts in the 5-day and 10-day remdesivir groups was...
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<td>significantly different than that of the standard care group. <strong>Note:</strong> Effect of remdesivir on SARS-CoV-2 viral load was not assessed. Limitations of this study include the open-label design and use of an ordinal scale to evaluate outcomes that was not ideal for detecting differences in pts with moderate COVID-19.</td>
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<td><strong>Phase 3 adaptive, randomized, double-blind, placebo-controlled trial (NCT04280705; NIAID Adaptive COVID-19 Treatment Trial 1 [ACTT-1]) in hospitalized adults with COVID-19:</strong> Pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10 or until hospital discharge or death) or placebo. All pts received supportive care according to the standard of care for the trial site hospital. The primary outcome was time to recovery, defined as the first day within 28 days after enrollment when clinical status met criteria for category 1, 2, or 3 on an 8-category ordinal scale (i.e., discharged from hospital with or without limitations on activities or requirement for home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). A total of 1062 pts were randomized with 541 assigned to remdesivir and 521 assigned to placebo (intention-to-treat population). Baseline demographics and clinical characteristics (e.g., age, disease severity, comorbidities at study enrollment, time to initiation of treatment after symptom onset) were similar in both groups. A total of 957 pts (90.1%) had severe disease (i.e., required mechanical ventilation, required supplemental oxygen, had SpO₂ ≤94% on room air, or had tachypnea with respiratory rate ≥24 breaths/minute) at study enrollment, and the median time from symptom onset to randomization was 9 days (range: 6-12 days). Final trial data indicated <strong>shorter median time to recovery in the remdesivir group (10 days) vs the placebo group (15 days); recovery rate ratio 1.29.</strong> Those who received remdesivir were more likely to have clinical improvement at day 15 than those who received placebo (odds ratio 1.5). Kaplan-Meier estimates of mortality by day 15 were 6.7% in the remdesivir group and 7.9% in the placebo group. Concomitant use of remdesivir and chloroquine or hydroxychloroquine is <strong>not recommended;</strong> FDA warns that there is in vitro evidence that chloroquine antagonizes intracellular metabolic activation and antiviral activity of remdesivir.</td>
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<sup>a</sup> Data from FDA, NIAID, and others. References: 20, 26, 33, 46.
group vs 11.9% in the placebo group (hazard ratio 0.55); by day 29, mortality was 11.4 and 15.2%, respectively (hazard ratio 0.73). Posthoc analysis of efficacy based on disease severity at enrollment suggested that benefits of remdesivir were most apparent in hospitalized pts receiving low-flow oxygen (recovery rate ratio 1.45); the recovery rate ratio in the subgroup of pts on mechanical ventilation or ECMO at enrollment was 0.98. \(^{42}\) There was no observed benefit of remdesivir compared with placebo in the subgroup with mild to moderate disease (defined as SpO\(_2\) >94% on room air or a respiratory rate <24 beats/minute without supplemental oxygen) at enrollment; however, the number of pts in this subgroup was relatively small. Although there was no observed difference in time to recovery in subgroups requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO at enrollment, the trial was not powered to detect differences in outcomes within subgroups and there is uncertainty about the effects of remdesivir on the course of COVID-19 in patients who are mechanically ventilated or on ECMO. \(^{20}\)

**Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY):** The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. \(^{24,51}\) From March 22 to October 4, 2020, 2750 pts were randomized to receive remdesivir (200 mg on day 1, then 100 mg on days 2-10) with local standard of care and 2725 pts were randomized to remdesivir control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (2743 pts in remdesivir group and 2708 pts in standard of care group) indicated that remdesivir did not reduce in-hospital mortality (either
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<td>overall or in any subgroup defined by age or ventilation status at study entry) and did not reduce the need for initiation of ventilation or the duration of hospitalization. The log-rank death rate ratio for remdesivir in the ITT population was 0.95; 301/2743 pts treated with remdesivir (12.5%) and 303/2708 pts treated with standard of care (12.7%) died. Ventilation was initiated after randomization in 295 pts in the remdesivir group and 284 pts in the standard of care group. (^4)</td>
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<td>Data from the manufacturer’s compassionate use program (adults): Preliminary data are available for a cohort of 53 adults from multiple sites in the US, Italy, Japan, and other countries who were hospitalized with severe COVID-19 and received treatment with remdesivir; 40 pts received the full 10-day regimen (200 mg IV on day 1, then 100 mg IV on days 2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects. (^6) Note: Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load.</td>
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**Data from the manufacturer’s compassionate use program (pediatric pts):** The manufacturer announced that preliminary data are available for 77 pediatric pts treated with remdesivir in the compassionate use program. Analysis of day-28 data indicated that 73% of these pediatric pts were discharged from the hospital, 12% remained hospitalized but on ambient air, and 4% had died. There were 39 critically ill pediatric pts who required invasive mechanical ventilation at baseline and 80% of these pts recovered; there were 38 pediatric pts who did not require invasive ventilation and 87% of these pts recovered. No new safety signals were identified for remdesivir in this population. 34

**Data from the manufacturer’s compassionate use program (pregnant and postpartum women):** The manufacturer announced that preliminary data are available for 86 pregnant and postpartum women treated with remdesivir in the compassionate use program. Analysis of data for these pts (median age 33 years) indicated that 96% of the pregnant women and 89% of the postpartum women achieved improvement in oxygen support levels. Those with more severe illness at baseline achieved similarly high rates of clinical recovery (93 or 89% in those who were pregnant or postpartum, respectively). Pregnant women not on invasive oxygen support at baseline had the shortest median time to recovery (5 days), and both pregnant and postpartum women on invasive ventilation at baseline had similar median times to recovery (13 days). No new safety signals were identified for remdesivir in this population; the most common adverse events were due to underlying disease and most laboratory abnormalities were grades 1–2. 35

**Phase 2/3 single-arm, open-label trial in pediatric patients (NCT04431453; CARAVAN):** The manufacturer (Gilead) initiated a trial to evaluate safety, tolerability, pharmacokinetics, and efficacy of remdesivir in pediatric pts (birth to <18 years of age) with laboratory-confirmed COVID-19. 35
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<th>Drug(s)</th>
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<th>Trials or Clinical Experience</th>
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<td>Phase 3 adaptive, randomized, double-blind trial compared a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib in hospitalized adults (NCT04401579; ACTT-2): Pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for a total treatment duration of 10 days or until hospital discharge) with either oral baricitinib (4 mg once daily for 14 days or until hospital discharge) or placebo. The primary end point was time to recovery through day 29 (defined as discharged without limitations on activities, discharged with limitations on activities and/or requiring home oxygen, or still hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). Data for 1033 pts (515 in the remdesivir and baricitinib group and 518 in the remdesivir alone group) indicate that those who received the combined regimen were more likely to have better clinical outcomes than those who received remdesivir alone. Based on results of this trial and other data, FDA issued an emergency use authorization (EUA) for baricitinib to permit use of the drug in combination with remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric pts ≥2 years of age. (See Baricitinib in this Evidence Table.)</td>
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<td>Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with interferon beta-1a (NCT04492475; ACTT-3): This iteration of NIAID’s Adaptive COVID-19 Treatment Trial (ACTT) is evaluating possible benefits of using interferon beta-1a in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection. Inclusion criteria include evidence of lung involvement (radiographic infiltrates, SpO(_2) of 94% or lower on room air, or requiring supplemental oxygen or mechanical ventilation); exclusion criteria include need for ECMO, prior treatment with ≥3 doses of remdesivir, treatment with any interferon preparation within the previous 2 weeks, prior treatment with convalescent plasma or IGIV or various</td>
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<td>other drugs used for management of COVID-19. Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization up to 10 days total) with either sub-Q interferon beta-1a (44 mcg once daily on days 1, 3, 5, and 7 during hospitalization for a total of 4 doses) or placebo.</td>
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<td>Randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with tocilizumab (NCT04409262; REMDACTA): This trial is evaluating possible benefits of using tocilizumab (an interleukin-6 [IL-6] inhibitor) in conjunction with remdesivir in hospitalized patients 12 years of age or older with severe COVID-19 pneumonia. Pts will be randomized to receive remdesivir (IV loading dose on day 1, then once-daily IV maintenance doses on days 2-10) with either tocilizumab (single IV infusion on day 1) or placebo.</td>
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<td>Phase 3 randomized, double-blind, placebo-controlled, adaptive trial sponsored by NIAID to evaluate safety, tolerability, and efficacy of a regimen of remdesivir vs a regimen of remdesivir with investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hyperimmune globulin intravenous [hIGIV]) in hospitalized adults (NCT04546581; ITAC): Pts with documented COVID-19 and duration of symptoms ≤12 days will be randomized to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily during hospitalization for up to 10 days total) with either placebo or investigational anti-SARS-CoV-2 hIGIV (single IV dose of 400 mg/kg). (See Immune Globulin in this Evidence Table.)</td>
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<td>Phase 3 randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of remdesivir for treatment of COVID-19 in outpatients (NCT 04501952): Manufacturer (Gilead) initiated a study to evaluate a 3-day regimen of IV remdesivir in adults and pediatric pts ≥12 years of age with early-stage COVID-19 to determine efficacy in an outpatient setting for reducing the rate of hospitalization or death.</td>
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Monoclonal antibodies (mAbs) used in the treatment or prevention of infectious diseases are engineered versions of antibodies naturally produced by the immune system in response to invading viruses or other pathogens.  

mAbs that are specific for certain infectious agents or their toxins (e.g., respiratory syncytial virus, Bacillus anthracis, Clostridioides difficile) have been used for the treatment or prevention of infections caused by these agents. 1

Clinical trials have been initiated to evaluate several different SARS-CoV-2-specific mAbs, including the following:

Casirivimab and Imdevimab (REGN10933 and REGN10987; REGN-COV2): Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of casirivimab and imdevimab for treatment of COVID-19 in hospitalized adults (NCT04426695). 22 Initial study protocol included 4 different cohorts of pts (i.e., on low-flow oxygen, not requiring oxygen, on high-flow oxygen without mechanical ventilation, on mechanical ventilation) to be randomized to receive casirivimab and imdevimab (administered together) or placebo. 22 The manufacturer announced that further enrollment of hospitalized pts requiring high-flow oxygen or mechanical ventilation was terminated following a recommendation from the independent data monitoring committee (IDMC) based on a potential safety signal and unfavorable risk/benefit profile in such pts. Enrollment of hospitalized pts not requiring oxygen or on low-flow oxygen is continuing as recommended by the IDMC. 37 The manufacturer announced preliminary data analyses (not peer reviewed) for pts hospitalized with laboratory-confirmed COVID-19 who were on low-flow oxygen (defined as maintaining O2 saturation of >93% via nasal cannula, simple mask, or similar device) and were randomized to receive 2.4 g of casirivimab and imdevimab (1.2 g of each mAb; low dose), 8 g of casirivimab and imdevimab (4 g of each mAb; high dose), or placebo in addition to standard of care (67% received remdesivir and 74% received systemic corticosteroids). Results of the preliminary analysis (i.e., futility analysis) indicated that the mAb regimen had sufficient efficacy to warrant continuing the trial. Data for the 217 pts seronegative for endogenous antibodies against SARS-CoV-2 at baseline indicated that casirivimab and imdevimab treatment reduced the time-weighted average daily viral load through day 7 by -0.54 log10. Because mAbs generally have long half-lives, it is likely that only a single dose of the SARS-CoV-2-specific mAbs may be required. 3

Bamlanivimab (LY-CoV555): Emergency use authorization (EUA) dosage and administration of bamlanivimab for treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization: Single dose of 700 mg given by IV infusion; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. 53

** Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016):** Emergency use authorization (EUA) dosage and administration of bamlanivimab and etesevimab for treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization: Single dose of 700 mg of bamlanivimab and 1.4 g of etesevimab administered together after dilution as a single IV infusion; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. 65

Casirivimab and Imdevimab (REGN10933 and REGN10987): Emergency use authorization (EUA) dosage and administration of casirivimab and imdevimab for treatment of mild to moderate COVID-19 in adults and pediatric patients. Because mAbs generally have long half-lives, it is likely that only a single dose of the SARS-CoV-2-specific mAbs may be required. 3

Bamlanivimab (LY-CoV555): Emergency use authorization (EUA) dosage and administration of bamlanivimab for treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization: Single dose of 700 mg given by IV infusion; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. 53

FDA issued an Emergency Use Authorization (EUA) for bamlanivimab on November 9, 2020 that permits use of the drug for the treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization. FDA states that, based on a review of topline data from the planned interim analysis of an ongoing randomized, double-blind, placebo-controlled, phase 2 trial of bamlanivimab monotherapy in outpatients with mild to moderate COVID-19 (BLAZE-1; NCT04427501), it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization and, when used under the conditions of the EUA, the known and potential benefits of bamlanivimab for treatment of...
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<td>Casirivimab and Imdevimab (REGN10933 and REGN10987; REGN-COV2):</td>
<td>Combination of two different recombinant neutralizing lgG mAbs (casirivimab and imdevimab) that bind to non-overlapping epitopes on the S protein RBD of SARS-CoV-2 and block the virus from binding to the human ACE2 receptor. Preclinical studies demonstrated neutralizing activity in vitro and protective effects against SARS-CoV-2 infection and viral replication in animal models.</td>
<td>Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of casirivimab and imdevimab (administered together for treatment of COVID-19 in outpatients (NCT04425629). Results of a preplanned interim analysis that included the first 275 outpatients enrolled in the phase 1/phase 2 portion of this trial have been published. Enrolled pts were randomized 1:1:1 to receive a single IV infusion of 2.4 g of casirivimab and imdevimab of each mAb; low dose) or 8 g of casirivimab and imdevimab (4 g of each mAb; high dose), or placebo in addition to usual standard of care. All pts had SARS-CoV-2 infection confirmed by testing &amp; had symptom onset ≤72 hours prior to randomization and had symptom onset ≤72 hours prior to randomization. Results of this interim analysis indicated that casirivimab and imdevimab reduced viral load and there was a positive trend in reduction of medical visits; benefits were greatest in those who had not mounted their own effective immune response. Key end points included the time-weighted average change in viral load from baseline through 7 and percentage of pts with at least one COVID-19-related medically attended visit through day 29. The least-squares mean difference (combined data for both dosage regimens vs placebo) in the time-weighted average change in viral load from baseline through day 7 was −0.56 log&lt;sub&gt;10&lt;/sub&gt; copies/mL among pts who were serum antibody-negative at baseline (95% CI, −1.02 to −0.11) and −0.41 log&lt;sub&gt;10&lt;/sub&gt; copies/mL (95% CI, −0.71 to −0.10) in the overall trial population. At least one medically attended visit was reported in 6 or 3% of pts in the pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progression to severe COVID-19 and/or hospitalization: Single dose of 1.2 g of casirivimab and 1.2 g of imdevimab administered together as a single IV infusion over at least 60 minutes via pump or gravity; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. ** Concerns about medication errors and variations in packaging: The manufacturer is alerting healthcare providers that casirivimab and imdevimab are packaged separately but must be administered together after dilution as a single IV infusion only. Although some cartons and vials of the drugs may be labeled &quot;for intravenous infusion or subcutaneous injection&quot;, the drugs must be administered together by IV infusion only as specified in the EUA. Casirivimab and imdevimab may be supplied as two different vial sizes (1332 mg/11.1 mL or 300 mg/2.5 mL), instructions for preparing the casirivimab and imdevimab solution for IV infusion (e.g., number of vials) specified in the EUA. The fact sheet for healthcare providers must be followed to ensure the correct dose. Some cartons and vials of casirivimab and imdevimab may be labeled REGN10933 and REGN10987, respectively.</td>
<td>** COVID-19 in such pts outweigh the known and potential risks.</td>
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** Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016): **

FDA issued an Emergency Use Authorization (EUA) for bamlanivimab and etesevimab on February 8, 2021 that permits combined use of the drugs for the treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization. FDA states that, based on a review of data from an ongoing randomized, double-blind, placebo-controlled phase 2/3 trial in outpatients with mild to moderate COVID-19 (BLAZE-1; NCT04427501), it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization and, when used under the conditions of the EUA, the known and potential benefits of bamlanivimab and etesevimab administered together for treatment of COVID-19 in such pts outweigh the known and potential risks. 

** Casirivimab and Imdevimab (REGN10933 and REGN10987): **

FDA issued an Emergency Use Authorization (EUA) for casirivimab and imdevimab on November 21, 2020 that permits combined use of these drugs for the treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization. FDA states that, based on a review of
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<td>on the S protein of SARS-CoV-2 complementary to the binding site of bamlanivimab; has high affinity for and effectively blocks the virus from binding to ACE2 host cell surface receptors; prophylactic and therapeutic effects against SARS-CoV-2 infection demonstrated in an animal model.</td>
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<td>VIR-7831 (GSK4182136): mAb that specifically targets the S protein of SARS-CoV-2; preclinical studies demonstrated affinity for and highly potent neutralizing activity against the virus; engineered for enhanced lung bioavailability and extended half-life.</td>
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<td>COVID-GUARD (STI-1409) and COVI-AMG (STI-2020): Both of these mAbs specifically target the S protein of SARS-CoV-2; preclinical studies demonstrated that both have neutralizing activity against SARS-CoV-2 in Vero E6 cells and protective effects against the virus in an animal model; STI-2020 is an affinity-matured version of STI-1409 and has greater in vitro potency than STI-1409.</td>
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<td>AZD7442: Contains two mAbs (AZD8895 and AZD1062) that specifically target SARS-CoV-2 at two non-overlapping sites; has an extended half-life and reduced Fc receptor binding.</td>
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<td>Note that various recombinant humanized monoclonal antibodies that target placebo or mAb group, respectively; among those who were antibody-negative at baseline, 15% in the placebo group and 6% in the mAb group reported such visits. The manufacturer subsequently announced results for an additional 524 outpatients enrolled in this trial and stated that analysis of data for these pts confirmed that a combined regimen of casirivimab and imdevimab significantly reduces viral load, is associated with reduced COVID-19-related medical visits, and is most beneficial in pts who are at risk for poor outcomes due to higher viral load and/or no detectable antibodies at baseline. There were no significant differences in virologic or clinical efficacy between the high- and low-dose casirivimab and imdevimab regimens. Data for the overall population (n=799) indicated that casirivimab and imdevimab (administered together) reduced COVID-19-related medical visits by 57% through day 29 compared with placebo. The phase 3 portion of this trial evaluating casirivimab and imdevimab for treatment of COVID-19 outpatients is continuing; a study arm that includes pediatric pts was added. Randomized, controlled, open-label, phase 3 trial with a casirivimab and imdevimab arm is evaluating the combined use of these mAbs (single IV infusion containing 4 g each of casirivimab and imdevimab) with standard of care vs standard of care alone in hospitalized COVID-19 pts ≥12 years of age (NCT04381936; RECOVERY).</td>
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<td>** Randomized, double-blind, placebo-controlled, phase 3 trial sponsored by the manufacturer (Regeneron) is evaluating safety, tolerability, and efficacy of a single sub-Q dose of casirivimab and imdevimab for prevention of SARS-CoV-2 infection in healthy, asymptomatic, household contacts of individuals infected with SARS-CoV-2 (NCT04452318). Initial study protocol only included adults; protocol was modified to include adults and adolescents ≥12 years of age weighing ≥40 kg. Manufacturer announced results of an exploratory analysis (not peer reviewed) for the first 409 evaluable participants seronegative for SARS-CoV-2 at baseline who were randomized phase 1/2 data from an ongoing randomized, double-blind, placebo-controlled, phase 1/2/3 trial of casirivimab and imdevimab in outpatients with mild to moderate COVID-19 (NCT04425629), it is reasonable to believe that casirivimab and imdevimab administered together may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization and, when used under the conditions of the EUA, the known and potential benefits of casirivimab and imdevimab for treatment of COVID-19 in such pts outweigh the known and potential risks.</td>
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<td>key immunologic and inflammatory mediators (e.g., complement, granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-6 [IL-6]) but do not target the SARS-CoV-2 virus are being investigated for the treatment of COVID-19. See Sarilumab, Siltuximab, and Tocilizumab in this Evidence Table.</td>
<td>to receive prophylaxis with casirivimab and imdevimab or placebo. The mAb regimen prevented symptomatic COVID-19 (no cases in 186 individuals who received the regimen compared with 8 cases in 223 individuals who received placebo) and also reduced the overall rate of symptomatic and asymptomatic infection (10 cases in 186 individuals who received the regimen compared with 23 cases in 223 individuals who received placebo).</td>
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<td>Bamlanivimab (LY-CoV555) alone or with Etesevimab (LY-CoV016):</td>
<td>Randomized, placebo-controlled, double-blind, sponsor-unblinded, single ascending dose, phase 1 study sponsored by the manufacturer (Eli Lilly) evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of an IV dose of bamlanivimab (LY-CoV555) in hospitalized adults with COVID-19. Study completed; results not yet published (NCT04411628).</td>
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<td>Randomized, placebo-controlled, phase 1 study sponsored by the manufacturer (Eli Lilly) evaluated safety, tolerability, pharmacokinetics, and immunogenicity of an IV dose of etesevimab (LY-CoV016) in healthy adults. Study completed; results not yet published (NCT04441931).</td>
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<td>Randomized, double-blind, placebo-controlled phase 2/3 study is evaluating efficacy and safety of bamlanivimab (LY-CoV555) used alone or in conjunction with etesevimab (LY-CoV016) for early treatment of COVID-19 in adults and adolescents ≥12 years of age who are outpatients with mild to moderate disease (NCT04427501; BLAZE-1). Results of a preplanned interim analysis of the 3 bamlanivimab monotherapy arms (single IV dose of 700 mg, 2.8 g, or 7 g) of the phase 2 portion of this ongoing study have been published. At the time of the interim analysis, data were available for 452 outpatients ≥18 years of age with mild or moderate COVID-19 (309 pts randomized to bamlanivimab and 143 randomized to placebo). Based on the primary outcome (change in SARS-CoV-2 viral load from baseline to day 42, 43, 48, 49, 64, 65 Benefits have not been observed when bamlanivimab or casirivimab and imdevimab were used in hospitalized pts; SARS-CoV-2-specific mAbs, such as bamlanivimab, bamlanivimab and etesevimab, or casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized COVID-19 pts requiring high flow oxygen or mechanical ventilation.</td>
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<td>** Allocation of bamlanivimab and the EUA for bamlanivimab and etesevimab and the EUA for casirivimab and imdevimab require that the dosage of these drugs recommended in their respective EUAs be administered via IV infusion by a healthcare provider in an outpatient setting where there is immediate access to medications to treat a severe infusion reaction such as anaphylaxis and ability to activate the emergency medical system (EMS) as necessary. The EUAs also require that healthcare facilities and healthcare providers administering bamlanivimab, bamlanivimab and etesevimab, or casirivimab and imdevimab comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch).</td>
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The EUA for bamlanivimab and etesevimab and the EUA for casirivimab and imdevimab for use under their respective EUAs is being directed by the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state and territorial health departments and the manufacturers. The drugs will be shipped directly from an authorized US distributor (e.g., AmerisourceBergen). To request these drugs for use under their respective EUAs, healthcare providers should contact...
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<td><strong>Bamlanivimab and Etesevimab</strong></td>
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<td>Randomized, double-blind, placebo-controlled phase 3 trial initiated by the manufacturer (Eli Lilly) in collaboration with NIAID is evaluating efficacy and safety of bamlanivimab (LY-CoV555) used alone or in conjunction with etesevimab (LY-CoV016) for prevention of SARS-CoV-2 infection in adult residents and staff of skilled nursing or assisted living facilities (NCT04497987; BLAZE-2). The manufacturer (Eli Lilly) announced results of data analyses for 965 study participants who tested negative for SARS-CoV-2 at baseline (299 residents and 666 staff) and were randomized to receive prophylaxis with bamlanivimab (4.2 g as a single dose) or placebo. At 8 weeks of follow-up, there was a significantly lower frequency of symptomatic COVID-19 (the primary end point) overall in the bamlanivimab group vs the placebo group (odds ratio 0.43). Subgroup analyses for the 299 residents also indicated a significantly lower frequency of symptomatic COVID-19 in their state health departments. Information on access to the drugs may be available at <a href="https://protect-public.hhs.gov/pages/therapeutics-distribution">https://protect-public.hhs.gov/pages/therapeutics-distribution</a>. <strong>Bamlanivimab:</strong> For additional information about the EUA, consult the bamlanivimab EUA letter of authorization, EUA fact sheet for healthcare providers, and EUA fact sheet for patients, parents and caregivers. <strong>Etesevimab:</strong> For additional information about the EUA, consult the etesevimab EUA letter of authorization, EUA fact sheet for healthcare providers, and EUA fact sheet for patients, parents and caregivers. NIH COVID-19 Treatment Guidelines Panel states that data are insufficient to date to recommend either for or against use of bamlanivimab or casirivimab and imdevimab for treatment of outpatients with mild to moderate COVID-19 and states that these SARS-CoV-2-specific mAbs should not be considered the standard of care. Given the possibility of limited supply, the panel states that outpatients at highest risk of COVID-19 progression should be prioritized to receive these mAbs under their respective EUAs and efforts should be made to ensure that communities most affected by COVID-19 have equitable access to the drugs. The panel states that pts hospitalized for COVID-19 should not receive bamlanivimab or casirivimab and imdevimab outside of a clinical trial. <strong>Pregnant women:</strong> NIH panel states that bamlanivimab or casirivimab and imdevimab should not be used during pregnancy.</td>
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<td>the bamlanivimab group vs the placebo group (odds ratio 0.20); there were 4 deaths attributed to COVID-19 in the residents and all occurred in the placebo group.</td>
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<td>Adaptive platform, randomized, placebo-controlled, phase 2/3 trial is evaluating safety and efficacy of bamlanivimab in outpatients with COVID-19 (NCT04518410; ACTIV-2).</td>
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<td>Multicenter, adaptive, randomized, placebo-controlled, phase 3 trial evaluating safety and efficacy of various therapeutics for hospitalized pts with COVID-19 sponsored by NIAID (NCT04501978; TICO; ACTIV-3): Trial included a treatment arm to evaluate bamlanivimab (LY-CoV555) with standard of care vs placebo with standard of care in hospitalized adults. NIAID announced that the bamlanivimab treatment arm was terminated following a recommendation from the independent data and safety monitoring board (DSMB) based on low likelihood of clinical benefit in hospitalized pts. Data for the 314 enrolled pts included in the prespecified interim futility assessment have been published. Enrolled pts were hospitalized with documented SARS-CoV-2 infection (duration of symptoms ≤12 days, no end-organ failure at baseline) and randomized 1:1 to receive bamlanivimab (163 pts) or placebo (151 pts). Pts also received remdesivir (95% of pts), corticosteroids (49% of pts), and supplemental oxygen when indicated. The futility assessment evaluated pulmonary function on day 5 based on a 7-category ordinal scale and indicated that a single IV infusion of bamlanivimab did not result in better clinical outcomes at day 5 compared with placebo. The odds ratio of being in a more favorable category in the bamlanivimab group compared with the placebo group was 0.85 (95% CI, 0.56 to 1.29; P = 0.45). Among 167 pts who were followed for at least 28 days or died within 28 days, 82 or 79% in the bamlanivimab or placebo group, respectively, had sustained recovery (rate ratio 1.06). The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or severe COVID-19 if the clinician thinks that the potential benefits outweigh potential risks.</td>
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<sup>a</sup>imdevimab should not be withheld from a pregnant woman who has a condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefits outweigh potential risks.
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<th>Drug(s)</th>
<th>AHFS Class</th>
<th>Rationale</th>
<th>Trials or Clinical Experience</th>
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<td>clinical grade 3 or 4 adverse events through day 5) was similar in the bamlanivimab and placebo group (19% and 14%, respectively).</td>
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<td><strong>VIR-7831 (GSK4182136):</strong></td>
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<td>Manufacturer (Vir Biotechnology) in collaboration with GlaxoSmithKline initiated a randomized, double-blind, placebo-controlled, phase 2/phase 3 trial to assess safety, tolerability, efficacy, and pharmacokinetics of a single IV dose of VIR-7831 for early treatment of COVID-19 in outpatients (NCT04545060; COMET-ICE).</td>
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<td>Manufacturer announced that an independent data monitoring committee has recommended that the study continue into the phase 3 portion based on a positive evaluation of safety and tolerability data from the phase 2 lead-in portion.</td>
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<td><strong>COVI-GUARD (STI-1499):</strong></td>
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<td>Manufacturer (Sorrento Therapeutics) initiated a randomized, placebo-controlled, dose-ranging, phase 1 study to evaluate safety, efficacy, and pharmacokinetics of single 10-, 30-, 100-, and 200-mg IV injections of COVI-GUARD in addition to standard of care for treatment of COVID-19 in hospitalized adults with moderate disease (NCT04454398); study withdrawn (difficulty recruiting).</td>
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<td><strong>COVI-AMG (STI-2020):</strong></td>
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<td>Manufacturer (Sorrento Therapeutics) initiated a randomized, double-blind, placebo-controlled, phase 1/2 study to evaluate safety, efficacy, and pharmacokinetics of single 40-, 100-, and 200-mg IV injections of COVI-AMG in adult outpatients with COVID-19 who are asymptomatic or have mild symptoms (NCT04584697).</td>
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<td><strong>AZD7442:</strong></td>
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<td>Double-blind, placebo-controlled, phase 1 trial initiated by the manufacturer (AstraZeneca) to evaluate safety, tolerability, and pharmacokinetics of IV and IM doses of AZD-7442 in healthy adults (NCT04507256).</td>
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<td>Drug(s)</td>
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<td><strong>Umifenovir</strong> (Arbidol®)</td>
<td>8:18.92</td>
<td>Antiviral</td>
<td>Limited data do not suggest benefit in pts with COVID-19.</td>
<td>Dosage recommended for treatment of COVID-19 in China: Adults, 200 mg orally 3 times daily for up to 10 days 5, 7</td>
<td>Not commercially available in the US</td>
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<td>Updated 1/14/21</td>
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<td>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses 4</td>
<td>Meta-analysis of 10 retrospective and 2 prospective, randomized controlled studies conducted in China (total of 1052 adults with laboratory-confirmed COVID-19; high heterogeneity) suggested that treatment with umifenovir was not associated with benefit in pts with COVID-19, as assessed by time to negative RT-PCR conversion, rate of negative RT-PCR on day 7, rate of fever or cough alleviation on day 7, hospital length of stay, or a composite endpoint of admission to intensive care unit, need for mechanical ventilation, or death, in studies that measured these endpoints. An increased rate of negative RT-PCR on day 14 was noted. 13</td>
<td>Dosage used in COVID-19 clinical trials: 200 mg orally 3 times daily for duration of 7-10 days or longer 2, 5, 6, 8</td>
<td>Efficacy for the treatment of COVID-19 not established</td>
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<td>Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza 4</td>
<td>Retrospective cohort study in 50 adults with COVID-19 in China suggests better viral suppression with umifenovir vs LPV/RTV. All pts received conventional therapy, including interferon α-2b. At 7 days after hospital admission, SARS-CoV-2 was undetectable in 50% of pts treated with umifenovir vs 23.5% treated with LPV/RTV; at 14 days, viral load undetectable in all pts treated with umifenovir vs 44.1% treated with LPV/RTV. Duration of positive SARS-CoV-2 RNA positive test was shorter with umifenovir vs LPV/RTV 8</td>
<td>Dosage recommended for treatment of COVID-19 in Russia: 200 mg orally every 6 hours for 5 days 11</td>
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<td>Drug(s)</td>
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<td>umifenovir</td>
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<td>Retrospective cohort study in 81 hospitalized, non-ICU adults with COVID-19 in China found no difference in clearance of SARS-CoV-2 virus between pts receiving umifenovir vs those who did not. At 7 days, SARS-CoV-2 undetectable in pharyngeal specimens in 33/45 pts (73.3%) treated with umifenovir vs 28/36 pts (77.8%) who did not receive umifenovir. No difference in median time from onset of symptoms to negative SARS-CoV-2 test (18 vs 16 days)</td>
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<td>umifenovir</td>
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<td>Open-label, prospective, randomized, multicenter study in 236 adults with COVID-19 in China (ChiCTR200030254): When favipiravir was compared with umifenovir, clinical recovery rate was greater in those treated with favipiravir than in those treated with umifenovir. (See Favipiravir in this Evidence Table.)</td>
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<td>Randomized, single-center, partially blinded trial in China (NCT04258885) evaluated efficacy of umifenovir in conjunction with standard care vs LPV/RTV in conjunction with standard care vs standard care without an antiviral in hospitalized adults with mild/moderate COVID-19. Data for the 86 enrolled pts suggest no difference in mean time for positive-to-negative conversion of SARS-CoV-2 nucleic acid in respiratory specimens and no difference in clinical outcomes between pts treated with umifenovir or LPV/RTV compared with no antiviral therapy.</td>
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\(a\) See Favipiravir in this Evidence Table.
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<th>Drug(s)</th>
<th>AHFS Class</th>
<th>Rationale</th>
<th>Trials or Clinical Experience</th>
<th>Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
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| Anakinra (Kineret<sup>®</sup>) | AHFS 92.36 Disease-modifying Anti-rheumatic Drug | Recombinant human interleukin-1 (IL-1) receptor antagonist<sup>1</sup> | IL-1 levels are elevated in patients with COVID-19; anakinra may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients<sup>2,3</sup><sup>,5,6</sup>  
Anakinra has been used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis. IL-1 levels are elevated in patients with these conditions. Case reports and series describe a favorable response to anakinra in these syndromes, including survival benefit in sepsis and reversing cytokine storm in adults with MAS after tocilizumab failure.<sup>7</sup> | There are case study data but no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19<sup>7</sup>  
**France**: A cohort study (Ana-COVID) included a prospective cohort of 52 adults with severe COVID-19 treated with anakinra plus standard of care and a historical comparison group of 44 patients who received standard and supportive care at Groupe Hospitalier Paris Saint-Joseph. Inclusion criteria included severe COVID-19-associated bilateral pneumonia on chest x-ray or lung CT scan, laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and an oxygen saturation of ≤93% under oxygen ≥6 L/min or deterioration (saturation ≤93% under oxygen 3 L/min with loss of 3% oxygen saturation in ambient air over previous 24 hours). Anakinra was given subcutaneously in a dosage of 100 mg twice daily on days 1–3, then 100 mg once daily from day 4–10. The primary outcome measure was a composite of either ICU admission for invasive mechanical ventilation or death. Admission to the ICU or death occurred in 13 (25%) of anakinra-treated patients and in 32 (73%) of patients in the historical comparison group.<sup>5</sup>  
**France**: A small case series (9 patients) of open-label anakinra treatment in hospitalized (non-ICU) adults with moderate to severe COVID-19 pneumonia has been published with encouraging results<sup>8</sup>  
**Italy**: Retrospective cohort study (part of NCT04318366) with high- or low-dose anakinra in adults with COVID-19, moderate to severe acute respiratory distress syndrome (ARDS), and hyperinflammation (defined as elevated serum C-reactive protein [CRP] and/or ferritin levels) managed without non-invasive ventilation outside of the ICU at a Milan hospital. Patients received standard therapy (hydroxychloroquine and lopinavir/ritonavir) and either high-dose anakinra (5 mg/kg twice daily by IV infusion for a median of 9 days followed by daily low-dose subcutaneous administration 100 mg) or against use of anakinra in the treatment of COVID-19<sup>7</sup>  
Some studies under way in Europe are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge<sup>9</sup>  
In a French case series and a French cohort study, anakinra was given subcutaneously in a dosage of 100 mg twice daily (i.e., every 12 hours) on days 1–3, then 100 mg once daily from day 4–10<sup>10</sup>  
A retrospective cohort study in Italy compared high-dose anakinra by IV infusion (5 mg/kg twice daily) and low-dose anakinra (100 mg twice daily) given subcutaneously<sup>10</sup>  
(Note: Anakinra is approved only for subcutaneous administration in the U.S.)<sup>1,7</sup> | Various dosage regimens are being studied<sup>1,8</sup>  
Trial protocol in Italy (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days<sup>7</sup>  
Some studies under way in Europe are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge<sup>9</sup>  
In a French case series and a French cohort study, anakinra was given subcutaneously in a dosage of 100 mg twice daily (i.e., every 12 hours) on days 1–3, then 100 mg once daily from day 4–10<sup>10</sup>  
A retrospective cohort study in Italy compared high-dose anakinra by IV infusion (5 mg/kg twice daily) and low-dose anakinra (100 mg twice daily) given subcutaneously<sup>10</sup>  
(Note: Anakinra is approved only for subcutaneous administration in the U.S.)<sup>1,7</sup> | NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of anakinra in the treatment of COVID-19<sup>7</sup>  
**Safety profile**: Well established in adults with sepsis and has been studied extensively in severely ill pediatric patients with complications of rheumatologic conditions; pediatric data on use in acute respiratory distress syndrome/sepsis are limited<sup>7</sup>  
**Pregnancy**: Limited evidence to date: unintentional first trimester exposure considered unlikely to be harmful<sup>2</sup> |

<sup>a</sup>See ASHP COVID-19 Resource Center for further details.
twice daily) for 3 additional days to prevent relapse) or low-dose anakinra (100 mg twice daily subcutaneously) and were compared with a historical cohort of patients who did not receive anakinra. At 21 days, high-dose anakinra was associated with reduced CRP levels and progressive improvement in respiratory function in 21 of 29 (72%) of patients; 5 patients (17%) were placed on mechanical ventilation and 3 patients (10%) died. High-dose IV anakinra appeared to be relatively well tolerated. Anakinra was discontinued in the low-dose subcutaneous anakinra group after 7 days because of a lack of improvement in CRP levels and clinical status. In the standard treatment alone group (retrospective cohort), 8 out of 16 patients (50%) showed respiratory improvement at 21 days; 1 patient (6%) was placed on mechanical ventilation and 7 patients (44%) died.

Italy: Phase 3 randomized, open-label, multicenter trial (NCT04324021) initiated by the manufacturer (Swedish Orphan Biovitrum) to evaluate efficacy and safety of anakinra or emapalumab with standard of care in reducing hyperinflammation and respiratory distress in patients with COVID-19 is recruiting.

Numerous other clinical trials evaluating anakinra in the treatment of COVID-19 are planned or under way, mainly in Europe.

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<th>Drug(s)</th>
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<td>Ascorbic acid</td>
<td>88:12 Vitamin C</td>
<td>Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress.</td>
<td>IV ascorbic acid: Phase 3 randomized, blinded, placebo-controlled trial (NCT03680274; LOVIT) evaluating effect of high-dose IV ascorbic acid on mortality and persistent organ dysfunction in septic ICU patients (including COVID-19 patients); other clinical trials of high-dose IV ascorbic acid for treatment of COVID-19 registered, including: 1 NCT04323514 NCT04401150 (LOVIT-COVID) NCT04395768 Oral ascorbic acid: Randomized, open-label study (NCT04342728; COVIDAtoZ) initiated to evaluate oral ascorbic acid (8 g daily), zinc, or both in combination in symptomatic outpatients receiving a positive COVID-19 test result; other clinical trials of outpatient IV ascorbic acid: Various dosages of IV ascorbic acid used in COVID-19 studies; 50 mg/kg IV every 6 hours for 4 days used in NCT03680274 and NCT04401150. 1 Various dosages of IV ascorbic acid used in sepsis studies; 50 mg/kg every 6 hours for 4 days used in CITRIS-ALI study; 50 mg/kg (maximum 3 g) every 12 hours for 48 hours used in ATESS study; 1.5 g every 6 hours used in VITAMINS, HYVCTTSSS, ACTS, and ORANGES studies, but treatment duration varied by study. 4, 8-10, 13-16 Oral ascorbic acid: NCT04342728: Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses. 1</td>
<td>Current clinical trial data not specific to COVID-19; additional study needed. 6 NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of ascorbic acid for the treatment of COVID-19 in critically ill patients. The panel states that there are no completed controlled trials of ascorbic acid in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of ascorbic acid in patients with sepsis or ARDS have shown variable efficacy and few safety concerns. 12 NIH COVID-19 Treatment Guidelines Panel also states that there are insufficient data to recommend either for or...</td>
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<td>Drug(s)</td>
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<td>Azithromycin</td>
<td>8:12.12</td>
<td><strong>Updated 2/11/21</strong></td>
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<td><strong>Adjunctive therapy in certain viral infections:</strong> Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza), there was no statistically significant difference in 90-day mortality rates or common cold: Effect of oral supplementation studied extensively; decreases duration of symptoms, may decrease incidence of common cold in individuals under heavy physical stress but not in overall population.</td>
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</table>
### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage | Comments
--- | --- | --- | --- | --- | ---
| Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated 2, 6, 8, 9, 11-14, 17, 35 | | | | |
| Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza) 10, 13 | | | | |
| Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the management of certain respiratory conditions (e.g., bronchiectasis, bronchiolitis, cystic fibrosis, COPD exacerbations, ARDS) 6, 8, 13 | | | | |
| clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not. 12 | | | | |
| **Adjunctive therapy in certain respiratory conditions**: Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS). 8 In a retrospective cohort study in pts with moderate or severe ARDS, a statistically significant improvement in 90-day survival was reported in those who received adjunctive azithromycin. 8 | | | | |
| **Clinical experience in pts with COVID-19**: Has been used for antibacterial coverage in hospitalized pts with COVID-19 15 | | | | |
| Use in conjunction with hydroxychloroquine in pts with COVID-19: Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), 7 open-label uncontrolled study in France (11 pts), 15 uncontrolled observational study in France (80 pts), 16 and larger uncontrolled observational study in France (1061 pts). 23 Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.) | | | | |
| Use in conjunction with hydroxychloroquine in hospitalized pts with COVID-19: Data from 2 retrospective studies that analyzed outcome data for hospitalized pts in New York treated with hydroxychloroquine with or without azithromycin indicate that use of the 4-aminoquinoline antimalarial with or without azithromycin is not associated with decreased in-hospital mortality. 30, 31 (See Hydroxychloroquine in this Evidence Table.) | | | | |
| **Open-label, randomized, multicenter trial in adults hospitalized with severe COVID-19 in Brazil (NCT04321278; COALITION II):** Patients were randomized 1:1 to receive oral azithromycin (500 mg once daily for 10 days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), 7 open-label uncontrolled study in France (11 pts), 15 uncontrolled observational study in France (80 pts), 16 and larger uncontrolled observational study in France (1061 pts). 23 Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.) | | | | |
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Although data are limited, bacterial pathogens in COVID-19 pts with community-acquired pneumonia (CAP) are likely the same as those seen in other pts with CAP. Therefore, if antibacterial coverage for CAP is indicated in COVID-19 pts, the usually recommended regimens for empiric treatment of CAP should be used. 22 Antimicrobial stewardship policies should be used to guide appropriate use of antibacterials in COVID-19 pts; such drugs should be discontinued if bacterial infection is not confirmed. 21

Data from various randomized, controlled clinical trials and retrospective studies have not shown evidence of clinical benefit when azithromycin was used alone or in conjunction with hydroxychloroquine for the treatment of COVID-19 in hospitalized pts. 21, 22, 30, 31, 34, 37, 38 There are data indicating that combined use of azithromycin and chloroquine or hydroxychloroquine may be associated with an increased risk of adverse cardiac effects. 21, 22, 23 (See Hydroxychloroquine in this Evidence Table.)

NIH COVID-19 Treatment Guidelines Panel **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in hospitalized pts and **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in nonhospitalized pts, except in the context of a clinical trial. 21

IDSA **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in hospitalized pts. 22

Because azithromycin and 4- aminoquinolines (hydroxychloroquine, chloroquine) are independently associated with QT prolongation, caution is advised if considering use of azithromycin with...
days) plus standard of care (n=214) or standard of care (control group; n=183). All pts received oral hydroxychloroquine (400 mg twice daily for 10 days) as part of standard of care; concomitant use of corticosteroids, other immunomodulators, antibiotics (no macrolides), and antivirals was allowed. Inclusion criteria required at least one severity criterion (use of oxygen supplementation at more than 4 L/minute, high-flow nasal cannula, noninvasive positive-pressure ventilation, or mechanical ventilation). Exclusion criteria included history of severe ventricular cardiac arrhythmia or QTc ≥480 msec in any ECG performed before randomization. The primary outcome was clinical status at day 15 based on a 6-level ordinal scale that ranged from not hospitalized (1) to death (6); the key secondary outcome was mortality at day 29. Results for the modified intention-to-treat (mITT) population (i.e., those with confirmed COVID-19) indicated that addition of azithromycin to standard of care was not superior to standard of care alone. At day 15, there was no difference in the proportional odds of being in higher categories on the 6-point ordinal scale between the azithromycin group and control group. At day 29, 42% of pts in the azithromycin group and 40% of those in the control group had died. There also was no difference between the groups in the proportion of pts with QTc interval prolongation (20% in azithromycin group and 21% in control group).

** Azithromycin in randomized, controlled, open-label, adaptive, platform trial (NCT04381936; RECOVERY): This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the azithromycin arm (now terminated), 2582 pts were randomized to receive azithromycin (500 mg by mouth, NG tube, or IV once daily for 10 days or until discharge, whichever came first) plus standard of care and 5181 pts were randomized to standard of care alone. The primary outcome was all-cause mortality at day 28. Results of this study indicated that azithromycin is not an effective treatment one of these drugs in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias.** 20-22, 25-28, 33

NIH panel states that macrolides (including azithromycin) should be used concomitantly with hydroxychloroquine (or chloroquine) *only* if necessary. In addition, because of the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the drugs are used sequentially. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving hydroxychloroquine (or chloroquine). 21

The benefits and risks of a combined regimen of azithromycin and hydroxychloroquine (or chloroquine) should be carefully assessed; if the regimen is used, diagnostic testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 20-22, 25-28, 33

(See Hydroxychloroquine in this Evidence Table.)
Baricitinib  (Olumiant®)  
Updated 12/17/20  
92:36 Disease-modifying Anti-rheumatic Drug

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| Baricitinib  | 92:36 Disease-modifying Anti-rheumatic Drug | Janus kinase (JAK) 1 and 2 inhibitor: disrupts regulators of endocytosis (AP2-associated protein kinase 1 [AAK1] and cyclin G-associated kinase [GAK]), which may help reduce viral entry and inflammation; also may interfere with intracellular virus particle assembly.  
Inhibits JAK1 and JAK2-mediated cytokine release; may combat cytokine release syndrome (CRS) in severely ill patients.  
Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19.  
Currently no known published controlled clinical trial evidence supporting efficacy or safety in patients with COVID-19  
In a small (12 patients) open-label study in Italy (NCT04358614), use of baricitinib (4 mg orally once daily for 2 weeks) in combination with lopinavir/ritonavir was evaluated in patients with moderate COVID-19 pneumonia.  
Baricitinib was well tolerated with no serious adverse events reported.  
Phase 3 adaptive, randomized, double-blind trial compared a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib in hospitalized adults (NCT04401579; ACTT-2): Inclusion criteria included laboratory-confirmed SARS-CoV-2 infection with at least one of the following: radiographic infiltrates by imaging, SpO₂ ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO. Patients were randomized to baricitinib dosage or placebo, whichever comes first. Not authorized for pediatric patients <2 years of age.  
Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1  
Optimal dosage and duration for treatment of COVID-19 not known (see Trials or Clinical Experience)  
Emergency use authorization (EUA) for baricitinib in combination with remdesivir: FDA issued an EUA on November 19, 2020 that permits use of baricitinib in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). FDA states that, based on review of data from a randomized, double-blind, placebo-controlled trial comparing baricitinib in combination with remdesivir to remdesivir alone (NCT04401579; ACTT-2), baricitinib data that were reviewed for the FDA-approved indication of rheumatoid arthritis, and data from populations studied for other indications (including pediatric patients), it is reasonable to believe that baricitinib may be effective in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in the patient population specified in the baricitinib EUA and, when used under... | 2 mg orally once daily, or 4 mg orally once daily |  
Emergency use authorization (EUA) for baricitinib in combination with remdesivir: FDA issued an EUA on November 19, 2020 that permits use of baricitinib in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). FDA states that, based on review of data from a randomized, double-blind, placebo-controlled trial comparing baricitinib in combination with remdesivir to remdesivir alone (NCT04401579; ACTT-2), baricitinib data that were reviewed for the FDA-approved indication of rheumatoid arthritis, and data from populations studied for other indications (including pediatric patients), it is reasonable to believe that baricitinib may be effective in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in the patient population specified in the baricitinib EUA and, when used under... |
randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for a total treatment duration of 10 days or until hospital discharge) with either baricitinib (4 mg orally once daily for 14 days or until hospital discharge) with either baricitinib (4 mg orally or through a nasogastric tube once daily for 14 days or until hospital discharge) or placebo. The primary end point was time to recovery through day 29 (defined as discharged without limitations on activities, discharged with limitations on activities and/or requiring home oxygen, or still hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). Data for 1033 patients in the intent-to-treat population (515 in the remdesivir and baricitinib group and 518 in the remdesivir alone group) indicate that those who received the combined regimen were more likely to have better clinical outcomes than those who received remdesivir alone. Use of the combined regimen of remdesivir and baricitinib met the primary end point of reduced time to recovery compared with use of remdesivir alone (median time to recovery was 7 days in those receiving the combined regimen vs 8 days in those receiving remdesivir). Patients treated with combined remdesivir and baricitinib were also more likely to have a better clinical status at day 15 compared with those receiving remdesivir alone. The proportion of patients who progressed to ventilation (noninvasive or invasive) by day 29 was lower in patients receiving combined remdesivir and baricitinib. In addition, the mortality rate at day 29 was 4.7% in those treated with the combined regimen and 7.1% in those treated with remdesivir alone. Based on results of this trial and other data, FDA issued an emergency use authorization (EUA) for baricitinib that permits use of the drug in combination with remdesivir for the treatment of COVID-19 in hospitalized patients when corticosteroids cannot be used. In rare circumstances when corticosteroids cannot be used, the panel recommends use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation. (See Remdesivir in this Evidence Table.) The panel recommends against the use of baricitinib in the absence of remdesivir, except in a clinical trial.

Adaptive phase 2/3 clinical trial: Open-label study planned to evaluate safety and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232)

The panel recommends dosage adjustment if baricitinib is administered concurrently with a strong OAT3 inhibitor. Consult the baricitinib EUA letter of authorization, EUA fact sheet for healthcare providers, and EUA fact sheet for patients, parents and caregivers for additional information.

NIH COVID-19 Treatment Guidelines Panel states that data are insufficient to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients when corticosteroids cannot be used. In rare circumstances when corticosteroids cannot be used, the panel recommends use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation. (See Remdesivir in this Evidence Table.) The panel recommends against the use of baricitinib in the absence of remdesivir, except in a clinical trial.

Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and many other drugs, however, dosage adjustment recommended when used with strong OAT3 inhibitors.

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<td>NIH COVID-19 Treatment Guidelines Panel and the EUA recommend dosage adjustment if baricitinib is administered concurrently with a strong OAT3 inhibitor.</td>
<td></td>
<td>The conditions described in the EUA, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients outweigh the known and potential risks. Consult the baricitinib EUA letter of authorization, EUA fact sheet for healthcare providers, and EUA fact sheet for patients, parents and caregivers for additional information. NIH COVID-19 Treatment Guidelines Panel states that data are insufficient to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients when corticosteroids cannot be used. In rare circumstances when corticosteroids cannot be used, the panel recommends use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation. (See Remdesivir in this Evidence Table.) The panel recommends against the use of baricitinib in the absence of remdesivir, except in a clinical trial. Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and many other drugs, however, dosage adjustment recommended when used with strong OAT3 inhibitors.</td>
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<tr>
<td>Colchicine</td>
<td>92:16 Antigout Agents</td>
<td>Exerts broad anti-inflammatory and immunomodulatory effects through multiple mechanisms, including inhibition of NOD-like receptor protein 3 (NLRP3) inflammasome assembly and disruption of cytoskeletal functions through inhibition of microtubule polymerization. May combat the hyper-inflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines. Limited anecdotal experience and clinical trial data reported to date in COVID-19. Retrospective review of computerized healthcare database found no difference in baseline use of colchicine (0.53 vs 0.48%) between patients with a positive RT-PCR result for SARS-CoV-2 (n = 1317) and those with a negative result (n = 13,203), suggesting a lack of protective effect for colchicine against SARS-CoV-2 infection; indication for and duration of colchicine use were unknown. Uncontrolled case series: 9 patients in community setting with COVID-19 received colchicine (1 mg orally every 12 hours on day 1, then 1 mg daily until third day of hospitalization).</td>
<td>Dosage in NCT04326790 (GRECCO-19): Colchicine loading dosage: 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin); maintenance dosage: 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing &lt;60 kg) until hospital discharge or maximum of 21 days. Dosage in another ongoing trial: Colchicine 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose is 1 mg if body weight ≥80 kg); dosage is reduced for renal impairment. Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days.</td>
<td>Safety and efficacy for treatment of COVID-19 not established. The potential for toxic doses of colchicine to affect alveolar type II pneumocytes (which may inhibit surfactant release and contribute to ARDS) and increase the risk of multiple-organ failure and disseminated intravascular coagulation (DIC) has been raised as a possible concern with the use of colchicine in COVID-19 patients.</td>
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<td>NLRP3 inflammasome activation results in release of interleukins, including IL-1β 3,5,6,8,11</td>
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<td>Several single-center, proof-of-concept or small comparative cohort studies conducted in hospitalized patients with COVID-19 suggest beneficial effects of colchicine on mortality and other clinical outcomes; in one observational study (not peer reviewed), mortality rate in patients with COVID-19 pneumonia was numerically lower in those receiving colchicine compared with those not receiving the drug, but the effect of the drug was not statistically significant; 80% of patients in the study received corticosteroids. The studies had substantial limitations, and larger well-designed studies are needed to further evaluate efficacy. Open-label, randomized, 16-hospital clinical trial (NCT04326790, GRECCO-19) in hospitalized adults with RT-PCR-confirmed COVID-19: 55 patients received colchicine plus standard treatment and 50 received standard treatment alone; colchicine was administered orally as a loading dose of 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin) followed by a maintenance dosage of 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing &lt;60 kg) until hospital discharge or for a maximum of 21 days. Most patients also received chloroquine or hydroxychloroquine (98%) and azithromycin (92%). Clinical deterioration (2-grade increase on a 7-grade ordinal scale) was observed in a greater proportion of control patients than colchicine-treated patients (7 patients [14%] vs 1 patient [1.8%]); cumulative 10-day event-free survival was higher with colchicine than with control (97 vs 83%). Baseline score on the 7-grade scale was 3 or 4 in 97% of study patients. No difference observed between the groups in baseline or peak high-sensitivity cardiac troponin or temperature &lt;37.5°C; colchicine was initiated at a median of 8 days (range: 6-13 days) after symptom onset and after 3-5 days of spiking fever despite acetaminophen or antibiotic treatment. Defervescence occurred within 72 hours in all patients. One patient was hospitalized because of persistent dyspnea and discharged after 4 days of oxygen therapy. Basis for diagnosis of COVID-19 not stated. Then 0.5 mg once daily for 27 days 1.</td>
<td></td>
<td>Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19 2.</td>
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peak C-reactive protein concentration. Small number of clinical events limited the statistical robustness of the results.  

Interim analysis (not peer reviewed) of a single-center, randomized, double-blind, placebo-controlled trial in hospitalized adults with moderate to severe, RT-PCR-confirmed COVID-19 with pneumonia (not requiring ICU admission): Analysis of first 38 patients randomized 1:1 to colchicine or placebo indicated shorter duration of oxygen supplementation (3 vs 7 days) and shorter hospital stay (6 vs 8.5 days) in colchicine group vs placebo group. One patient in each group required ICU admission. Median duration of symptoms prior to treatment was 9 days (colchicine group) or 7 days (placebo group). Colchicine dosage was 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose was 1 mg if body weight ≥80 kg); dosage was reduced for renal impairment. Standard concomitant treatment included 7-day azithromycin regimen, up to 10-day hydroxychloroquine regimen, and heparin with or without methylprednisolone (depending on oxygenation status).  

Phase 3, randomized, double-blind, placebo-controlled study (NCT04322682; COL-CORONA) initiated in adults ≥40 years of age with COVID-19 and at least one high-risk criterion to evaluate effect of colchicine on mortality, hospitalization rate, and need for mechanical ventilation; study excludes enrollment of currently hospitalized patients; enrollment target is approximately 6000 pts.  

Other registered randomized, parallel-group studies are evaluating the effects of colchicine on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in patients with COVID-19: NCT04322565, NCT04328480, NCT04350320, NCT04355143, NCT04392141, NCT04375202, NCT04360980, NCT04367168, NCT04403243, NCT04363437, NCT04416334, NCT04324463, NCT04527562, NCT04492358, NCT04381936.

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<tr>
<td>Corticosteroids</td>
<td>68:04</td>
<td>Potential anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia.</td>
<td>The current version of this document can be found on the ASHP COVID-19 Resource Center.</td>
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| **Updated 1/29/21**   | Adrenals   | Observational studies in other respiratory infections (e.g., SARS, MERS, influenza): In these studies, corticosteroid use was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). | The NIH COVID-19 Treatment Guidelines Panel recommends an IV or oral Dexamethasone dosage of 6 mg daily for up to 10 days or until hospital discharge, whichever comes first, in COVID-19 patients requiring mechanical ventilation and in patients who require supplemental oxygen but who are not mechanically ventilated. Although the clinical benefits of other corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone) are not clear, the panel recommends using total daily dosages of these drugs equivalent to dexamethasone 6 mg (IV or oral) as follows: |         | Data on the use of corticosteroids in COVID-19 are limited. |}
|                       |            | Randomized controlled studies in acute respiratory distress syndrome (ARDS): Systemic corticosteroid therapy has been studied in several randomized controlled studies for the treatment of ARDS; overall evidence is low to moderate in quality and most studies were performed prior to widespread implementation of lung protection strategies. | Evidence suggests that cytokine storm, a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), is a contributing factor in COVID-19-associated mortality. |         | - The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19. |}
|                       |            | Randomized, controlled, open-label, adaptive trial with a Dexamethasone arm (NCT04381936; RECOVERY): This trial was conducted to evaluate the effect of potential treatments (including low-dose dexamethasone) on all-cause mortality in hospitalized patients with COVID-19. The study enrolled patients with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the dexamethasone treatment arm, 2104 patients were randomized to receive dexamethasone (6 mg once daily orally or IV for up to 10 days) plus standard care and 4321 patients were randomized to receive standard care alone. Preliminary data analysis indicates that overall 28-day mortality was reduced in patients receiving dexamethasone compared with those receiving standard care alone with the greatest benefit observed in patients requiring mechanical ventilation at enrollment. Overall, 22.9% of patients receiving dexamethasone and 25.7% of those receiving standard care died within 28 days of study enrollment. In patients receiving dexamethasone, the incidence of death was lower than that in the standard care group among those receiving mechanical ventilation (29.3% vs 41.4%) and among those receiving supplemental oxygen without invasive mechanical ventilation (23.3% vs 26.2%). However, no survival benefit was observed with dexamethasone and there was a possibility of harm in patients who did not require respiratory support at enrollment; the incidence of death in such patients may improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low. | The Surviving Sepsis Campaign COVID-19 recommends not using systemic corticosteroids in nonhospitalized COVID-19 patients with mild to moderate COVID-19 or in hospitalized patients with COVID-19 who do not require supplemental oxygen. |         |  |
### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage | Comments
--- | --- | --- | --- | --- | ---
| **Dexamethasone** | | | receiving dexamethasone compared with standard care was 17.8 vs 14%, respectively. Dexamethasone was associated with a reduction in 28-day mortality among patients with symptoms for >7 days compared with those having more recent symptom onset. Dexamethasone treatment also was associated with a shorter duration of hospitalization and a greater probability of discharge within 28 days with the greatest effect observed among patients receiving invasive mechanical ventilation at baseline. | **Continuous IV infusion of Hydrocortisone** 200 mg/day for 7 days, followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days) was used in the CAPE COVID study. If a patient’s respiratory and general status sufficiently improved by day 4, a shorter treatment regimen of Hydrocortisone was used at a dosage of 200 mg/day for 4 days followed by 100 mg/day for 2 days and then 50 mg/day for 2 days (total of 8 days). | **Note:** Data regarding potential adverse effects, efficacy in combination with other treatments (e.g., remdesivir), and efficacy in other patient populations (e.g., pediatric patients and pregnant women) not available to date. 24, 32, 33 | **European Society of Intensive Care Medicine** recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. 13

Based on preliminary findings from the RECOVERY trial, the NIH COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone (6 mg daily for up to 10 days or until hospital discharge, whichever comes first) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. (See Remdesivir in this Evidence Table for recommendations from the NIH guidelines panel regarding use of dexamethasone with or without remdesivir in COVID-19 patients based on disease severity.)

The NIH guidelines panel states that prolonged use of systemic corticosteroids in patients with COVID-19 may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus, strongyloidiasis, tuberculosis). The risk of reactivation of latent infections following a 10-day course of dexamethasone (6 mg once daily) is not well established. When initiating dexamethasone in patients with COVID-19, appropriate screening and treatment to reduce the risk of Strongyloides hyperinfection in those at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) or fulminant reactivations of HBV should be considered. 24, 37, 38

The NIH guidelines panel also states that it is not known at this time whether other corticosteroids will have a similar benefit as dexamethasone. However, if

Dexamethasone randomized, controlled, open-label, multicenter study (NCT04327401; CoDEX): This trial was conducted to determine whether IV dexamethasone increases the number of ventilator-free days among patients with COVID-19-associated ARDS. The study enrolled adults with COVID-19 and moderate or severe ARDS who were receiving mechanical ventilation from 41 ICUs in Brazil. In the dexamethasone treatment arm, 151 patients were randomized to receive dexamethasone (20 mg IV once daily for 5 days followed by 10 mg IV once daily for another 5 days or until ICU discharge) plus standard care; 148 patients were randomized to receive standard care alone. The primary study end point was ventilator-free days (defined as number of days alive and free from mechanical ventilation) during the first 28 days. Preliminary data analysis indicates that use of IV dexamethasone plus standard care was associated with a higher mean number of ventilator-free days (6.6 days) compared with those receiving standard care alone (4 days). Although there was no significant difference in all-cause mortality at 28 days between the treatment groups, the trial was terminated early after results of the RECOVERY trial became available and, therefore, likely underpowered to determine secondary outcomes such as mortality. Dexamethasone was not associated with an increased risk of adverse

A fixed dosage of IV Hydrocortisone (50 or 100 mg every 6 hours for 7 days) or a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours for up to 28 days in the presence of clinically evident shock) was used in the REMAP-CAP study. 41

European Society of Intensive Care Medicine recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. 13
effects in this study population of critically ill COVID-19 patients. 26, 39

**Hydrocortisone randomized, double-blind sequential trial (NCT02517489; CAPE COVID):** This trial was conducted to evaluate the effect of low-dose hydrocortisone compared with placebo on treatment failure in critically ill patients with COVID-19-related acute respiratory failure. The study enrolled adults with COVID-19-associated acute respiratory failure from 9 ICUs in France. In the hydrocortisone treatment arm, 76 patients received a continuous IV infusion of hydrocortisone at an initial dosage of 200 mg/day for 7 days followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days; some patients received a shorter regimen); 73 patients received placebo. The primary study endpoint was treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy) on day 21. Treatment failure on day 21 occurred in 42.1% of patients in the hydrocortisone group compared with 50.7% of patients in the placebo group. The difference between the treatment groups was not statistically significant; however, the study was discontinued early after results of the RECOVERY trial were announced and, therefore, likely underpowered to determine a statistically and clinically important difference in the primary outcome. 24, 40

**Hydrocortisone multicenter, ongoing, international open-label trial using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 corticosteroid domain, adults from 8 countries with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive a fixed 7-day regimen of IV hydrocortisone (50 or 100 mg every 6 hours), a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours when shock was clinically evident), or no hydrocortisone or other corticosteroid. The primary study end point was organ support-free days (defined as days alive with room air and not requiring supplemental oxygen). IDSA suggests against using corticosteroids in hospitalized patients with nonsevere COVID-19 without hypoxemia (i.e., defined as patients with SpO2 > 94% on room air and not requiring supplemental oxygen). 25

The WHO Guideline Development Group strongly recommends the use of systemic corticosteroids (e.g., dexamethasone 6 mg orally or IV daily or hydrocortisone 50 mg IV every 8 hours for 7-10 days) over no systemic corticosteroid therapy for the treatment of patients with severe and/or critical COVID-19, regardless of hospitalization status. This treatment recommendation includes critically ill patients with COVID-19 who could not be hospitalized or receive oxygen supplementation because of resource limitations. This treatment recommendation is less clear for populations under-represented in recent clinical trials (e.g., children, patients with tuberculosis, immunocompromised individuals); however, the risk of not using dexamethasone is not available, the panel recommends using alternative corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone). 24

IDSA suggests the use of dexamethasone over no dexamethasone therapy in hospitalized patients with severe, but noncritical, COVID-19 (i.e., defined as patients with SpO2 ≤ 94% on room air including those who require supplemental oxygen). IDSA recommends the use of dexamethasone in hospitalized, critically ill patients with COVID-19 (i.e., defined as patients who are receiving mechanical ventilation or ECMO including those with end organ dysfunction as seen in cases of septic shock or ARDS). These experts suggest the use of dexamethasone 6 mg orally or IV daily for 10 days or until hospital discharge, whichever comes first, or substitution of equivalent daily dosages of other corticosteroids (e.g., methylprednisolone 32 mg, prednisone 40 mg) if dexamethasone is unavailable. However, IDSA suggests against using corticosteroids in hospitalized patients with nonsevere COVID-19 without hypoxemia (i.e., defined as patients with SpO2 > 94% on room air and not requiring supplemental oxygen). 25
and free of ICU-based respiratory or cardiovascular support) within 21 days. The 7-day fixed regimen and the shock-dependent regimen of hydrocortisone were associated with a 93 and 80% probability of benefit in terms of organ support-free days compared with no hydrocortisone. However, the trial was discontinued early after results of the RECOVERY trial were announced and no treatment strategy met the prespecified criteria for statistical superiority, precluding definitive conclusions. In addition, serious adverse effects were reported in 2.6% of patients in the study (4 patients receiving the fixed-dosage regimen and 5 patients receiving the shock-dependent regimen compared with 1 patient receiving no hydrocortisone).

Prospective meta-analysis of studies using systemic corticosteroids (i.e., dexamethasone, hydrocortisone, or methylprednisolone) from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group: This meta-analysis pooled data from 7 randomized clinical trials in 12 countries that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The primary outcome was all-cause mortality up to 30 days after randomization to treatment. Administration of systemic corticosteroids was associated with lower all-cause mortality at 28 days compared with usual care or placebo (222 deaths among 678 patients who received corticosteroids and 425 deaths among 1025 patients who received usual care or placebo). The effect of corticosteroids on reduced mortality was observed in critically ill patients who were and were not receiving mechanical ventilation at randomization and also in patients from the RECOVERY trial who required supplemental oxygen with or without noninvasive ventilation but who were not receiving invasive mechanical ventilation at the time of randomization. The odds ratios for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone. The optimal dosage and duration of corticosteroid treatment could not be determined from this analysis; however, there was no evidence suggesting that a

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higher dosage of corticosteroids was associated with greater benefit than a lower dosage. The authors also concluded that there was no suggestion of an increased risk of serious adverse effects associated with corticosteroid use. 24, 42

Methylprednisolone randomized, parallel, double-blind, placebo-controlled, phase IIb trial (NCT04343729; Metcovid): This trial was conducted to evaluate the effect of a short course of IV methylprednisolone compared with placebo in hospitalized adults with suspected COVID-19 infection from a single center in Brazil. Patients were enrolled prior to laboratory confirmation of COVID-19 to avoid treatment delays. The presence of COVID-19 was later confirmed based on RT-PCR testing in 81.3% of these patients. 24, 47 At time of enrollment, 34% of patients in each treatment group required invasive mechanical ventilation. Supplemental oxygen was required in 51% of patients receiving methylprednisolone and in 45% of those receiving placebo. 24 In the methylprednisolone treatment arm, 194 patients received IV methylprednisolone at a dosage of 0.5 mg/kg twice daily for 5 days; 199 patients received placebo. A modified intent-to-treat analysis was conducted; the primary study end point was 28-day mortality. Overall, the 28-day mortality rate was 37.1 or 38.2% in patients who received methylprednisolone or placebo, respectively, showing no significant difference in overall mortality between the treatment groups. However, a subgroup analysis found a lower mortality rate in patients >60 years of age who received methylprednisolone compared with placebo (46.6 vs 61.9%, respectively). Patients >60 years of age reportedly had a higher degree of systemic inflammatory disease as manifested by increased median levels of C-reactive protein (CRP) compared with patients ≤60 years of age. In patients ≤60 years of age, there was a higher incidence of fatal outcomes in the methylprednisolone group. The authors concluded that caution is needed when using corticosteroids in patients with less severe COVID-19 since a trend toward more harm was noted in the younger age group. Note: Limitations that oral corticosteroids used for the treatment of an underlying condition prior to COVID-19 infection (e.g., primary or secondary adrenal insufficiency, rheumatologic diseases) should not be discontinued. Supplemental or stress dosages of corticosteroids may be indicated on an individual basis in patients with such conditions. 24 (See Corticosteroids [inhaled] in this Evidence Table for recommendations for use of inhaled corticosteroids in COVID-19 patients with asthma or COPD.)

Rheumatology experts, including members of the American College of Rheumatology COVID-19 Clinical Guidance Task Force, state that abrupt discontinuation of corticosteroid therapy in patients with rheumatologic diseases should be avoided regardless of COVID-19 exposure or infection status. These experts also state that if indicated, corticosteroids should be used at the lowest effective dosage to control manifestations, but also acknowledge that higher dosages may be necessary in the context of severe, vital organ-threatening rheumatologic disease even following COVID-19 exposure. 28-30

Endocrinology experts state that patients with primary or secondary adrenal insufficiency who are receiving prolonged corticosteroid therapy should follow usual steroid “sick day rules” since these individuals may not be able to mount a normal stress response in the event of COVID-19 infection. 15, 26 If such individuals develop symptoms such as fever and a dry continuous cough, they should immediately double their daily oral corticosteroid dosage and continue with this regimen until the fever subsides. 15 These guidelines also apply to patients who are receiving prolonged therapy (> 3 months) with corticosteroids for underlying inflammatory conditions, including asthma, allergy, and rheumatoid arthritis. 19 In such patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral

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*Dosagea: The current version of this document can be found on the ASHP COVID-19 Resource Center. Copyright © 2021, American Society of Health-System Pharmacists, Inc. All rights reserved. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.*
of this study include the following: single-center study with a moderate sample size, longer median time from symptom onset to treatment administration compared with other corticosteroid studies, shorter treatment duration and higher equivalent corticosteroid dosage compared with the RECOVERY trial, and higher baseline mortality of the patient population possibly limiting the generalizability of the results to populations with lower baseline mortality. 24, 47

Methylprednisolone multicenter, observational, longitudinal study (NCT04323592): This trial was conducted to evaluate the association between use of prolonged, low-dose methylprednisolone treatment and ICU admission, intubation, or all-cause death within 28 days (composite primary end point) in patients with severe COVID-19 pneumonia admitted to 14 respiratory high-dependency units in Italy. A total of 173 patients were enrolled in the study with 83 patients receiving methylprednisolone plus standard care and 90 patients receiving standard care alone. In the methylprednisolone treatment arm, patients received a loading dose of IV methylprednisolone 80 mg at study entry followed by IV infusion of the drug at a dosage of 80 mg daily at a rate of 10 mL/hr for at least 8 days until achievement of either a PaO2/FIO2 (P/F ratio) >350 mm Hg or CRP levels <20 mg/L. Subsequently, twice-daily administration of either oral methylprednisolone 16 mg or IV methylprednisolone 20 mg was given until achievement of a P/F ratio >400 mm Hg or CRP levels reached <20% of the normal range. The composite primary end point was reached by 22.9 or 44.4% of patients in the group receiving methylprednisolone or standard care alone, respectively. Therefore, use of methylprednisolone was associated with a reduction in the risk of ICU admission, invasive mechanical ventilation, or death within 28 days (adjusted hazard ratio: 0.41). Specifically, 18.1 or 30% of patients required ICU admission and 16.9 or 28.9% of patients required invasive mechanical ventilation in those receiving methylprednisolone or standard care alone, respectively. In addition, use of corticosteroids may be necessary. 19, 26 Administration of physiologic stress doses of corticosteroids (e.g., IV hydrocortisone 50-100 mg 3 times daily) and not pharmacologic doses should be considered in all cases to avoid potentially fatal adrenal failure. 19, 20 Additional study is needed to determine the optimum corticosteroid stress dosage regimen in patients with COVID-19. 16, 27 There is some evidence suggesting that continuous IV infusion of hydrocortisone (following an initial IV bolus dose) may provide more stable circulating cortisol concentrations in patients with adrenal insufficiency and reduce the potentially harmful effects of peak and trough concentrations of cortisol on the immune system. 26, 27

Pregnancy considerations: For pregnant women with COVID-19, the NIH COVID-19 Treatment Guidelines Panel states that a short course of corticosteroids that cross the placenta (i.e., betamethasone, dexamethasone) is routinely used for fetal benefit (e.g., to hasten fetal lung maturity). Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for this short course of corticosteroid therapy, the panel recommends the use of dexamethasone in pregnant women with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. 24

The WHO Guideline Development Group recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24-34 weeks’ gestation when there is no clinical evidence of maternal infection and adequate maternal and newborn care are available. In cases where a pregnant woman presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroids may outweigh the risk of potential harm to the woman. The balance of benefits and risks for the woman and preterm infant should be considered during the informed decision-making process. 41

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methyprednisolone was associated with a 28-day lower risk of all-cause mortality than use of standard care alone (7.2 vs 23.3%, respectively) with an adjusted hazard ratio of 0.29. Overall, there was no difference in adverse effects between treatment groups with the exception of increased reports of hyperglycemia and mild agitation in the methylprednisolone-treated patients; no adverse effects resulted in drug discontinuation. The authors concluded that early, low-dose, prolonged therapy with methylprednisolone resulted in decreased ICU burden, reduced need for invasive mechanical ventilation, and lower mortality along with improvement in systemic inflammation and oxygenation markers in hospitalized patients with severe COVID-19 pneumonia at high risk of progression to acute respiratory failure. 48

**Retrospective, case-control study using systemic corticosteroids (i.e., methylprednisolone, prednisone):** This trial was conducted to evaluate the efficacy of early, low-dose, short-term therapy with systemic methylprednisolone or prednisone in hospitalized adults from a single center in China with non-severe COVID-19 pneumonia. A total of 475 patients were enrolled with 55 of these patients receiving early, low-dose corticosteroids. Methylprednisolone 20 or 40 mg IV daily was administered to 50 of these patients for 3-5 days, and oral prednisone 20 mg daily (equivalent dosage to methylprednisolone) was administered to 5 such patients for 3 days. Corticosteroid therapy was initiated within a median of 2 days following hospital admission. A total of 420 patients received standard therapy (no corticosteroids); using propensity score matching, 55 of these patients were selected as matched controls. The primary outcome was the rate of patients who developed severe disease and mortality. In the corticosteroid treatment arm, 12.7% of patients developed severe disease compared with 1.8% of patients in the control group. There was one death in the group receiving methylprednisolone and none in the control group. Regarding secondary outcomes, duration of fever, virus clearance time, and length of hospital stay were all significantly longer in patients receiving methylprednisolone.

**Pediatric considerations:** The safety and efficacy of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality rates are significantly lower for pediatric patients with COVID-19 than for adult patients with the disease. Therefore, results of this trial should be interpreted with caution for patients <18 years of age. The NIH COVID-19 Treatment Guidelines Panel states that use of dexamethasone may be beneficial in pediatric patients with respiratory disease due to COVID-19 who are receiving mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on an individual basis, and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of corticosteroids for the treatment of COVID-19 in pediatric patients, including in those with multisystem inflammatory syndrome in children (MIS-C). 24

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corticosteroids compared with no corticosteroid therapy.\(^{49}\) Because of the finding that early, low-dose, short-term systemic corticosteroid therapy was associated with worse clinical outcomes in hospitalized adult patients with non-severe COVID-19 pneumonia, the authors concluded that the study results do not support the use of corticosteroids in this population.\(^{49}\) However, it is difficult to interpret these results because of potential confounding factors inherent in the nonrandomized study design.\(^{24}\) It is unclear if the results of this study apply to corticosteroids other than methylprednisolone.\(^{24}\)

Methylprednisolone multicenter quasi-experimental study with single pretest and posttest (NCT04374071): This trial was conducted to evaluate the efficacy of early, short-term therapy with systemic methylprednisolone in hospitalized adults with confirmed moderate to severe COVID-19 from a multicenter health system in Michigan. A total of 213 patients were enrolled with 132 patients receiving early therapy with IV methylprednisolone at dosages of 0.5-1 mg/kg daily in 2 divided doses for 3 days plus standard care and 81 patients receiving early therapy with standard care alone. The primary end point was a composite based on the need for ICU transfer, progression to respiratory failure requiring mechanical ventilation, or in-hospital all-cause mortality. The primary composite end point occurred at a significantly lower rate in the group receiving early corticosteroid therapy (34.9%) compared with the group receiving early therapy with standard care alone (54.3%). The early corticosteroid group had a median time to initiation of methylprednisolone of 2 days compared with 5 days for the standard care group. The median hospital length of stay was significantly reduced from 8 to 5 days in patients receiving early corticosteroid therapy compared with those receiving early therapy with standard care alone. ARDS occurred in 26.6% of patients receiving early corticosteroid therapy compared with 38.3% of those in the standard care group. The authors concluded that early, short-term therapy with methylprednisolone in patients with moderate to mild COVID-19 pneumonia was associated with a lower rate of clinical failure compared with standard care alone.

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\(^{a}\) Methylprednisolone 0.5-1 mg/kg daily in 2 divided doses for 3 days.
severe COVID-19 may prevent disease progression and improve clinical outcomes. **Note:** Limitations of this study include the following: differences were noted in the baseline characteristics of the comparator groups; some patients in the standard care group received corticosteroids, but initiation of therapy was significantly later than in the early corticosteroid group; and patient follow-up for both treatment groups was limited to 14 days.  

**Methylprednisolone open-label, multicenter, randomized, controlled study (NCT04244591):** This recently completed trial compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to acute respiratory failure; results have not yet been posted.  

**Retrospective, observational study of systemic corticosteroid use in patients with COVID-19 from a New York hospital (Keller et al):** Data are available for 1806 patients hospitalized with COVID-19 between Mar 11 and Apr 13, 2020. Patients included in the analysis were those treated with systemic corticosteroids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone) within the first 48 hours of hospital admission (140 patients) and those not treated with corticosteroids (1666 patients) as the control group. Treatment and control groups were similar except that corticosteroid-treated patients were more likely to have a history of COPD, asthma, rheumatoid arthritis, or lupus, or to have received corticosteroids in the year prior to admission. Primary goal of the study was to determine whether early systemic corticosteroid treatment was associated with reduced mortality or need for mechanical ventilation. Overall, early use of systemic corticosteroids was not associated with in-hospital mortality or mechanical ventilation. However, there was a significant treatment effect based on C-reactive protein (CRP) levels. Early use of corticosteroids in patients with initial CRP levels of ≥20 mg/dL was associated with a significantly reduced risk of mortality or need for mechanical ventilation (odds ratio: 0.23).
Conversely, such treatment in patients with initial CRP levels of <10 mg/dL was associated with a significantly increased risk of mortality or need for mechanical ventilation (odds ratio: 2.64). The authors state that these findings suggest that appropriate selection of COVID-19 patients for systemic corticosteroid treatment is critical to maximize the likelihood of benefit and minimize the risk of harm. Note: The limitations of the observational study design should be considered when interpreting these results. Corticosteroid dosages used in patients included in this study not provided. Further study is needed to determine the role of CRP levels in guiding the use of corticosteroid treatment in patients with COVID-19. 36

Retrospective study of systemic corticosteroids and/or other immunosuppressive therapies and their effect on COVID-19 infection in patients with chronic immune-mediated inflammatory arthritis (Favalli et al): This study evaluated the frequency and characteristics of symptomatic COVID-19 infection in relation to use of different immunosuppressive agents in such patients. Data are available from a cross-sectional survey administered to 2050 adults receiving follow-up care at arthritis outpatient clinics of 2 large academic hospitals in Italy. Patients surveyed had arthritis of long duration (median of 10 years) and 62% were receiving therapy with biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) alone or in combination with conventional synthetic DMARDs; approximately one-third of these patients were also receiving concomitant long-term treatment with systemic corticosteroids. Laboratory-confirmed COVID-19 or highly suspected infection (based on close contact with a confirmed COVID-19 case within 14 days prior to onset of symptoms) was reported in 1.1 or 1.4% of patients, respectively. In this study, corticosteroid treatment was independently associated with an increased risk of COVID-19 infection, especially at prednisone dosages ≥ 2.5 mg daily. The use of corticosteroids was confirmed to independently predict increased risk of COVID-19 infection regardless of
comorbidities, precautions taken to prevent infection, and contacts with COVID-19 cases. Conversely, treatment with biologic/targeted synthetic DMARDs was associated with a reduced risk of COVID-19 infection. Limitations of this study include its retrospective nature and the definition of COVID-19 cases based on patient survey results. The authors state these data should not result in indiscriminate discontinuance of systemic corticosteroids in patients with chronic immune-mediated inflammatory arthritis, but underscore the importance of a benefit-risk assessment in individual patients.40

Dexamethasone, hydrocortisone, methylprednisolone, or prednisone studies for treatment of COVID-19 pneumonia or ARDS: Registered clinical trials that have been initiated or underway include: 22

NCT03852537
NCT04263402
NCT04273321
NCT04329650
NCT04344730
NCT04348305
NCT04359511
NCT04374071
NCT04395105

Methylprednisolone non-randomized pilot study (NCT04355247): Trial has been initiated to evaluate use of the drug for the prevention of COVID-19 cytokine storm and progression to respiratory failure.22

Corticosteroids (inhaled) Updated 1/29/21

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<td>Corticosteroids (inhaled)</td>
<td>68:04 Adrenals</td>
<td>Inhaled corticosteroids may mitigate local inflammation and inhibit virus proliferation.35, 44</td>
<td>There are currently no results from randomized controlled studies specifically evaluating use of inhaled corticosteroids in patients with COVID-19.34, 44, 45 Early reports of an unexpectedly low prevalence of chronic respiratory conditions among outpatient and hospitalized COVID-19 patients resulted in speculation that respiratory treatments, specifically inhaled corticosteroids, may have a protective effect against SARS-CoV-2.45, 46 Retrospective, observational study of inhaled corticosteroid use in patients with COPD or asthma and associated risk of COVID-19-related death in the UK (Schultze et al): This study was designed to</td>
<td>Initial dosage of orally inhaled ciclesonide used in the published case series from Japan of 3 patients with COVID-19 pneumonia was 200 mcg 2 times daily. If necessary, the dosage was increased to 400 mcg 3 times daily. The authors suggested continued use of ciclesonide oral inhalation for about 14 days or longer.35</td>
<td>NIH COVID-19 Treatment Guidelines Panel recommends that inhaled corticosteroids used daily for the management of asthma and COPD to control airway inflammation should not be discontinued in patients with COVID-19. The panel also states that no studies to date have investigated the relationship between inhaled corticosteroids in these clinical settings and virus acquisition, severity of illness, or viral transmission.24 Currently, there is no clinical evidence supporting adverse or beneficial effects of premorbid use or continued administration of inhaled corticosteroids in patients with acute respiratory</td>
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assess the role of routine use of inhaled corticosteroids on COVID-19-related mortality. Data were extracted from primary care electronic health records and linked with mortality data for a cohort of patients with COPD (n = 148,557) and another cohort with asthma (n = 818,490) who were prescribed standard respiratory treatments within the 4 months prior to the index date. In patients with COPD, an increased risk of COVID-19-related death (hazard ratio: 1.39) was reported after adjusting for age and comorbidities among those who were prescribed inhaled corticosteroids combined with a long-acting β-agonist and/or long-acting antimuscarinic compared with those prescribed a long-acting β-agonist and long-acting antimuscarinic. In patients with asthma, an increased risk of COVID-19-related death (hazard ratio: 1.55) was reported in patients who were prescribed high-dose inhaled corticosteroids compared with those prescribed a short-acting β-agonist only; however, there was no increased risk of death (hazard ratio: 1.14) in asthma patients receiving low- or medium-dose inhaled corticosteroids compared with nonusers of inhaled corticosteroids. Sensitivity analyses suggest there may be other factors driving the increased risk of death observed with use of inhaled corticosteroids, including underlying disease differences between individuals that are not captured in the health records. The results of this study do not support evidence of benefit or harm with routine use of inhaled corticosteroids on COVID-19-related mortality among individuals with COPD or asthma.  

A small case series from Japan observed possible clinical benefit in 3 patients with mild to moderate COVID-19 pneumonia following oral inhalation of ciclesonide; however, without a control group, it is not known whether the patients would have improved spontaneously.  

Various clinical trials evaluating the use of inhaled corticosteroids (e.g., budesonide, ciclesonide) in patients with COVID-19 are registered at clinicaltrials.gov.  

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| Triamcinolone | | | | | infections due to coronaviruses. Randomized controlled clinical studies are needed to assess the benefits of inhaled corticosteroids for treatment of COVID-19 in patients with and without chronic respiratory conditions.  

34, 44

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<td>Inhaled prostacyclins (e.g., epoprostenol, iloprost)</td>
<td>48:48 Vasodilating Agents</td>
<td>Selective pulmonary vasodilators; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19</td>
<td>Available evidence suggests that inhaled prostacyclins can improve oxygenation, but have no known mortality benefit, in patients with ARDS. It is not clear whether or how COVID-19-associated ARDS differs from ARDS related to other etiologies.</td>
<td>In patients with ARDS, various dosages of inhaled epoprostenol have been used; dosages up to 50 ng/kg per minute (titrated to response) have been used in clinical studies. In several observational studies in mechanically ventilated patients with COVID-19, inhaled epoprostenol was administered at an initial dosage of 50 ng/kg per minute (based on ideal body weight).</td>
<td>The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against the use of inhaled prostacyclins in COVID-19 patients with severe ARDS. The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment.</td>
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Updated 1/29/21

Inhaled epoprostenol has been suggested as an alternative to inhaled nitric oxide due to similar efficacy, lower potential for systemic adverse effects, lower cost, and ease of delivery.

Experience with inhaled iloprost is more limited, but the drug is thought to have a similar theoretical benefit as epoprostenol in patients with ARDS.

Results of a retrospective, single-center, observational study in intubated patients with COVID-19 and refractory hypoxemia did not show significant improvement in oxygenation metrics following treatment with inhaled epoprostenol or inhaled nitric oxide. In this study, 38 patients initially received inhaled epoprostenol (starting dose of 0.05 mcg/kg per minute, continued based on PaO2 response); 11 patients who did not respond to epoprostenol were transitioned to inhaled nitric oxide (starting dose of 20 ppm, titrated up to 80 ppm based on PaO2 response). Although 42.1% of patients who received epoprostenol and 63.6% of patients who received nitric oxide were considered responders (defined as an increase in PaO2/FiO2 by >10%), there were no significant changes in other oxygenation parameters or clinical outcomes.

In another retrospective observational study in 80 mechanically ventilated COVID-19 patients, clinically significant improvement in PaO2/FiO2 (defined as an increase by 10% from baseline values) was observed in 50% of the patients following treatment with inhaled epoprostenol (initial dose of 50 ng/kg per minute delivered through the ventilator tubing); however, the benefit was generally modest and there was wide variability in response.

Numerous limitations of the observational studies described above preclude definitive conclusions.

Inhaled prostacyclins may be included in some COVID-19 clinical trials registered at clinicaltrials.gov.
Interferons (IFNs) modulate immune responses to some viral infections; 2, 7, 19 in vitro studies indicate only weak induction of IFN following SARS-CoV-2 infection, and a possible role for IFNs in prophylaxis or early treatment of COVID-19 has been suggested as a component of combination therapy (e.g., background regimen), see antiviral entries in this Evidence Table.

Clinical trials are currently evaluating IFN beta-1a or IFN beta-1b, generally added to other antivirals, for treatment of COVID-19, including: 16

- NCT04492475 (IFN beta-1a)
- NCT04449380 (IFN beta-1a)
- NCT02753707 (IFN beta-1a)
- NCT04465695 (IFN beta-1b)
- NCT04494399 (IFN beta-1b)
- NCT0467655 (IFN beta-1b)
- NCT04324463 (IFN beta)
- NCT04343768 (IFN beta-1a, IFN beta-1b)
- NCT04552379 (peginterferon [pegIFN] beta-1a)

PegIFN beta-1a also is being evaluated for postexposure prophylaxis of SARS-CoV-2 infection (NCT04552379). 16

Open-label, randomized study in hospitalized adults with COVID-19, mostly mild disease (NCT04276688): IFN beta-1b 8 million units was given sub-Q on alternate days for 1, 2, or 3 doses (when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset) in conjunction with 14-day regimen of LPV/RTV and ribavirin. 16, 18

In an open-label, randomized study in hospitalized adults with severe COVID-19, IFN beta-1b 250 mcg was given sub-Q every other day for 2 weeks. 22

In the SOLIDARITY study, most IFN-treated patients received three 44-mcg doses of IFN beta-1a sub-Q over 6 days. 23

Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established.

Relative effectiveness of different IFNs against SARS-CoV-2 not established. 12

NIH COVID-19 Treatment Guidelines Panel recommends against use of IFNs for treatment of severe or critical COVID-19, except in the context of a clinical trial. The panel also states there are insufficient data to recommend either for or against use of IFN beta for the treatment of early (i.e., <7 days from symptom onset) mild or moderate COVID-19. No benefit was observed with use of IFNs for treatment of other severe or critical coronavirus infections (SARS, MERS), and toxicity of IFNs outweighs the potential for benefit. IFNs may have antiviral activity early in the course of SARS-CoV-2 infection; however, there are insufficient data to assess the potential benefit of IFN use during early disease versus the risk of toxicity. 11

Surviving Sepsis Campaign COVID-19 subcommittee states that there is insufficient evidence to issue a recommendation on use of interferons, alone or in combination with antivirals, in critically ill adults with COVID-19. 12

Interferon alfa via inhalation is included in national guidelines from China as a possible option for treatment of COVID-19. 13
Type 3 IFNs (IFN lambda) are thought to provide important immunologic defense against respiratory viral infections \(^3, 4, 6, 7, 19\) and may have less potential than type 1 IFNs to produce systemic inflammatory response, including inflammatory effects on respiratory tract; \(^4, 7, 19\) IFN lambda receptor is expressed mainly on epithelial (including respiratory epithelial) cells and neutrophils, and is distinct from the ubiquitous type 1 IFN receptor; \(^2, 4, 7, 19\) despite different receptors and expression patterns, type 1 and type 3 IFNs activate similar signaling cascades; \(^4, 7, 19\) unknown whether limited receptor distribution might also affect efficacy.\(^4\)

Open-label, randomized study in adults hospitalized with severe COVID-19: Regimen of IFN beta-1b (250 mcg sub-Q every other day for 2 weeks) plus Iran national protocol medications was compared with national protocol alone (control). Protocol included a 7- to 10-day regimen of lopinavir/ritonavir or atazanavir/ritonavir and hydroxychloroquine. All patients required respiratory support (mainly oxygenation through facemask [80%]) but none were intubated at baseline. Median time from symptom onset to randomization was 8 days. Total of 80 patients were randomized (40 to each treatment group); analyses were based on data for 33 patients per treatment group after exclusion of those who withdrew consent, were enrolled in another study, or received <4 IFN doses. Median time to clinical improvement (defined as ≥2-category improvement in a 6-category ordinal scale) was shorter in the IFN group than in the control group (9 vs 11 days). A smaller proportion of IFN-treated patients required ICU admission (42 vs 67%). There was no difference in duration of hospitalization, intubation rate, length of ICU stay, or all-cause 28-day mortality.\(^25\)

Open-label, randomized study in Iran in hospitalized adults with severe suspected or RT-PCR-confirmed COVID-19: IFN beta-1a (12 million units sub-Q 3 times weekly for 2 weeks) plus standard care (7- to 10-day regimen of hydroxychloroquine plus lopinavir/ritonavir or azatavir/ritonavir) \(^n = 42\) was compared with standard care (control; \(n = 39\)). Time to clinical response (primary outcome; defined as hospital discharge or 2-score improvement in a 6-category ordinal scale) did not differ significantly between the IFN beta-1a group and the control group \(9.7 \text{ vs } 8.3 \text{ days}\); durations of hospital stay, ICU stay, and mechanical ventilation also did not differ.

Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage | Comments
---|---|---|---|---|---
Type 3 IFNs (IFN lambda) | | | | Peginterferon lambda-1a 180 mcg sub-Q; number of doses (1 dose or 2 doses given 1 week apart) depends on the protocol.\(^5\) |
For postexposure prophylaxis of CoV-2 infection in adults (NCT04344600): Two 180-mcg sub-Q doses of peginterferon lambda-1a given 1 week apart.\(^5\) |
Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY; NCT04315948): The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. Interim results have been reported, including results for the IFN beta-1a treatment arm. From March 22 to October 4, 2020, 2063 patients were randomized to receive IFN (given in conjunction with lopinavir and ritonavir \( n = 651 \) or standard of care \( n = 1412 \)) and 2064 patients were randomized to IFN control (either lopinavir and ritonavir or standard of care, for the respective IFN regimens). Most IFN-treated patients received three 44-mcg doses of IFN beta-1a sub-Q over 6 days; where IV IFN was
available, patients on high-flow oxygen, ventilators, or ECMO received 10 mcg IV once daily for 6 days. Preliminary data analysis for the intention-to-treat (ITT) population indicated that IFN did not reduce in-hospital mortality (either overall or in any subgroup defined by age or ventilation status at study entry) and did not reduce the need for initiation of ventilation or the duration of hospitalization. The log-rank death rate ratio for IFN in the ITT population was 1.16; 243/2050 patients treated with IFN (12.9%) and 216/2050 control patients (11%) died. About one-half of the patients randomized to receive IFN or IFN control received corticosteroids; this did not appear to affect the death rate ratio. The clinical relevance of the difference in the pharmacokinetic profiles of sub-Q and IV IFN is unclear.  23, 28

Phase 2, randomized, double-blind, multi-center, placebo-controlled study (NCT04385095; SG016) evaluating SNG001 (inhaled IFN beta-1a) in adults with COVID-19: In the in-hospital portion of the study, patients received SNG001 (IFN beta-1a 6 million units via nebulizer once daily for up to 14 days) plus standard care or placebo plus standard care. The intention-to-treat population for the interim analysis included 48 patients treated with SNG001 and 50 patients given placebo. More patients in the SNG001 group had hypertension (69 vs 41%) and received oxygen at baseline (77 vs 58%), while more patients in the control group had diabetes mellitus (33 vs 12%) or cardiovascular disease (30 vs 19%). Median duration of symptoms before initiation of treatment was 10 days. Clinical outcomes were assessed on the WHO ordinal scale for clinical improvement; statistical models were adjusted for baseline and demographic factors. Hazard ratio for time to recovery (2.19) during the 14-day treatment period and odds ratios for recovery (3.19) and for improvement (2.32) on day 15 or 16 favored SNG001 over placebo. The study has been extended to include 120 patients in the home setting.  16, 22, 27, 29

Aerosolized IFN alfa (not commercially available in U.S.) has been used in China in children and adults for treatment of
COVID-19, but limited clinical data presented to date. In a retrospective study of 77 hospitalized adults with moderate COVID-19 disease who received aerosolized IFN alfa-2b (5 million units twice daily) \((n = 7)\), umifenovir (Arbidol®) \((n = 24)\), or both drugs \((n = 46)\), time from symptom onset to negative RT-PCR result in throat swab appeared to be shorter in those receiving IFN alfa-2b alone or in combination with umifenovir compared with those receiving umifenovir alone; this exploratory study was small and nonrandomized, and treatment groups were of unequal size and demographically unbalanced in age, comorbidities, and time from symptom onset to treatment.

Retrospective cohort study in 446 hospitalized patients who received antiviral therapy for COVID-19 suggested that early IFN alfa-2b therapy (within first 5 days of hospitalization) was associated with reduced in-hospital mortality while late IFN alfa-2b therapy was associated with increased mortality and delayed recovery. In this study, 48.4% of patients received early IFN therapy, 6% received late IFN therapy, and 46% received no IFN. Median time from symptom onset to admission was 6 days, and median time from admission to first IFN dose was 2 or 8.5 days in the early or late IFN group, respectively. Median duration of IFN therapy was 10 or 8.5 days in the early or late IFN group, respectively.

Preliminary, retrospective, single-center, matched case-control study in 104 patients hospitalized with COVID-19 suggested that IFN alfa-2b therapy (100,000 units by inhalation 4 times daily for 7 days) did not reduce the duration of viral shedding. Duration of viral shedding (based on 2 consecutive negative RT-PCR results) was not significantly different between the matched-pair groups (12 days in 32 IFN-treated patients vs 15 days in 32 control patients [no IFN treatment]).

Sub-Q peginterferon lambda-1a (not commercially available in U.S.) is being evaluated for treatment (e.g., NCT04354259) and postexposure prophylaxis (e.g., NCT04344600) of SARS-CoV-2 infection.
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<tr>
<th>Drug(s)</th>
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<th>Rationale</th>
<th>Trials or Clinical Experience</th>
<th>Dosage*</th>
<th>Comments</th>
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<tr>
<td>Nitric oxide (inhaled)</td>
<td>48:48 Vasodilating Agent</td>
<td>Selective pulmonary vasodilator with bronchodilator and vasodilatory effects in addition to other systemic effects mediated through cGMP-dependent or independent mechanisms; may be useful for supportive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19.</td>
<td>The available evidence indicates that inhaled nitric oxide can modestly improve oxygenation in patients with ARDS, but has no mortality benefit and may cause possible harm (e.g., renal impairment). It is not clear whether or how COVID-19-associated ARDS differs from ARDS related to other etiologies. Evidence supporting the use of inhaled nitric oxide in COVID-19 patients is currently limited. Various case reports, case series, and observational studies have described the use of inhaled nitric oxide in mechanically ventilated patients with COVID-19. Findings generally have been inconsistent, with some improvement in oxygenation reported in some studies and minimal to no improvement in others; various dosages of inhaled nitric oxide were used and patients were receiving other therapies confounding interpretation of the data. In a small cohort (n=6) of pregnant women with hypoxic respiratory failure secondary to COVID-19, intermittent twice-daily treatments with high-dose inhaled nitric oxide (160-200 ppm for 30 minutes to 1 hour administered to spontaneously breathing patients using a mask) improved systemic oxygenation. The decision to use a high dose of inhaled nitric oxide was based on prior reports showing broad antimicrobial effects of such high doses. However, fetal parameters and the development of acute kidney injury (a known complication of nitric oxide therapy) were not monitored. Results of a retrospective, single-center, observational study in intubated patients with COVID-19 and refractory hypoxemia did not show significant improvement in oxygenation metrics following treatment with inhaled epoprostenol or inhaled nitric oxide. In this study, 38 patients initially received inhaled epoprostenol (starting dose of 0.05 mcg/kg per minute, continued based on PaO₂ response); 11 patients who did not respond to epoprostenol were transitioned to inhaled nitric oxide (starting dose of 20 ppm, titrated up to 80 ppm).</td>
<td>In the Chen et al. study in severe SARS patients, nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) Dosages of inhaled nitric oxide used in patients with COVID-19 have varied. (See Trials or Clinical Experience.)</td>
<td>The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign recommend against the routine use of inhaled nitric oxide in mechanically ventilated adults with COVID-19 and ARDS. These experts state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; however, if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment.</td>
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In a report describing administration of inhaled nitric oxide (initial dose 30 ppm; mean duration of therapy 2.1 days) to 39 spontaneously breathing patients with laboratory-confirmed COVID-19 (29 were initially admitted to the general medical floor and 24 of these patients later required transfer to the ICU), approximately half of the patients did not require invasive mechanical ventilation after treatment. These findings suggest a role of inhaled nitric oxide in preventing progression of hypoxic respiratory failure; however, randomized controlled studies are needed.

In a single-center prospective study, 34 critically ill adults with COVID-19 received inhaled nitric oxide (10 ppm administered through the inspiratory limb of the ventilator tubing when \( \text{PaO}_2/\text{FiO}_2 < 150 \)). A response (defined as improvement in \( \text{PaO}_2/\text{FiO}_2 \) of >20% during the 30 minutes following administration) was achieved in 65% of the patients.

Nitric oxide may be included in some COVID-19 clinical trials registered at clinicaltrials.gov.

### Ruxolitinib (Jakafi®)

**Updated 1/29/21**

**10:00 Antineoplastic Agents**

Janus kinase (JAK) 1 and 2 inhibitor: 7 may potentially combat cytokine release syndrome (CRS) in severely ill patients 4, 5. May reduce inflammation via JAK inhibition, but study based on artificial intelligence (AI)-derived methodology suggests that clinically tolerated concentrations of ruxolitinib may be unlikely to reduce viral

Although some small studies have suggested possibility of benefit from ruxolitinib in patients with COVID-19, a placebo-controlled, phase 3 trial in patients with COVID-19-associated cytokine storm failed to confirm any clinical benefits.

**Single-hospital retrospective chart review:**

Based on the hospital's COVID-19 treatment algorithm, patients with severe COVID-19 were prospectively stratified using a newly developed clinical inflammation score (CIS; maximum score = 16); those identified as being at high risk for systemic

Various dosages are being evaluated 3, 10

**Phase 3 study (NCT04362137):** Ruxolitinib 5 mg orally twice daily for 14 days with possible extension to 28 days was ineffective. 10, 19

**Phase 3 study (NCT04377620):** Ruxolitinib 5 or 15 mg orally twice daily (approximately every 12 hours) is being studied. 12

**NIH COVID-19 Treatment Guidelines Panel recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial.** 8

**Severe reactions** requiring drug discontinuance observed in 2 COVID-19 patients following initiation of ruxolitinib: purpuric lesions with thrombocytopenia and deep-tissue infection in one patient, and progressive decrease in hemoglobin and erythrodermic rash over the whole body surface area in the
infectivity by disrupting regulators of endocytosis (e.g., AP2-associated protein kinase 1 [AAK1]).

Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19.\textsuperscript{5,7}

Trials or Clinical Experience

- Patients received ruxolitinib treatment; 14 patients received ruxolitinib (median cumulative dose: 135 mg [52.5-285 mg], median treatment duration: 9 days [5-17 days]) initiated at a median of 15.5 days (5-24 days) after symptom onset. A decrease in CIS of ≥25% from baseline to day 7 was observed in 12 of 14 patients. At baseline, 10 required noninvasive ventilation, 3 required supplemental oxygen, and 1 required invasive ventilation.\textsuperscript{14}

- Prospective, randomized, single-blind, placebo-controlled study in adults with severe COVID-19: Patients received ruxolitinib (5 mg orally twice daily) plus standard care (n = 20) or placebo (ascorbic acid 100 mg orally twice daily) plus standard care (n = 21); no significant difference observed between ruxolitinib and placebo in time to clinical improvement (defined as hospital discharge or a 2-point improvement on a 7-category ordinal scale) although median time to improvement was numerically shorter with ruxolitinib (12 vs 15 days). Chest CT improvement observed at day 14 in greater proportion of ruxolitinib-treated vs placebo-treated patients (90 vs 62%). By day 28, 3 patients had died (all 3 in placebo group). Note: Median time from symptom onset to randomization was 20 days; most patients in both treatment groups received systemic corticosteroids (71%) and antivirals (90%). Study excluded critically ill and ventilator-dependent patients. Interpretation is limited by small sample size.\textsuperscript{13}

- Compassionate use of ruxolitinib in mainly older adults with RT-PCR-confirmed COVID-19 with severe respiratory manifestations but not requiring invasive mechanical ventilation in Italy: Patients (n = 34) received ruxolitinib (5 mg twice daily, increased to 10 mg twice daily or 25 mg daily if respiratory function not improved); ruxolitinib was initiated at a median of 8 days after symptom onset; median dose was 20 mg daily and median treatment duration was 13 days. Median patient age was 80.5 years (53% were ≥80 years of age and 35% were 60-79 years of age); 85% of patients received systemic corticosteroids (71%) and antivirals (90%). Study excluded critically ill and ventilator-dependent patients. Interpretation is limited by small sample size.\textsuperscript{19}

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<th>Trials or Clinical Experience</th>
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<td>infectivity by disrupting regulators of endocytosis (e.g., AP2-associated protein kinase 1 [AAK1]).\textsuperscript{16} (See Baricitinib entry in this table.) Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19.\textsuperscript{5,7}</td>
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\textsuperscript{a}Dosage information is approximate and may vary based on specific patient needs and clinical decision-making.
had ≥2 comorbidities. Concomitant therapies included hydroxychloroquine (91%), antimicrobials (77%), antivirals (62%), and corticosteroids (29%). Cumulative incidence of clinical improvement (decrease of ≥2 categories on a 7-category ordinal scale within 28 days) was 82%; overall survival at day 28 was 94%. Clinical improvement was not affected by low-flow versus high-flow oxygen support but was less frequent in patients with PaO₂/FiO₂ ratio <200.17

**Compassionate use of ruxolitinib in combination with eculizumab** (a terminal complement inhibitor) in adults with RT-PCR-confirmed COVID-19 and associated pneumonia or acute respiratory distress syndrome (ARDS) in Italy: Consecutive patients received ruxolitinib (10 mg twice daily for 14 days) and eculizumab (900 mg IV once weekly for 2 or 3 doses) (n = 7) or best available therapy (n = 10; control). Greater improvement in median PaO₂ and PaO₂/FiO₂ ratio and greater increase in platelet count observed on day 7 in patients receiving ruxolitinib and eculizumab compared with control patients. All patients received antibiotic prophylaxis (azithromycin) and all patients except 2 in control group received hydroxychloroquine; greater proportion of patients in the ruxolitinib and eculizumab group compared with the control group received low-dose corticosteroids (5/7 vs 3/10) and sub-Q heparin (7/7 vs 5/10). Randomized, controlled trials needed to confirm these preliminary data.15

**Small retrospective cohort study of adults with RT-PCR-confirmed COVID-19 and associated ARDS**: Total of 18 patients with PaO₂/FiO₂ ratio of 100 to <200 and rapid clinical worsening of respiratory function received ruxolitinib (20 mg twice daily for initial 48 hours, with subsequent stepwise dosage reductions based on response, for a maximum of 14 days of treatment); ruxolitinib was initiated at a median of 9 days after symptom onset. Other therapies were used according to local practice. Clinical improvements in respiratory function within 48 hours and avoidance of mechanical ventilation reported in 16 patients;
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|         |            |           | spontaneous breathing with pO₂ >98% reported on day 7 in 11 patients; no response reported in 2 patients. No patients died.  
**Phase 3 randomized, double-blind, placebo-controlled, global clinical trial (NCT04362137; RUXCOVID) failed to confirm efficacy of ruxolitinib** in 432 patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Novartis/Incyte).  
1, 10, 19 Manufacturer announced results (not peer reviewed) indicating that ruxolitinib (5 mg orally twice daily for 14 days, with possible extension to 28 days) plus standard care did not reduce the proportion of patients experiencing severe complications (death, respiratory failure requiring mechanical ventilation, or ICU admission) by day 29, compared with standard care alone (12 vs. 11.8%); in addition, no clinically relevant benefits were observed among secondary or exploratory end points, including mortality rate by day 29 and time to recovery. 19  
**Phase 3, randomized, double-blind, placebo-controlled clinical trial (NCT04377620; RUXCOVID-DEVENT) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in patients ≥12 years of age with COVID-19-associated acute respiratory distress syndrome (ARDS) who require mechanical ventilation (sponsored by Incyte) 12**  
**Expanded-access (managed-access, compassionate use) program (NCT04337359)** available for eligible adults and children ≥6 years of age with **severe or very severe COVID-19** illness; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) 1,2  
**Expanded-access program (NCT04355793)** available for emergency treatment of **cytokine storm** from COVID-19 infection in adults and pediatric patients ≥12 years of age; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) 9  
Other clinical trials evaluating ruxolitinib in COVID-19 also may be registered at clinicaltrials.gov. 3 |
### Sarilumab (Kevzara®)

**Updated 2/11/21**

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<th>Drug(s)</th>
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<td>Sarilumab</td>
<td>92:36 Disease-modifying Anti-rheumatic Drug</td>
<td>Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Sarilumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients.</td>
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**Results** from randomized clinical trials evaluating efficacy of sarilumab in the treatment of patients with COVID-19 have been conflicting. Based on encouraging results in China with a similar drug, tocilizumab, a large, U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled, adaptively designed study (NCT04315298) evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 was performed. Patients in this study were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Randomization was stratified by severity of illness (e.g., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids. In the phase 2 part of the study, sarilumab at both dosages reduced C-reactive protein (CRP) levels. The primary efficacy outcome measure in phase 3 was the change on a 7-point scale; this phase was modified to focus on the 400-mg dose of sarilumab in the critically ill patient group. During the course of the trial, there were many amendments that increased the sample size and modified the dosing strategies, and multiple interim analyses were performed. The results did not demonstrate a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied.

A second manufacturer-sponsored phase 3 clinical trial was conducted in countries outside the U.S. (Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Spain) in 420 severely or critically ill patients hospitalized with COVID-19 who did not meet its primary endpoint and key secondary endpoint when sarilumab was compared with placebo in addition to usual hospital care. Although not statistically significant, trends were observed toward a decrease in duration of hospital stay, an acceleration in time to improved clinical outcomes, reduced mortality in the critically ill patient group not seen in the severely ill group, and a shortened time to discharge.

**Large US-based controlled study (NCT04315298):** Dosage of 400 mg IV as a single dose or multiple doses (based on protocol criteria); the lower-dose (200-mg) treatment arm was discontinued following a preliminary analysis of study results (see Trials or Clinical Experience).

In the REMAP-CAP trial, patients received a single 400-mg IV dose. Note: IV formulation not commercially available in the U.S., but was studied in the above-mentioned clinical trial. The sub-Q formulation is not FDA-labeled to treat cytokine release syndrome (CRS) in the U.S.

**NIH COVID-19 Treatment Guidelines** Panel has revised recommendations regarding the use of the IL-6 inhibitors tocilizumab and sarilumab in patients with COVID-19 based on results from REMAP-CAP and other trials. In patients who are within 24 hours of admission to the ICU and require invasive or non-invasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min oxygen flow), the Panel states that there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19. Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug. The Panel presented the following considerations:

1. In view of the results from the REMAP-CAP trial, some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure. However, too few patients in REMAP-CAP received sarilumab for the Panel to assess its efficacy in the treatment of patients who meet the above criteria.

2. In patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab or sarilumab for the treatment of COVID-19, except in a clinical trial.
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| **Multicenter, ongoing, international open-label trial (not peer reviewed) using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 immune modulation therapy domain, adults with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive either tocilizumab (353 patients; 8 mg/kg by IV infusion over 1 hour; dose may be repeated 12-24 hours later) or sarilumab (48 patients; single 400-mg dose by IV infusion over 1 hour) or standard care (402 patients; control group; corticosteroids were included as standard of care) within 24 hours of commencing organ support in an intensive care unit. Over 80% of the patients in the study received corticosteroids. The primary outcome was an ordinal scale combining in-hospital mortality and days free of organ support to day 21. Compared with standard care, treatment with sarilumab or tocilizumab decreased in-hospital mortality (mortality was 22% for sarilumab and 28% for tocilizumab vs 36% for the standard of care). Compared with standard of care, sarilumab and tocilizumab also improved in-hospital survival and increased the number of organ support-free days. 

**Italian case series (Benucci et al.)** describes 8 patients hospitalized with COVID-19 pneumonia at one hospital in Florence treated with sarilumab (initial 400-mg IV dose followed by 200-mg IV doses after 48 and 96 hours) in addition to standard therapy (hydroxychloroquine, azithromycin, darunavir, cobicistat, enoxaparin). Treatment was started within 24 hours of hospitalization. Sarilumab was used in these patients because of a lack of tocilizumab at this institution. Seven of the patients demonstrated an improvement in oxygenation and lung echo score and were discharged within 14 days; the remaining patient died in 13 days. |
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<td>Sirolimus (Rapamune®)</td>
<td>92:44</td>
<td>Immunosuppressive agent; mammalian target of rapamycin (mTOR) inhibitor</td>
<td>Clinical trials evaluating sirolimus for the treatment of COVID-19 are planned or underway including the following trials: NCT04341675 (SCOPE) NCT04374903 (COVID19-HOPE) NCT04461340 NCT04482712 (RAPA-CARDS)</td>
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<td>Although possible clinical application, current data not specific to COVID-19; additional study needed.</td>
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Various clinical trials evaluating sarilumab for the treatment of COVID-19 are registered at clinicaltrials.gov.

For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610).
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| Tocilizumab (Actemra®) | 92:36 Disease-modifying Anti-rheumatic Drug | Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients 1-3, 6, 9,10, 14 | **Results from randomized clinical trials evaluating efficacy of tocilizumab in the treatment of patients with COVID-19 have been conflicting.** 9, 15, 18, 21  
In preliminary data from a non-peer-reviewed, single-arm, observational Chinese trial (Xu et al.) involving 21 patients with severe or critical COVID-19 infection, patients demonstrated rapid fever reduction and a reduced need for supplemental oxygen within several days after receiving tocilizumab (initially given as a single 400-mg dose by IV infusion; this dose was repeated within 12 hours in 3 patients because of continued fever) 3  
In a retrospective, observational study in China (Luo et al.) involving 15 patients moderately to critically ill with COVID-19, tocilizumab (80-600 mg per dose) was given, and was used in conjunction with methylprednisolone in 8 of the patients. About one-third of the patients received 2 or more doses of tocilizumab. Elevated C-reactive protein (CRP) levels rapidly decreased in most patients following treatment, and a gradual decrease in IL-6 levels was noted in patients who stabilized following tocilizumab administration. Clinical outcomes were equivocal. 10 | Tocilizumab is typically given IV to treat cytokine release syndrome (CRS) and in patients with COVID-19; however, the drug has been given subcutaneously in some patients 9, 17  
The subcutaneous formulation of tocilizumab is not intended for IV use 9  
**In the REMAP-CAP trial, patients received a single dose of 8 mg/kg based on actual body weight (up to a maximum of 800 mg) by IV infusion; this dose could be repeated 12-24 hours later at the discretion of the treating clinician 21**  
**Based on the results from the REMAP-CAP trial, some members of the NIH COVID-19 Treatment Guidelines Panel would administer a single 8-mg/kg dose of tocilizumab by IV infusion (up to a maximum of 800 mg) in addition to dexamethasone 4**  
US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA): Evaluated an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose was given if symptoms worsened or showed no improvement 8, 18  
1) In view of the results from the REMAP-CAP trial, some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure. However, too few patients in | **NIH COVID-19 Treatment Guidelines Panel has revised recommendations regarding the use of the IL-6 inhibitors tocilizumab and sarilumab in patients with COVID-19 based on results from REMAP-CAP and other trials. In patients who are within 24 hours of admission to the ICU and require invasive or non-invasive mechanical ventilation or high-flow oxygen (>0.4 FiO2/30 L/min oxygen flow), the Panel states that there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19. Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug. The Panel presented the following considerations:** 3 |
A single-center, retrospective observational study of 20 kidney transplant recipients in Italy with COVID-19 hospitalized for pneumonia included 6 patients who received tocilizumab. Half of the patients experienced reduced oxygen requirements and 2 (33%) showed improved radiologic findings following administration; 2 (33%) of the 6 tocilizumab-treated patients died.  

**Italy:** A prospective, open, single-arm, multicenter study evaluated use of tocilizumab in 63 hospitalized adults with severe COVID-19. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg) based on drug availability; a second dose given within 24 hours was administered to 52 of the 63 patients. Following tocilizumab administration, fevers resolved in all but one patient within 24 hours and C-reactive protein (CRP), ferritin, and D-dimer levels declined from baseline to day 14. The PaO2/FiO2 ratio improved between admission and Day 7. Overall mortality was 11%. Tocilizumab appeared to be well tolerated.  

Zhang et al. from China reported on a patient with COVID-19 and multiple myeloma who appeared to be successfully treated with tocilizumab.  

**France:** An investigator-initiated, multicenter, open-label, randomized clinical trial (CORIMUNO-TOCI, NCT04331808) evaluated tocilizumab in patients hospitalized at Assistance Publique – Hôpitaux de Paris hospitals in Paris. Sixty-four out of 131 adults with moderate to severe COVID-19 pneumonia not requiring intensive care upon admission were randomized to receive tocilizumab 8 mg/kg (1–2 doses) along with standard of care, and 67 patients were randomized to receive standard of care alone. Tocilizumab did not reduce scores on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) to <5 on day 4 but may have reduced the risk of noninvasive ventilation, mechanical ventilation, or death by day 14. No difference in day 28 mortality was found.  

**US/Global randomized, placebo-controlled trial:** Manufacturer (Roche) conducted a randomized, double-blind, placebo-controlled trial using tocilizumab. The Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial used a single 8-mg/kg IV dose (up to a maximum dose of 800 mg).  

REMAP-CAP received sarilumab for the treatment of patients who met the above criteria.  

2) In patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab or sarilumab for the treatment of COVID-19, except in a clinical trial.  

The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study.
controlled phase 3 trial (COVACTA; NCT04320615) in collaboration with the US Health and Human Services’ Biomedical Advanced Research Development Authority (BARDA). The study evaluated safety and efficacy of tocilizumab in combination with standard of care compared with placebo in adults hospitalized with severe COVID-19 pneumonia. The trial failed to meet its primary endpoint of improved clinical status at week 4 (determined using a 7-point scale to assess clinical status based on need for intensive care and/or ventilator use and requirement for supplemental oxygen) and several key secondary endpoints, including the key secondary endpoint of reduced patient mortality.18

Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial: In this investigator-driven, randomized, placebo-controlled trial (NCT04356937), 243 adults with confirmed severe COVID-19, hyperinflammatory states, and at least 2 of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or need for supplemental oxygen in order to maintain \( \text{SpO}_2 >92\% \) were randomly assigned in a 2:1 ratio to receive standard care plus a single IV dose of either tocilizumab (8 mg/kg) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. Secondary efficacy outcomes were clinical worsening and discontinuation of supplemental \( \text{O}_2 \) among patients who had been receiving it at baseline, both assessed in time-to-event analyses. 58% of the enrolled patients were men, median age was 59.8 years (range: 21.7 to 85.4 years), and 45% of patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group compared with the placebo group was 0.83 (\( P = 0.64 \)), and the hazard ratio for disease worsening was 1.11 (\( P = 0.73 \)). At 14 days, 18% of the pts in the tocilizumab group and 14.9% of those in the placebo group had worsening of disease. Median time to discontinuation of supplemental \( \text{O}_2 \) was 5 days in the tocilizumab group and 4.9 days in the placebo group (\( P = 0.69 \)). At 14 days, 24.6% of patients in the tocilizumab group and 21.2% of those in the placebo group were still
receiving supplemental O₂. Patients who received tocilizumab had fewer serious infections than patients who received placebo. Tocilizumab was not found to be effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 in this study. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide.¹⁵

** Multicenter, ongoing, international open-label trial (not peer reviewed) using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 immune modulation therapy domain, adults with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive either tocilizumab (353 patients; 8 mg/kg by IV infusion over 1 hour; dose may be repeated 12-24 hours later) or sarilumab (48 patients; single 400-mg dose by IV infusion over 1 hour) or standard care (402 patients; control group; corticosteroids were included as standard of care) within 24 hours of commencing organ support in an intensive care unit. Over 80% of the patients in the study received corticosteroids. The primary outcome was an ordinal scale combining in-hospital mortality and days free of organ support to day 21. Compared with standard care, treatment with sarilumab or tocilizumab decreased in-hospital mortality (mortality was 22% for sarilumab and 28% for tocilizumab vs 36% for the standard of care). Compared with standard of care, sarilumab and tocilizumab also improved in-hospital survival and increased the number of organ support-free days.⁹,¹⁰

Various clinical trials valuating tocilizumab for the treatment of COVID-19 are registered at clinicaltrials.gov.⁵

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Vitamin D  
*Updated 1/28/21* | 88:16 Vitamin D | Vitamin D receptor is expressed on immune cells (e.g., B cells, T cells, antigen-presenting cells); these cells can synthesize and respond to active vitamin D. 10, 11  
Vitamin D modulates innate and adaptive immune responses; may downregulate proinflammatory cytokines and upregulate anti-inflammatory cytokines, increase T regulatory cell activity, and reduce cytokine storm induced by innate immune system. 10, 12, 13 | Only limited prospective clinical trial evidence regarding efficacy of vitamin D supplementation for treatment or prevention of COVID-19.  
**Prevention of respiratory infections:** Efficacy of vitamin D supplementation for prevention of influenza or other respiratory infections is unclear. 15  
Meta-analysis of 25 randomized, double-blind, placebo-controlled trials including a total of 11,321 participants, either healthy or with comorbidities, indicated a protective effect for oral vitamin D supplementation against acute respiratory infection. 5  
A second systematic review and meta-analysis of 15 randomized controlled trials involving approximately 7000 healthy individuals found that vitamin D supplementation did not reduce the risk of respiratory infections compared with placebo or no treatment. 11  
**Outcomes in critically ill patients:** Results of 2 randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with vitamin D deficiency (but not with COVID-19) indicated that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D3; patients in VITdAL-ICU also received oral maintenance doses (90,000 units monthly for 5 months). 6, 7 | Various dosages of vitamin D are being evaluated for prevention or treatment of COVID-19. 4  
High concentrations of vitamin D may cause hypercalcemia and nephrocalcinosis; 1 currently no convincing scientific evidence that very high intake of vitamin D will be beneficial in preventing or treating COVID-19. 14  
**NIH COVID-19 Treatment Guidelines Panel** states that there are insufficient data to recommend either for or against use of vitamin D for prevention or treatment of COVID-19. 1  
Joint guidance from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF), and International Osteoporosis Foundation (IOF) emphasizes importance of obtaining the recommended daily dosage of vitamin D; for those unable to obtain recommended durations of direct sun exposure during the pandemic, recommended intake of vitamin D can be obtained through supplemental vitamin D. The joint guidance states that current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19. 2  
Advisory statement from the UK National Institute for Health and Care Excellence (NICE) states that there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. However, all individuals should continue to follow current recommendations on daily vitamin D supplementation to maintain bone and muscle health during the pandemic. 5 |

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Vitamin D deficiency also is more common in older patients and patients with obesity and hypertension (factors potentially associated with worse COVID-19 outcomes).\(^1, 20, 21, 23-25, 27\)

Association also suggested between vitamin D and diabetes mellitus (a condition also associated with worse COVID-19 outcomes).\(^20, 22, 27\)

Clinical trials are evaluating the relationship between vitamin D concentration and COVID-19 disease severity and mortality (e.g., NCT04394390, NCT04403932, NCT04487951, NCT04628000);\(^4\) some retrospective observational data suggest an association between vitamin D concentration and COVID-19 risk or severity/mortality,\(^15-18, 28, 29, 32\) but may not account for potential confounding factors.\(^17-19, 29\)

Meta-analysis of 26 observational studies reporting vitamin D concentrations in adults and elderly patients with COVID-19 suggested an association between vitamin D deficiency and COVID-19 severity; however, potential for bias in most of the studies was considered high.\(^36\)

Prospective observational study in non-elderly adults admitted to a COVID-19 care center indicated higher prevalence of vitamin D deficiency (defined as serum 25-hydroxyvitamin D concentration <20 ng/mL) on admission (97 versus 32%) in patients with severe COVID-19 disease.

Supplemental oral vitamin D (single 80,000-unit dose) given shortly after COVID-19 diagnosis (n = 16) did not improve outcomes.\(^35\)

**Randomized, open label, pilot study in hospitalized adults with confirmed COVID-19:** Total of 76 patients were randomized 2:1 to receive oral calcifediol (0.532 mg on day of admission, then 0.266 mg on days 3 and 7 followed by 0.266 mg weekly until discharge or ICU admission) in conjunction with standard care (including 6-day hydroxychloroquine regimen and 5-day azithromycin regimen) or standard care alone (control). ICU admission was reported for 1/50 calcifediol-treated patients (2%) and 13/26 control patients (50%). All calcifediol-treated patients were discharged; 24 control patients were discharged and 2 died. The odds ratio for ICU admission in calcifediol-treated patients vs control patients was 0.02; odds ratio was 0.03 after adjustment for the higher prevalence of hypertension and type 2 diabetes mellitus in the control group. Data on serum vitamin D concentrations were not available. Larger placebo-controlled trials with well-matched groups are needed to confirm these pilot results.\(^33\)

**Randomized, double-blind, placebo-controlled trial (NCT04449718; not peer reviewed)** in 240 hospitalized adults with severe COVID-19: Vitamin D supplementation (single oral 200,000-unit dose of cholecalciferol) increased 25-hydroxyvitamin D concentrations but failed to improve clinical outcomes compared with placebo. No significant differences in duration of hospital stay (7 vs 7 days), mortality rate (7 vs 5.1%), ICU admission (15.8 vs 21.2%), or need for mechanical ventilation (7 vs 14.4%) were observed between the vitamin D and placebo groups, respectively. Mean baseline 25-hydroxyvitamin D concentration was approximately 21 ng/mL in both groups. Following the intervention, 86.7% of vitamin D recipients vs 10.9% of placebo recipients had 25-hydroxyvitamin D concentrations >30 ng/mL, and 6.7% of vitamin D recipients vs 51.5% of placebo recipients had 25-hydroxyvitamin D deficiency (concentration <20 ng/mL).\(^38\)
requiring ICU admission (n = 63) compared with asymptomatic, SARS-CoV-2-positive patients admitted to isolation ward (n = 91); inflammatory markers (ferritin, interleukin-6) were elevated in vitamin D-deficient versus non-deficient patients.  

Results of a Mendelian randomization study (not peer reviewed) do not support a protective role for increased 25-hydroxyvitamin D concentrations with respect to COVID-19 outcomes and may suggest harm. The study used genetic determinants of serum 25-hydroxyvitamin D from a genome-wide association study and meta-analysis of >443,734 individuals of European ancestry to estimate the effect of increased 25-hydroxyvitamin D concentrations on COVID-19 susceptibility and severity. Genetically increased concentrations of the vitamin had no clear effect on susceptibility, but tended to increase the odds ratio of hospitalization (2.34) and severe disease requiring hospitalization and respiratory support (2.21). Some analyses suggested worse outcome with increasing concentrations of the vitamin.  

Other clinical trials are evaluating effects of vitamin D supplementation on COVID-19-associated clinical outcomes, including NCT04344041, NCT04386850, NCT04407286, NCT04482673, NCT04435119, NCT04411446, NCT04552951, NCT04502667, and NCT04621058.  

Clinical trials also are evaluating efficacy of vitamin D supplementation for prevention of COVID-19, including NCT04386850, NCT04482673, NCT04535791, and NCT04579640.  

Results of a Mendelian randomization study (not peer reviewed) do not support a protective role for increased 25-hydroxyvitamin D concentrations with respect to COVID-19 outcomes and may suggest harm. The study used genetic determinants of serum 25-hydroxyvitamin D from a genome-wide association study and meta-analysis of >443,734 individuals of European ancestry to estimate the effect of increased 25-hydroxyvitamin D concentrations on COVID-19 susceptibility and severity. Genetically increased concentrations of the vitamin had no clear effect on susceptibility, but tended to increase the odds ratio of hospitalization (2.34) and severe disease requiring hospitalization and respiratory support (2.21). Some analyses suggested worse outcome with increasing concentrations of the vitamin.  

Clinical trials also are evaluating efficacy of vitamin D supplementation for prevention of COVID-19, including NCT04386850, NCT04482673, NCT04535791, and NCT04579640.  

Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day  

Some clinicians have recommended an elemental zinc intake of 30-50 mg/day in the short-term treatment of influenza and coronavirus infections.  

Despite some anecdotal claims in the media that zinc is effective in treating COVID-19, it is unclear whether zinc supplementation is beneficial in the prophylaxis and/or treatment of COVID-19; further study is needed. NIH COVID-19 Treatment Guidelines Panel states that there are insufficient
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<td>Zinc deficiency increases proinflammatory cytokine concentrations (interleukin-1 [IL-1], IL-6, TNF alpha) and decreases antibody production; zinc supplementation increases the ability of polymorphonuclear cells to fight infection.</td>
<td>Combination with other supplements (including vitamin C, vitamin D, and selenium) and drugs (including hydroxychloroquine).</td>
<td>Appropriate dosage regimen not established in either the prophylaxis or treatment of COVID-19; various supplementation regimens being evaluated in clinical trials, with a maximum dosage of zinc sulfate of 220 mg (50 mg of elemental zinc) twice daily.</td>
<td>Oral zinc supplementation likely safe in dosages up to 40 mg of elemental zinc daily in adults; safety of dosages exceeding those used in the management of the common cold not known.</td>
<td>Clinical data to recommend either for or against use of zinc in the treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel recommends against using zinc supplementation above the RDA for the prevention of COVID-19, except in a clinical trial.</td>
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<td>Possible antiviral activity; zinc appears to inhibit virus RNA polymerase activity and viral replication in an in vitro and cell culture model of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1).</td>
<td>High-dose zinc supplementation reduced the duration but not severity of common cold symptoms compared with placebo in a meta-analysis.</td>
<td>Retrospective observational study in New York City (Carlucci et al; non-peer-reviewed): Data were collected from electronic medical records to compare outcomes between hospitalized patients with COVID-19 who received hydroxychloroquine, azithromycin, and zinc (411 patients) and those who received hydroxychloroquine and azithromycin alone (521 patients). Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or duration of ICU stay, but patients in the treatment group that included zinc were discharged home more frequently and the need for ventilation, ICU admission, and mortality or transfer to hospice for patients not admitted to the ICU were all reduced in univariate analyses. After adjusting for the timing of when zinc was added to the protocol, findings remained significant for increased frequency of being discharged home and reduction in mortality or transfer to hospice in the zinc-treated patients. Because of the study design and its limitations, the authors state that this study should not be used to guide clinical practice, but that the observations do support initiation of randomized controlled trials investigating zinc in patients with COVID-19.</td>
<td>Appropriate clinical data to recommend either for or against use of zinc in the treatment of COVID-19.</td>
<td>Adverse effects may include nausea (possibly dose dependent), vomiting, and changes in taste. Long-term zinc supplementation may cause copper deficiency with adverse hematologic and neurologic effects; zinc supplementation for as little as 10 months has been associated with copper deficiency. Intranasal administration should be avoided because of reports of prolonged or permanent loss of the sense of smell; intranasal zinc formulations are no longer commercially available in the US. Potential for interactions with iron and copper, certain antibiotics (e.g., quinolones, tetracyclines), and other medications.</td>
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<td>ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)</td>
<td>24:32 Renin-Angiotensin-Aldosterone System Inhibitor</td>
<td><strong>Hypothetical harm:</strong> Human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2). Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs. Increased expression of ACE2 may potentially facilitate COVID-19 infections. <strong>Hypothetical benefit:</strong> ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.</td>
<td>Only limited data available to date evaluating the effect of these drugs on COVID-19 infection. Large, observational study analyzed a cohort of pts tested for COVID-19 to evaluate the relationship between previous treatment with 5 common classes of antihypertensive agents (including ACE inhibitors, ARBs) and the likelihood of a positive or negative test result for COVID-19 as well as the likelihood of severe COVID-19 illness among pts who tested positive: Study included data obtained from a large health network in New York City for 12,594 pts who were tested for COVID-19 from Mar 1 to Apr 15, 2020. Among these pts, 4357 (34.6%) had a history of hypertension. Of these patients, 2573 (59.1%) tested positive for COVID-19. Among the 2573 pts with hypertension and positive results for COVID-19, 634 pts (24.6%) had severe disease (i.e., indicated by ICU admission, mechanical ventilation, or death). Results of COVID-19 testing were stratified in propensity-score-matched patients with hypertension according to previous treatment with selected antihypertensive agents. Propensity-score matching was based on age, sex, race, BMI, medical history, various comorbidities, and other classes of medications. The authors stated that no substantial increase was observed in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive in association with any single antihypertensive class (including ACE inhibitors, ARBs). <strong>Large, population-based case-control study was conducted to evaluate the association between the use of RAAS blockers (including ACE inhibitors, ARBs) and the risk of COVID-19:</strong> Study included data obtained from a regional healthcare database in the Lombardy region of Italy for 6272 case pts with confirmed severe COVID-19 acute respiratory syndrome from Feb 21 to Mar 11, 2020 who were matched to 30,759 controls based on sex,</td>
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American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) recommend continuation of treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents. These experts state there is a lack of experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients receiving ACE inhibitors or ARBs. Further study is needed. NIH COVID-19 Treatment Guidelines Panel states patients who are receiving an ACE inhibitor or ARB for cardiovascular disease (or other indications) should continue receiving these drugs. The panel recommends against use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial. These experts state there is a lack of sufficient clinical evidence demonstrating that ACE inhibitors or ARBs have any impact on the susceptibility of individuals to SARS-CoV-2 or on the severity or outcomes of COVID-19 infection. Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections. Abrupt withdrawal of RAAS inhibitors in high-risk patients (e.g., heart failure patients, patients with prior myocardial infarction) may lead to clinical instability and adverse health outcomes.

Updated 2/11/21
Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to evaluate the relationship between cardiovascular disease and preexisting treatment with ACE inhibitors or ARBs with COVID-19 (Mehra et al; now retracted): Original publication included multinational data for 8910 pts hospitalized with COVID-19 between Dec 20, 2019 and Mar 15, 2020 that were obtained from a global healthcare data collaborative. The authors concluded that those data confirmed previous observations suggesting that underlying cardiovascular disease is independently associated with an increased risk of death in hospitalized pts with COVID-19. They also stated that they were not able to confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital mortality. 10 Note: This published study has now been retracted by the publisher at the request of the original authors. Concerns were raised with respect to the veracity of the data and analyses that were the basis of the authors' conclusions. 11,12

Multicenter, prospective study in a cohort of hospitalized pts with confirmed COVID-19 infection to evaluate the association of antihypertensive therapy with ACE inhibitors or ARBs and the risk of severe COVID-19 or worsening of clinical outcomes (NCT04357535; Hakeam et al): Data are...
available for 338 patients from 4 hospitals in Saudi Arabia. On the day of hospital admission, 245 of these patients (72.5%) were receiving ACE inhibitors or ARBs; 197 of these patients continued such antihypertensive therapy during hospitalization. On the day of hospital admission, 93 patients (27.5%) were receiving antihypertensive therapy (e.g., calcium-channel blockers, β-blockers, thiazide diuretics) that did not include either ACE inhibitors or ARBs. The primary study end point was the rate of developing severe COVID-19 on the day of hospitalization. The key secondary end point was a composite of mechanical ventilation and in-hospital mortality. In the study cohort, 98 patients (29%) met the WHO criteria for severe COVID-19 on the day of hospitalization. However, use of ACE inhibitors or ARBs was not associated with development of severe COVID-19 (odds ratio: 1.17). Use of ACE inhibitors or ARBs prior to hospitalization also was not associated with ICU admission, mechanical ventilation, or in-hospital mortality. In addition, continuing such antihypertensive therapy during non-ICU hospitalization was associated with decreased mortality (odds ratio: 0.22). The authors concluded that patients with hypertension or cardiovascular disease receiving therapy with ACE inhibitors or ARBs prior to hospitalization for COVID-19 do not appear to be at increased risk for severe infection upon hospital admission. In addition, ICU admission, mechanical ventilation, and mortality are not associated with use of ACE inhibitors or ARBs prior to hospitalization. Because of a lower risk of mortality, the authors advise that ACE inhibitor or ARB therapy be continued in pts with COVID-19 during hospitalization. However, because of study limitations, randomized controlled trials are needed for further assessment of the effects of ACE inhibitors or ARBs on COVID-19.

** Multicenter, open-label, randomized study in hospitalized pts with mild to moderate COVID-19 to evaluate the effect of discontinuation versus continuation of ACE inhibitors or ARBs on clinical outcomes (NCT04364893; Lopes et al): Data are available for 659 adults from 29...
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<td>hospitals in Brazil who were receiving ACE inhibitors or ARBs prior to hospitalization. In the primary analysis, 334 of these patients were randomized to discontinue ACE inhibitors or ARBs and 325 patients were assigned to continue use of such medication for 30 days. The primary study end point was the number of days alive and out of the hospital from randomization through 30 days. Key secondary end points included death during the 30-day follow-up period, cardiovascular death, and COVID-19 progression. No significant difference was observed in the mean number of days alive and out of the hospital for patients in the discontinuation group (21.9 days) compared with patients in the continuation group (22.9 days). There were also no significant differences between the discontinuation and the continuation groups in the incidence of death (2.7 versus 2.8%, respectively), cardiovascular death (0.6 versus 0.3%, respectively), or COVID-19 progression (38.3 versus 32.3%, respectively). The authors concluded that these findings do not support the routine discontinuation of ACE inhibitors or ARBs among hospitalized patients with mild to moderate COVID-19 when there is an indication for such use. Limitations of this trial include the open-label study design and the lack of generalizability of results to COVID-19 patients in other settings. The study also was not designed to evaluate the effect of ACE inhibitors or ARBs on susceptibility to COVID-19.</td>
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<td>Clinical trials underway (losartan): Initiation of losartan in adults with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009).</td>
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<td>Initiation of the drug in adults with COVID-19 not requiring hospitalization; primary outcome measure: treatment failure resulting in hospital admission (NCT04311177).</td>
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<td>Other clinical trials evaluating the effect of continuing or discontinuing treatment with ACE inhibitors or ARBs on clinical outcomes in patients with COVID-19 are registered at clinicaltrials.gov.</td>
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<td>Anticoagulants</td>
<td>20:12.04 Anti-coagulants</td>
<td>Patients with COVID-19, particularly those with severe disease, may develop a hypercoagulable state, which can contribute to poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).</td>
<td>Limited data from a retrospective study in China showed reduced mortality in COVID-19 patients with severe sepsis-induced coagulopathy or markedly elevated D-dimer levels (&gt;6 x ULN) who received prophylactic anticoagulation (low molecular weight heparin [LMWH] or unfractionated heparin [UFH]).</td>
<td>See Comments column for available dosage-related information.</td>
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**Pathogenesis of COVID-19-related coagulopathy not completely known, but may be associated with endothelial cell activation and other factors contributing to an uncontrolled immunothrombotic response to the virus.**  
Lupus anticoagulants have not been detected in some patients with COVID-19 who present with prolonged aPTT, but should be interpreted with caution because of a high rate of false positive test results. Whether these antibodies play a role in the pathogenesis of COVID-19 thrombosis is not known.

The available evidence to inform the clinical management of COVID-19-associated coagulopathy is continuously evolving.

Several organizations (e.g., NIH, WHO, CDC, American Society of Hematology, International Society for Thrombosis and Haemostasis, Anticoagulation Forum, Mayo Clinic) have published interim guidance for anticoagulation management in patients with COVID-19.

These experts agree that hospitalized patients with COVID-19 should receive prophylactic-dose anticoagulation for the prevention of VTE unless there are contraindications.

However, many questions remain unanswered (e.g., type and intensity of anticoagulation, duration of anticoagulation, use of biomarkers for VTE risk stratification) because of lack of evidence from randomized controlled trials.

VTE risk should be assessed in all hospitalized patients with COVID-19.

While initial reports suggested that bleeding is infrequent in COVID-19 patients, more information regarding the risk of bleeding is emerging.

Standard risk factors for bleeding should be considered and patients should be individually assessed to balance risk of thrombosis with risk of bleeding.

The NIH COVID-19 Treatment Guidelines Panel recommends prophylactic-dose anticoagulation for VTE prophylaxis in all hospitalized adults with COVID-19 unless contraindicated. In pregnant patients hospitalized with severe COVID-19, prophylactic-dose anticoagulation is recommended if there are no contraindications to its use; if antithrombotic therapy is prescribed prior to the diagnosis of COVID-19 in a pregnant patient, such therapy should be continued. For hospitalized children with COVID-19, indications for VTE prophylaxis should be considered and patients should be individually assessed to balance risk of thrombosis with risk of bleeding.

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Such thrombotic findings are the basis for anticoagulant therapy in COVID-19 patients; some anticoagulant agents also may have antiviral and anti-inflammatory properties. Without severe disease were initiated on standard-dose VTE prophylaxis, while those with severe disease (defined as requiring ICU-level care or D-dimer level greater than 2.5 mg/L FEU and without indications for therapeutic anticoagulation) were considered for escalated-dose thromboprophylaxis (enoxaparin 0.5 mg/kg twice daily or heparin IV infusion titrated to anti-factor Xa levels 0.3-0.5 U/mL in patients with renal failure). The observed rates of VTE (7.3%) and overall thromboembolic events (12%) were lower in this study compared with earlier reported rates, which the authors suggest may be related to early implementation of an escalating thromboprophylactic strategy.

Another retrospective study evaluated the impact of a tailored anticoagulant approach (risk stratification based on D-dimer and other clinical and laboratory parameters) in COVID-19 patients admitted to the ICU. Standard anticoagulant prophylaxis was used in 83 patients (44%); high-intensity prophylaxis was used in 75 patients (40%); therapeutic anticoagulation was used in 24 patients (12.8%) who had confirmed or clinical suspicion of VTE. The overall rate of thrombotic events in this study was 12.2%, which the authors state is lower than previously reported with severe COVID-19 in the ICU. Major bleeding occurred in 2.7% of patients who received the high-intensity prophylactic regimen and in 21% of patients who received therapeutic anticoagulation.

In a small (n=20), open-label, phase 2 study, administration of therapeutic-dose enoxaparin in mechanically ventilated COVID-19 patients was associated with improved oxygenation (PaO₂/FiO₂ ratio), decreased D-dimer levels, and a higher rate of successful liberation from mechanical ventilation compared with prophylactic-dose anticoagulation. The study was insufficiently powered to assess mortality.

In a single-center retrospective study that evaluated bleeding rates in adults with COVID-19 who received different dose levels of anticoagulation, use of therapeutic-

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### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage | Comments
---|---|---|---|---|---

**Dosage**

- LMWH is generally preferred for VTE prophylaxis; however, specific drug characteristics (e.g., pharmacokinetics, route of administration, drug interaction potential), patient-specific factors (e.g., renal function), and practical concerns (e.g., need for frequent monitoring, convenience of administration, risk of medical staff exposure) may influence choice of anticoagulant. There is currently debate about the appropriate intensity of anticoagulation for VTE prevention in COVID-19 patients. Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, some clinicians suggest a more aggressive anticoagulation strategy using intermediate or therapeutic dosages of anticoagulants in such patients; however, current data is limited (see Trials or Clinical Experience Column) and well-designed randomized controlled studies are needed to evaluate these approaches.

- Based on expert opinion, the Anticoagulation Forum suggests increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, heparin 7500 units sub-Q 3 times daily, or low-intensity heparin infusion) for critically ill patients (e.g., in the ICU) with confirmed or suspected COVID-19.

- More recent guidelines issued by the American Society of Hematology discourages the empiric use of therapeutic-dose anticoagulation in COVID-19 patients without any other indication for therapeutic anticoagulation outside a clinical trial.
Dose anticoagulation was significantly associated with an increased risk of major bleeding.\(^6\)

In another single-center retrospective study, empiric treatment with therapeutic-dose anticoagulation in COVID-19 patients admitted to the ICU provided no mortality benefit over standard prophylaxis and was associated with an increased risk of clinically significant adverse effects.\(^6\)

All of the currently available studies assessing various anticoagulant types and dosing in COVID-19 patients have important limitations such as their retrospective nature, small sample size, confounding variables (e.g., other treatments administered), and lack of information and consistency with regard to anticoagulation indication, doses, and regimens.\(^28, 31, 38, 40, 42, 44, 45, 50, 52, 61, 62\)

A meta-analysis performed by the American Society of Hematology found no difference in risk of VTE and mortality between patients treated with prophylactic dose anticoagulation and those treated with higher doses of anticoagulation; critically ill patients who received intermediate- or therapeutic-dose anticoagulation had lower odds of PE (OR 0.09) but higher odds of major bleeding (OR 3.84).\(^28\)

NIH is evaluating safety and efficacy of various anticoagulants for the treatment and prevention of COVID-19-associated coagulopathy in a series of adaptive platform trials (The Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV] studies). The trials will evaluate anticoagulants in different patient populations including outpatient, inpatient, and convalescent.\(^41\)

As of December 21, 2020, enrollment of patients requiring ICU-level care (defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or ECMO support) in 3 multiplatform trials (REMAP-CAP, AT-TACC, ACTIV-4A) was paused due to interim pooled analysis demonstrating futility of

NIH states that there are currently insufficient data to recommend for or against the use of therapeutic anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial setting.\(^28\)

Extended VTE prophylaxis after hospital discharge is not routinely recommended in patients with COVID-19, but may be considered based on the same protocols and risk-benefit analysis as for patients without COVID-19.\(^15, 27, 28, 30, 32\)

Although a relationship between markedly elevated D-dimer levels and mortality has been shown, whether this can be applied to predicting or managing VTE risk is not known.\(^5, 6, 7, 30, 32, 33\)
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<td>therapeutic-intensity anticoagulation in reducing the need for organ support compared with standard-dose prophylaxis. A potential for harm cannot be excluded in this group of patients since increased bleeding is a known complication of high-dose anticoagulation. $^4$ $^5$ $^8$ Enrollment is continuing for hospitalized patients who do not require ICU support in these trials to determine whether there is any benefit from full-dose anticoagulation. $^5$ $^8$ NIH has reported interim results of the above multiplatform trials in the moderately ill cohort. Based on data collected from more than 1000 moderately ill hospitalized patients with COVID-19 (identified as those not in the ICU and not receiving organ support such as mechanical ventilation at trial enrollment), preliminary findings showed that full-dose anticoagulation was superior to prophylactic doses in reducing the need for ventilation or other organ support. $^6$ $^3$ Full results of the study are required for complete analysis of these findings. Additional clinical trials have been initiated or currently are underway to evaluate anticoagulant strategies in patients with COVID-19, including the following: $^{12}$ $^{43}$ $^{47}$ NCT04512079 (FREEDOM), NCT04406389 (IMPACT), NCT04362085, NCT04486508 (INSPIRATION), NCT04373707 (COVI-DOSE), NCT04372589 (ATTACC), NCT04345848 (COVID-HEP), NCT04416048 (COVID-PREVENT), NCT04367831 (IMPROVE), NCT04377997, NCT04354155 (COVAC-TP), NCT04394377 (ACTION), NCT04360824, NCT04444700 (RAPID-BRAZIL), NCT04466670, NCT04401293, NCT04393805 (HETHICO)</td>
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COVID-19 Convalescent Plasma

**Updated 2/11/21**

Plasma obtained from patients who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2 may provide short-term passive immunity to the virus; theoretically, such immunity may prevent or contribute to recovery from the infection, possibly as the result of viral neutralization and/or other mechanisms. 1,5,24,25

Convalescent plasma therapy has been used in the treatment of other viral diseases with various degrees of success. 16,20,22,24,25

In patients with SARS-CoV-1 infection, use of convalescent plasma was reported to shorten the duration of hospitalization and decrease mortality. 6-8,24 SARS patients who received convalescent plasma less than 14 days after onset of symptoms had better outcomes than those who received such plasma later in the course of the disease. 1,2,6-8

Although data are available from multiple studies evaluating use of COVID-19 convalescent plasma, many of these are nonrandomized, uncontrolled, observational, or retrospective studies in patients receiving multiple other treatments. 5,20-29,52 While there is some evidence suggesting possible benefits of COVID-19 convalescent plasma in the treatment of COVID-19, the specific role of convalescent plasma is unclear and additional data are needed from well-controlled, adequately powered, randomized clinical trials. 24,25

Study with retrospectively matched control in US (Liu et al): Preliminary (non-peer-reviewed) data from a study of 39 hospitalized adults with severe to life-threatening COVID-19 who received ABO-compatible COVID-19 convalescent plasma (2 units [total volume approximately 500 mL] infused IV over 1-2 hours), obtained from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 or greater, suggest that stable or improved supplemental oxygen requirements by post-transfusion day 14 were more likely in these convalescent plasma recipients than in the matched control group not treated with convalescent plasma (odds ratio: 0.86); this effect appeared to be confounded by use of therapeutic anticoagulants, but not by other types of drugs (i.e., azithromycin, broad-spectrum antibiotics, hydroxychloroquine, corticosteroids, antivirals, interleukin-1 [IL-1] and IL-6 inhibitors) or duration of symptoms before admission. Overall, survival was improved in patients in the convalescent plasma group compared to the control group; after adjusting for covariates, data suggest a significant improvement in survival in non-intubated patients (hazard ratio: 0.19) receiving convalescent plasma, but not in the small cohort of intubated patients (hazard ratio: 1.24). Subgroup analyses suggested a survival benefit of convalescent plasma among nonintubated patients, in those who received treatment earlier in the course of disease, and those who received therapeutic anticoagulation. No significant transfusion-related morbidity or mortality was observed in patients receiving convalescent plasma. 52

**Emergency use authorization (EUA) high-titer COVID-19 convalescent plasma dosage and administration for hospitalized patients and those with impaired humoral immunity:** Consider initiating therapy with one high-titer unit (approximately 200 mL) of COVID-19 convalescent plasma given IV through a peripheral or central venous catheter according to standard institutional transfusion guidelines. Additional high-titer COVID-19 convalescent plasma units may be administered based on the prescribing physician’s medical judgment and the patient’s clinical response. 37,38

Smaller volumes or prolonged transfusion times may be necessary in patients with impaired cardiac function and heart failure. 38

Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. 11,25

There are no convalescent blood products currently licensed by the FDA. COVID-19 convalescent plasma is regulated as an investigational product. 11,37

**Emergency use authorization (EUA) for high-titer COVID-19 convalescent plasma:** FDA issued an EUA on August 23, 2020 that permitted use of convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA was reissued in its entirety on February 4, 2021 to authorize the use of high-titer COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19, early in the course of disease, and in those hospitalized with COVID-19 who have impaired humoral immunity. Use of low-titer COVID-19 convalescent plasma is no longer authorized under the EUA. This EUA is based on historical evidence using convalescent plasma in previous outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) for COVID-19 convalescent plasma sponsored by the Mayo Clinic, and additional studies (including randomized controlled trials). 37 The EUA requires healthcare providers to provide convalescent plasma recipients with the Fact Sheet for Patients and Parents/Caregivers and to inform recipients of the significant known and potential risks and benefits of emergency use of COVID-19 convalescent plasma. 7,38,39

Healthcare facilities and healthcare providers administering high-titer COVID-19 convalescent plasma must comply with certain mandatory record keeping and reporting requirements (including adverse event reporting). 38 Consult the EUA, 37 EUA fact sheet for healthcare providers, 7 and EUA fact sheet for patients and parents/
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<td>Uncontrolled case series in US (Salazar et al): 316 adults with severe and/or life-threatening COVID-19 disease received convalescent plasma (one or two units) in addition to multiple other treatments (e.g., antivirals, anti-inflammatory agents). At the time of an interim analysis, outcomes of 136 convalescent plasma recipients who reached day 28 post-transfusion were compared with two sets of propensity score-matched controls at 28 days after admission. These data suggested a trend toward benefit of convalescent plasma, particularly in patients who were transfused early (i.e., within 72 hours of admission) with high-titer convalescent plasma (i.e., anti-spike protein receptor binding domain titer ≥1:1350).</td>
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**Cochrane systematic review:** Analysis of 19 published studies (2 RCT, 8 controlled non-randomized studies of interventions [NRSIs], 9 non-controlled NRSIs) evaluating convalescent plasma in adults with COVID-19 (total of 38,160 study participants, of whom 36,081 received COVID-19 convalescent plasma) found low to very low confidence in the efficacy and safety of this treatment approach. |

**Systematic review (Joyner et al; non-peer-reviewed):** Analysis of pooled data (total of 804 COVID-19 patient outcomes) from 12 studies (3 RCT, 5 matched-control, 4 case series) evaluating convalescent plasma in hospitalized adults with severe or life-threatening COVID-19 found evidence favoring efficacy of this therapeutic approach. The risk of death was substantially reduced in hospitalized COVID-19 patients transfused with convalescent plasma compared to matched patients receiving standard therapy (OR: 0.43, p <0.001). **Note:** There were several limitations to this analysis including aggregating mortality data across study populations that varied by dose and timing of convalescent plasma administration, geographic region, and duration of follow-up. |

**Open-label, randomized, controlled study in Netherlands (Gharbharan et al; ConCOVID study):** Preliminary (non-peer-reviewed) data from a study of 86 caregivers for additional information. The EUA states that high-titer COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. FDA states that adequate and well-controlled randomized trials remain necessary to determine optimal product attributes and to identify appropriate subpopulations for its use and that ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on issuance of the EUA.

The NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend for or against the use of convalescent plasma in patients with COVID-19.

The Surviving Sepsis Campaign COVID-19 subcommittee suggests that convalescent plasma not be used routinely in critically ill adults with COVID-19 because efficacy and safety not established and uncertainty surrounding optimal preparation of convalescent plasma.

**Appropriate criteria for selection of patients to receive investigational COVID-19 convalescent plasma, optimal time during the course of the disease to receive such therapy, and appropriate dosage (e.g., volume, number of doses) not determined. Current data suggest clinical benefit is associated with transfusion of high-titer convalescent plasma early in the course of the disease (e.g., prior to respiratory failure requiring intubation and mechanical ventilation) and in those with impaired humoral immunity. Limited clinical evidence suggests the potential therapeutic window following symptom onset may be longer in patients with suppressed or deficient humoral immunity.**

Analysis of key safety indicators in 20,000 adults who participated in a US FDA Expanded Access Program.
hospitalized adults with COVID-19 found no significant difference in mortality, duration of hospital stay, or disease severity on day 15 in patients treated with convalescent plasma (300 mL of convalescent plasma containing anti-SARS-CoV-2 neutralizing antibody titers of ≥1:80 as determined by a SARS-CoV-2 plaque reduction neutralization test) compared with standard of care.

**Note:** Anti-SARS-CoV-2 antibodies were detected at baseline in 53/66 patients who had been symptomatic for 10 days prior to study enrollment. Neutralizing antibodies were detected in 44/56 (79%) patients tested with median titers comparable to the donors (1:160). These findings raised concerns about the potential benefit of convalescent plasma in the study population and the study was terminated. 44

**Open-label, randomized, controlled study in China (Li et al):** Results of this study in 103 adults with severe or life-threatening COVID-19 found no significant difference in time to clinical improvement within 28 days, mortality, or time to hospital discharge in patients treated with convalescent plasma (containing a high titer of antibody to SARS-CoV-2) plus standard of care compared with standard of care alone. 28

Convalescent plasma therapy was well tolerated by the majority of patients; 2 cases of transfusion-associated adverse events were reported. 29 There was a signal of possible benefit in the subgroup of patients with severe COVID-19 disease. 28, 29 However, the study had several limitations that preclude any definite conclusions, including the possibility of being underpowered as the result of early termination because of the lack of available patients. 28, 29 In addition, most patients received convalescent plasma treatment at least 14 days after symptom onset and it is unclear whether earlier treatment would have resulted in greater benefit. 28, 29

**Open-label, single-arm, phase 2 study (Ibrahim et al):** Data from a study of 38 severely or critically ill hospitalized adults with COVID-19 who received convalescent plasma (up to 2 transfusions of 200 mL of convalescent plasma containing IgG titers of 1:320) found a significant

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|         |            |           | reduction in mortality (13 versus 55%, respectively) and hospital length of stay (15.4 versus 33 days, respectively) in those who were severely ill compared with those who were critically ill. **Note:** Severely ill patients received convalescent plasma approximately 14.6 days following hospital admission and 12.6 days following symptom onset while on high-flow oxygen supplementation without evidence of acute respiratory distress syndrome (ARDS). Critically ill patients received convalescent plasma approximately 16.4 days following hospital admission and 23.1 days following symptom onset after developing ARDS; these patients also had been on ventilation support for an average of 10.6 days prior to transfusion of convalescent plasma. Transient transfusion reaction (fever and hematuria) was observed within 2 hours of transfusion of convalescent plasma in one patient with severe illness. 45
Open-label, randomized, controlled study in India (Agarwal et al; PLACID trial): Preliminary (non-peer-reviewed) data from a study of 464 moderately ill adults hospitalized with COVID-19 found no significant difference in 28-day mortality or progression to severe disease in patients treated with convalescent plasma (2 transfusions of 200 mL) plus standard of care compared with standard of care alone. Convalescent plasma therapy was well tolerated by the majority of patients; adverse effects included local infusion site reaction, chills, nausea, bradycardia, dizziness, pyrexia, tachycardia, dyspnea, and IV catheter blockage. 46
Open-label, randomized, controlled study in Chile (Balcells et al): Preliminary (non-peer-reviewed) data from a study of 58 adults hospitalized within 7 days of COVID-19 symptom onset with risk factors for disease progression and without mechanical ventilation found no significant difference in composite outcome of death, mechanical ventilation, or prolonged hospital admission (>14 days) in patients who received convalescent plasma (up to two transfusions of 200 mL) immediately following hospital admission compared with those who received convalescent plasma at clinical deterioration. Two patients were critically ill.

### Additional pathways (outside of the EUA) for administering or studying the use of investigational COVID-19 convalescent plasma:

1. **Clinical Trials:** Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional IND regulatory pathway. 11
2. **Intermediate-size Population Expanded Access IND:** FDA is accepting requests for expanded access INDs for use of COVID-19 convalescent plasma in patients with serious or immediately life-threatening COVID-19 who are not eligible or are unable to participate in randomized clinical trials. Consult the FDA guidance document for specific information on applying for an expanded access IND for more than a single patient. 11
3. **Single Patient Emergency Expanded Access IND (IND):** Licensed physicians seeking to administer COVID-19 convalescent plasma to individual patients with serious or life-threatening COVID-19 may request an individual patient expanded access IND from the FDA. Consult the FDA guidance document for specific information on applying for a single patient IND. 11

#### Donor eligibility:
The FDA guidance states that COVID-19 convalescent plasma for use under the EUA or for use under an IND may be collected from individuals who meet the following qualifications: 11

1. Laboratory-confirmed evidence of COVID-19 infection in individuals who had symptoms or laboratory-confirmed evidence from 2 different tests in those who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19. 11
2. Complete resolution of symptoms for at least 14 days before donation (a negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor). 11
3. Male donors, female donors who have never been pregnant, or female donors who have been tested since...
developed severe respiratory deterioration within 6 hours after transfusion of convalescent plasma and were categorized as possible transfusion-associated acute lung injury (TRALI) type II. The FDA guidance states that COVID-19 convalescent plasma should not be collected from individuals who have received an investigational COVID-19 vaccine, unless they had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA and received the COVID-19 vaccine after diagnosis of COVID-19 and are within 6 months after complete resolution of COVID-19 symptoms. This is to ensure that COVID-19 convalescent plasma collected from vaccinated donors contains sufficient antibodies directly related to their immune response to COVID-19 infection.

**SARS-CoV-2 antibody titers in donor plasma:** COVID-19 convalescent plasma for use under the EUA or an IND must be tested to determine suitability before release. Information on tests acceptable for use in the manufacture of high-titer COVID-19 convalescent plasma and respective qualifying results may be found in the EUA.
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<td>were reported (i.e., thromboembolic or thrombotic event, sustained hypotensive event requiring IV vasopressor, cardiac event); however, 55/87 thromboembolic or thrombotic complications and 569/643 cardiac events were judged to be unrelated to convalescent plasma transfusion. 11</td>
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<td>Retrospective subset analyses of Mayo Clinic expanded access protocol in US: FDA analysis of a subset of 4330 patients indicated no difference in 7-day mortality between patients who received high-titer convalescent plasma and those who received low-titer convalescent plasma; however, subgroup analysis suggested improvement in 7-day mortality in nonintubated patients who received high-titer convalescent plasma compared with those who received low-titer convalescent plasma (11 vs 14%, respectively). Post-hoc analysis of nonintubated patients who were &lt;80 years of age and transfused with convalescent plasma within 72 hours of COVID-19 diagnosis suggested an improvement in 7-day mortality between patients who received high-titer convalescent plasma and those who received low-titer convalescent plasma (6.3 vs 11.3%, respectively). Mayo Clinic analysis of a subset of 3082 patients indicated no difference in 30-day mortality between patients who received high-titer convalescent plasma and those who received low-titer convalescent plasma; however, similar to the FDA analysis, post-hoc subgroup analyses suggested a benefit of high-titer convalescent plasma transfused within 3 days of COVID-19 diagnosis in nonintubated patients who were &lt;80 years of age. Antibody titers for the FDA analysis were measured by the Broad Institute using a pseudovirus assay and antibody titers for the Mayo Clinic analysis were measured using the Ortho Clinical Diagnostics COVID-19 IgG assay.</td>
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<td>Open-label, prospective study (Madariaga et al): The relationship between clinical and serologic parameters in a group of COVID-19 convalescent plasma donors and antibody responses in recipients of convalescent plasma was evaluated. SARS-CoV-2 anti-receptor binding domain (anti-RBD) and anti-spike antibody titers ranged</td>
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|        |            |           | from 0 to 1:3892 and 0 to 1:3289, respectively, in 103 convalescent plasma donors; mean duration of COVID-19 symptoms in the plasma donors was 11.9 days and mean interval between symptom onset and convalescent plasma donation was 45.1 days; predictors of higher antibody titers in the donors included advanced age, fever, absence of myalgia, fatigue, ABO blood type, and previous hospitalization. In this study, 10 hospitalized adults with severe or life-threatening COVID-19 received 1 or 2 units (approximately 300 mL per unit administered IV over 4 hours) of ABO-compatible COVID-19 convalescent plasma (units had SARS-CoV-2 anti-RBD antibody titers of 1:73 to 1:3892 and anti-spike antibody titers of 1:69 to 1:2921) within 21 days after symptom onset and 80% of these patients had a significant increase in SARS-CoV-2 anti-spike and anti-RBD antibody titer by post-transfusion day 3 and were discharged after clinical improvement; antibody titers in the convalescent plasma recipients were independent of donor antibody titer. SARS-CoV-2 antibody titers in the convalescent plasma recipients continued to increase for up to 14 days in 4 recipients; however, 2 severely ill patients receiving extracorporeal membrane oxygenation (ECMO) who received convalescent plasma on day 20-21 of illness and had SARS-CoV-2 anti-spike antibody titers of up to 1:13,833 on day 0 had a decrease in antibody titer after receiving convalescent plasma. No convalescent plasma recipients experienced toxicity associated with the transfusion or clinical deterioration or worsening of disease status immediately related to plasma transfusion. Convalescent plasma transfusion was safe in high-risk individuals in this study (i.e., immunosuppressed, end-stage renal disease).  

**Randomized, double-blind, placebo-controlled study in Argentina (Libster et al):** Results of this study in 160 geriatric patients (≥75 years of age or 65–74 years of age with ≥1 coexisting condition) with mild COVID-19 who received convalescent e antibody titer of >1:1000 or placebo (250 mL of 0.9% sodium chloride injection) plasma (250 mL with a SARS-CoV-2 anti-spike within 72 hours of symptom onset
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<td>found a significant reduction in risk of progression to severe respiratory disease (16 versus 31%, respectively; relative risk 0.52). However, the study was terminated early because of the lack of available patients and, therefore, is likely underpowered. 51</td>
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<td>Retrospective matched cohort study (Rogers et al; non-peer-reviewed) of hospitalized COVID-19 patients at 3 Rhode Island medical centers indicated no significant difference in in-hospital mortality or rate of hospital discharge in patients who received convalescent plasma within a median of 7 days after symptom onset; however, subgroup analysis suggested a significantly increased hospital discharge rate among convalescent plasma recipients 65 years of age or older. 43</td>
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<td>Retrospective matched cohort study (Yoon et al; non-peer-reviewed) of hospitalized COVID-19 patients at a New York medical center indicated no significant difference in all-cause mortality at 28 days in adults who received convalescent plasma (200 mL containing SARS-CoV-2 anti-spike antibody titers &gt;1:2430) within 72 hours of admission. Subgroup analysis suggested a 4-fold decrease in mortality (8.8 vs 29.4%) and deterioration in oxygenation or mortality (11.8 vs 35.3%) in convalescent plasma recipients &lt;65 years of age compared with propensity score-matched patients who did not receive convalescent plasma. 50</td>
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<td>Retrospective study (Salazar et al; non-peer-reviewed) of adults diagnosed with COVID-19 and hospitalized with pneumonia in 215 hospitals in Argentina suggested clinical benefit of convalescent plasma in such patients; a significant reduction in 28-day unadjusted mortality was observed in convalescent plasma recipients compared with those who did not receive convalescent plasma (25.5 vs 38%). 49</td>
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<td>Multiple clinical trials are ongoing globally to evaluate use of COVID-19 convalescent plasma in various settings (e.g., postexposure prophylaxis, treatment of different stages of the disease); some are registered at clinicaltrials.gov.</td>
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| Famotidine    | 56:28.12   | Histamine H₂ Antagonists                       | Computer-aided, structure-based, virtual screening of libraries of compounds against SARS-CoV-2 proteins suggested potential for famotidine to interact with viral proteases involved in coronavirus replication.<sup>1,4</sup> However, computer-aided modeling suggested binding affinity is weak and combined use with other antivirals would likely be required.<sup>14</sup> Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19. *Randomized, double-blind, placebo-controlled, comparative trial (NCT04370262)* is evaluating high-dose IV famotidine plus standard care vs placebo plus standard care in hospitalized adults with moderate to severe COVID-19; targeted enrollment is at least 942 patients.<sup>5</sup> Other randomized clinical trials also evaluating famotidine for treatment of COVID-19, including NCT04504240.<sup>5</sup> *Retrospective cohort study (NCT04389567)* of 10 outpatients self-medicating with high-dose famotidine following onset of symptoms consistent with COVID-19; No hospitalizations reported; all patients reported symptomatic improvement within 1-2 days, with continued improvement over 14-day period. Patients were symptomatic for 2-26 days before initiating famotidine. Total of 7 patients had PCR-confirmed COVID-19, 2 had serologic confirmation of antibodies against SARS-CoV-2, and 1 had clinical diagnosis only. Famotidine dosage of 80 mg 3 times daily was reported by 6 patients (range: 20-80 mg 3 times daily); median reported duration of use was 11 days (range: 5–21 days); high-dose famotidine generally was well tolerated. Data were collected by telephone interviews and written questionnaires. Patients retrospectively provided symptom scores on a 4-point ordinal scale. Potential exists for placebo effect, recall bias, and enrollment bias; symptomatic improvement also could reflect treatment-independent convalescence.<sup>8</sup> *Retrospective matched cohort study of COVID-19 patients hospitalized, but not requiring intubation within the first 48 hrs, at a single New York medical center indicated that the risk for the composite outcome of death or intubation was reduced (mainly due to difference in mortality) in patients who received famotidine within 24 hours of hospital admission (n = 84) vs those who did not receive the drug.*<sup>9</sup> Dosage in NCT04370262: Famotidine is being given IV in 120-mg doses (proposed total daily dosage of 360 mg) for maximum of 14 days or until hospital discharge, whichever comes first.<sup>5</sup> Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage;<sup>6</sup> the study excludes patients with creatinine clearance (CrCl) ≤50 mL/minute, including dialysis patients;<sup>5</sup> renally impaired patients may be at increased risk of adverse CNS effects since drug halflife is closely related to CrCl.<sup>6</sup> Safety and efficacy for treatment of COVID-19 not established.<sup>5</sup> IDSA suggests against using famotidine for the sole purpose of treating COVID-19 in hospitalized patients with severe COVID-19 outside of the context of a clinical trial.<sup>9</sup>

*Updated 12/17/20*
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<td>not receiving the drug (14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors&lt;sup&gt;3&lt;/sup&gt;</td>
<td>(n = 1536); overall, 21% of patients met the composite outcome (8.8% were intubated and 15% died); the finding appeared to be specific to the H&lt;sub&gt;2&lt;/sub&gt; antagonist and to COVID-19, as the investigators reported observing no protective effect with proton-pump inhibitors or in non-COVID-19 patients. Home use of famotidine was documented on admission in 15% of patients who received the drug in hospital vs 1% of those who did not; 28% of all famotidine doses were IV; 47% of doses were 20 mg, 35% were 40 mg, and 17% were 10 mg; the median duration of use was 5.8 days, and the total median dose was 136 mg (63-233 mg).&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Retrospective, matched, single-center, observational study in hospitalized patients with RT-PCR-confirmed COVID-19: In-hospital mortality (14.5 vs 26%) and the combined end point of death or intubation (7.2 vs 13.8%) were reduced in patients who received famotidine (n = 83) compared with a propensity score-matched group of patients who did not receive the drug (n = 689). Famotidine use was identified from electronic medical records and was defined as IV or oral use at any dosage within 7 days before or after COVID-19 screening and/or hospitalization; in the famotidine group, 66% received the drug in hospital only, and 29% received the drug both before and during hospitalization. Median total in-hospital dose was 80 mg (range: 40-160 mg) given over a median of 4 days (range: 2-8 days). There were no significant differences between the groups with respect to baseline demographics, comorbidities, or severity of illness or in concomitant use of hydroxychloroquine, remdesivir, azithromycin, or corticosteroids.&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Retrospective territory-wide cohort study (not peer reviewed) in Hong Kong investigating the association between famotidine use and COVID-19 severity: In this cohort of 952 adults hospitalized with COVID-19, 51 patients (5.4%) had severe disease; 23 patients (2.4%) received famotidine and 4 patients (0.4%) received proton-pump inhibitors (PPIs), as determined on the day of</td>
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<td>HMG-CoA Reductase Inhibitors (statins)</td>
<td>24:06 Antilipemic Agents</td>
<td>In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects, which may prevent acute lung injury.</td>
<td>Data from randomized controlled trials are lacking on the use of statins in pts with COVID-19. Retrospective cohort studies in various settings and meta-analyses conducted using data from retrospective studies have conflicting results regarding the benefit of statin treatment on disease severity or mortality and/or recovery time in pts with COVID-19.</td>
<td>NIH COVID-19 Treatment Guidelines Panel states pts who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy. The panel recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial.</td>
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<td>Statins</td>
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<td>Retrospective cohort studies:</td>
<td>In a study of 13,981 pts in China hospitalized with COVID-19, statin use during hospitalization was associated with lower risk of mortality. The 28-day all-cause mortality was 22% lower in pts who received statins during hospitalization compared with pts who did not receive statins. Among propensity-score-matched pts (861 pts in the statin group vs 3444 matched pts in the non-statin group), the risk of 28-day all-cause mortality was 42% lower in pts who received statins during hospitalization compared with those who did not receive statins. In addition, lower incidence of invasive mechanical ventilation was observed in the statin-treated pts. The authors note that pts in the statin group were older and had a higher prevalence of comorbidities and more severe symptoms at baseline; matched non-statin pts therefore had more severe baseline symptoms and comorbidities than unmatched pts, which could account for the increased mortality in the non-statin group after propensity score matching.</td>
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<td>Pts with cardiovascular disease are at an increased risk of serious COVID-19 infections.</td>
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<td>In pts with active COVID-19 who may develop severe rhabdomyolysis, it may be advisable to withhold statin therapy for a short period of time.</td>
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<td>Most statins are substrates for the CYP450 system; potential for drug interactions.</td>
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<td>Clinicians should ensure that their high-risk primary prevention (for ASCVD) pts are on guideline-directed statin therapy.</td>
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<td>Statins affect ACE2 as part of their function in reducing endothelial dysfunction.$^2,^8$</td>
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(NCT04407273; STACOV), statin use prior to hospitalization was associated with a lower in-hospital mortality rate compared with no statin use (19.8 vs 25.4%), particularly in pts who continued statin therapy during hospitalization (17.4%). Approximately 58% of the 581 pts receiving statins prior to hospitalization continued therapy at the same dosage during hospitalization. In this study, propensity matching failed to achieve similar baseline characteristics between statin and non-statin pts; pts were therefore matched using a genetic matching method.20

A study of 2147 pts hospitalized with COVID-19 at 2 hospitals in China found an association between statin use and lower mortality and improved clinical outcomes compared with no statin use. In this study, 11.6% of patients were receiving statin therapy prior to admission that was continued during hospitalization. After propensity score matching, statin use was associated with a lower risk of death, ARDS, and ICU admission compared with no statin use (adjusted hazard ratios: 0.251, 0.232, and 0.381, respectively).24

In a study of 842 pts hospitalized with COVID-19 at multiple centers in Italy, statin use was not associated with a difference in in-hospital mortality compared with no statin use. In this study, 21% of pts were receiving statin therapy prior to admission. After propensity score matching, although pts receiving statin therapy presented with worse disease severity (as assessed by the National Early Warning Score [NEWS]) and worse radiological features compared with non-statin pts, there was no difference in in-hospital mortality between statin and non-statin pts. The study also found that although pts receiving high- or moderate-intensity statin therapy had worse clinical presentation of disease compared with those receiving low-intensity statin therapy, in-hospital mortality was similar between the groups.25

In a study of 170 pts hospitalized for COVID-19 at a single US center, statin use prior to admission was associated with reduced
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<td>risk of developing severe disease and, among those without severe disease, faster time to recovery. In this study, 27% of pts reported using statins within 30 days prior to hospitalization for COVID-19. Statin use was associated with a 71% lower risk of severe outcome (i.e., death or ICU admission). In addition, rate of recovery in pts without severe disease was higher (hazard ratio for recovery: 2.69) and median time to recovery was shorter for those who received statins. The beneficial effect of statin use on reduction of severe outcomes in pts with COVID-19 was greater than that observed in a large control cohort of COVID-19-negative pts. $^{12}$</td>
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<td>In a study of 249 pts hospitalized with COVID-19 at multiple US centers, statin use prior to hospitalization was associated with lower risk of invasive mechanical ventilation in some models, but there was no substantial association between statin use and in-hospital death or ICU admission. $^{16}$</td>
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<td>In a cohort analysis of 541 pts hospitalized with COVID-19 at a single center in Italy, the association between statin use prior to hospitalization and reduced mortality or disease severity was not statistically significant. $^{21}$</td>
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<td>Intensive care pts:</td>
<td>In a study of 87 pts admitted to the ICU with COVID-19 at a single US center, treatment with atorvastatin (40 mg daily) was associated with a reduced risk of death (adjusted hazard ratio: 0.38). $^{13}$</td>
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<td>Non-hospitalized pts:</td>
<td>In a study of 154 nursing home residents in Belgium with clinically suspected COVID-19 and/or positive PCR test for SARS-CoV-2, statin use was associated with absence of symptoms (i.e., asymptomatic infection) in this cohort; 45% of the 31 pts receiving statin therapy remained asymptomatic compared with 22% of the 123 pts not receiving statins. $^{10}$</td>
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<td>Preliminary findings from a meta-analysis (Kow &amp; Hasan) of 4 cohort or case-control studies which included a total of 8990 pts with COVID-19 suggest that statin use is</td>
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associated with a 30% reduction in risk of severe or fatal outcome in pts with COVID-19. However, another meta-analysis of 9 cohort or case-control studies (Hariyanto & Kurniawan) did not find an association between statin use and improved severity or mortality outcomes in pts with COVID-19. This meta-analysis included a total of 3449 pts with COVID-19 and included 2 of the same studies used in the Kow & Hasan analysis. A larger meta-analysis of observational studies (Scheen) found that statin use was not associated with reduced in-hospital mortality (13 studies with a total of 42,722 pts) or disease severity (11 studies with a total of 14,022 pts). In studies using multivariate analyses or adjusting for covariates, statin use was associated with lower rates of in-hospital mortality and reduced disease severity (adjusted odds ratio: 0.73). In addition, studies that utilized propensity-score matching for comparison found a statistically significant lower risk of in-hospital mortality in statin users compared with those not receiving statins (hazard ratios ranging from 0.48 to 0.88). The authors note that there was considerable heterogeneity between studies.

In pts with diabetes mellitus hospitalized with COVID-19, observational studies have also yielded conflicting results with regards to statin use. In a US single-center observational study, among 2266 pts with diabetes mellitus hospitalized with COVID-19, statin use during hospitalization was associated with reduced in-hospital mortality (hazard ratio 0.51). In addition, a large registry-based cohort study in England found an association between statin use (i.e., having a prescription for statins) and reduced COVID-19-related mortality in pts with type 2 diabetes mellitus. However, a cohort study of 2449 pts with type 2 diabetes mellitus hospitalized with COVID-19 at multiple centers in France (CORONADO study) found that statin use prior to hospitalization was associated with higher 7- and 28-day mortality compared with no statin use (odds ratio 1.74 and 1.46, respectively).

Other respiratory conditions:
Preliminary findings have shown mixed results with other respiratory illnesses;
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| **Immune Globulin**
*Updated 10/28/20* | 80:04 | Immune Globulin | Commercially available immune globulin (non-SARS-CoV-2-specific IGIV, IVIG, γ-globulin): Immune globulin derived from pooled plasma containing many antibodies normally present in adult human blood; used for replacement therapy or treatment of various immune and inflammatory disorders (e.g., primary or secondary humoral immunodeficiency, immune thrombocytopenic purpura) and also used to provide passive immunity to certain viral infections in other individuals.¹,²¹,²² | Some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in pts hospitalized with influenza and/or pneumonia.³⁶  

**Clinical trials evaluating statin use in COVID-19:**  
Multiple trials registered at clinicaltrials.gov (some listed below):⁹  
NCT04333407  
NCT04348695  
NCT04426084  

Investigational Anti-SARS-CoV-2 Hyperimmune Globulin (anti-SARS-CoV-2 hIGIV): Several manufacturers are collaborating to provide investigational anti-SARS-CoV-2 hIGIV on behalf of the CoVig-19 Plasma Alliance for the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) study (NCT04546581). The ITAC study is an international, multi-center, randomized, double-blind, placebo-controlled, adaptive phase 3 study sponsored by the NIAID to evaluate safety, tolerability, and efficacy of anti-SARS-CoV-2 hIGIV for treatment of hospitalized adults at risk for serious complications of COVID-19 disease. All enrolled patients will receive treatment with remdesivir.¹²,²⁵ (See Remdesivir in this Evidence Table.)  

**Commerically Available Immune Globulin (non-SARS-CoV-2-specific IGIV)** | Commercially available immune globulin (non-SARS-CoV-2-specific IGIV) may contain antibodies against some previously circulating coronaviruses.²,³,¹³,¹⁸ Antibodies that cross-react with SARS-CoV-1, MERS-CoV, and SARS-CoV-2 antigens have been detected in some currently available IGIV products; however, further evaluation is necessary to assess potential in vivo activity of such anti-SARS-CoV-2 antibodies using functional tests such as neutralization assays.¹⁸  

SARS Experience: IGIV has been used in the treatment of SARS.⁴,⁷,¹⁵ Benefits were unclear because of patient comorbidities, differences in stage of illness, and effect of other treatments;⁵ IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients.⁶,⁷  

Open-label, prospective, randomized, controlled study in the US (Sakoulas et al; NCT04411667): Preliminary (non-peer-reviewed) data from a study of 33 adults with COVID-19 and moderate to severe hypoxia (defined as SpO₂ ≤96% requiring ≥4 liters O₂ by nasal cannula) but not on mechanical ventilation found that IGIV significantly improved hypoxia and reduced some observable clinical deterioration.²⁴  

NIH states that there are insufficient data to recommend either for or against the use of investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hIGIV) for the treatment of COVID-19.¹⁶  

The Surviving Sepsis Campaign COVID-19 subcommittee suggests that commercially available IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, such preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury).¹⁸  

Role of commercially available immune globulin (non-SARS-CoV-2-specific IGIV) and investigational anti-SARS-CoV-2 hyperimmune globulin (anti-SARS-CoV-2 hIGIV) in the treatment of COVID-19 is unclear.¹⁶  

The NIH COVID-19 Treatment Guidelines Panel recommends against the use of commercially available IGIV (non-SARS-CoV-2-specific IGIV) for the treatment of COVID-19 except in the context of a clinical trial and states that current IGIV preparations are not likely to contain SARS-CoV-2 antibodies.¹⁶ This does not preclude the use of IGIV when it is otherwise indicated for the treatment of complications arising during the course of COVID-19 disease.¹⁶  

NIH states that there are insufficient data to recommend either for or against the use of investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hIGIV) for the treatment of COVID-19.¹⁶  

The Surviving Sepsis Campaign COVID-19 subcommittee suggests that commercially available IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, such preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury).¹⁸  

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<th>Drug(s)</th>
<th>AHFS Class</th>
<th>Rationale</th>
<th>Trials or Clinical Experience</th>
<th>Dosagea</th>
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<tr>
<td>Investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hyperimmune globulin intravenous [hiIGIV]): Concentrated immune globulin preparation containing specific antibody derived from pooled plasma of individuals who have recovered from COVID-19.16, 23</td>
<td>Investigational anti-SARS-CoV-2 hiIGIV preparations potentially could reduce dissemination and accelerate clearance of SARS-CoV-2 and theoretically may provide both immediate and long-term protection against the virus (e.g., for as long as one month).2, 16, 23</td>
<td>hospital length of stay and progression to mechanical ventilation in patients with alveolar-arterial (A-a) gradient ≤200 mm Hg treated with IGIV (Octagam® 10% 0.5 g/kg daily for 3 days) plus standard of care compared with standard of care alone. All 16 patients in the IGIV group received premedication with methylprednisolone (40 mg IV) prior to each IGIV dose and 5 of these received additional glucocorticoid therapy; 10/17 patients in the standard of care group received some glucocorticoid therapy.20</td>
<td>COVID-19 case reports in China (Cao et al): Treatment with IGIV at the early stage of clinical deterioration was reported to provide some clinical benefit in 3 adults with severe COVID-19; 2 patients also received antivirals and 1 patient also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration.8</td>
<td>COVID-19 clinical experience in China: IGIV has been used as an adjunct in the treatment of COVID-19 and has been mentioned in Chinese guidelines as a possible treatment option for severe and critically ill children with COVID-19.9-11, 14</td>
<td>Multicenter retrospective study in China: Among a cohort of 325 patients with severe or critical COVID-19 disease, no difference in 28-day or 60-day mortality was observed between patients who were treated with IGIV and those who were not treated with IGIV. However, patients who received IGIV were older and more likely to have coronary heart disease and critical status at study entry; patients also received numerous other treatments which limit interpretation of these findings.16, 19</td>
</tr>
<tr>
<td>Drug(s)</td>
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<td>Rationale</td>
<td>Trials or Clinical Experience</td>
<td>Dosage(^a)</td>
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<tr>
<td>Ivermectin (Stromectol(\textsuperscript{**}))</td>
<td>8:08 Anthelmintic</td>
<td>In vitro activity against some human and animal viruses (1,6)</td>
<td>Limited published clinical data to date evaluating use in the treatment of COVID-19</td>
<td></td>
<td>No published data to date from randomized, controlled clinical trials to support use in the treatment or prevention of COVID-19</td>
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<td>In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug (^6)</td>
<td>Pilot observational study comparing efficacy of add-on ivermectin in pts with mild to moderate COVID-19 (not peer reviewed): A total of 16 pts received a single dose of oral ivermectin (0.2 mg/kg) given on the day of hospital admission in addition to initiation of treatment with hydroxychloroquine and azithromycin, and results were compared with 71 pts who received hydroxychloroquine and azithromycin alone (matched controls). The primary outcome was percentage of pts cured (defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR tests from nasopharyngeal swabs at least 24 hours apart) within 23 days. The investigators reported that all 16 pts who received ivermectin were cured compared with 97% of pts who did not receive ivermectin and the mean duration of hospitalization was shorter in the ivermectin group (7.6 days) than in the control group (13.2 days). Note: These results need to be validated in a larger prospective trial. (11)</td>
<td></td>
<td>** Manufacturer (Merck) states that, to date, there is no scientific basis from preclinical studies for a potential therapeutic effect of ivermectin against COVID-19, no meaningful evidence of clinical activity or clinical efficacy of the drug in patients with COVID-19, and a concerning lack of safety data in the majority of studies. In addition, available data do not support the safety and...</td>
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<td>Retrospective cohort study of COVID-19 pts treated with ivermectin (Rajter et al):</td>
<td></td>
<td>** NIH COVID-19 Treatment Guidelines Panel states that data are insufficient to date to recommend either for or against the use of ivermectin for the treatment of COVID-19. These experts state that clinical trials reported to date have significant methodological limitations and incomplete information; results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19. (13)</td>
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<td>Drug(s)</td>
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<tr>
<td>Ivermectin</td>
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<td>Outcome data for 173 pts with confirmed COVID-19 who received oral ivermectin at any time during hospitalization (0.2-mg/kg dose; 13 pts received a second dose) in addition to usual care were compared with outcome data for 107 pts who received usual care. Usual care included hydroxychloroquine and/or azithromycin in most pts in both groups; use of these drugs and ivermectin was at the discretion of the treating physician. The primary outcome measure was all-cause in-hospital mortality; secondary outcome measures included mortality in the subgroup of pts with severe pulmonary involvement, length of hospital stay, and extubation rates in mechanically ventilated pts. For the unmatched cohort, overall mortality was lower in the ivermectin group (15%) than in the group not treated with ivermectin (25.2%); overall mortality in the matched cohort also was lower in the ivermectin group (13.3 vs 24.5%). Data for the subgroup of pts with severe pulmonary involvement also indicated lower mortality in the ivermectin group (38.8 vs 80.7%). There was no difference in duration of hospitalization between the groups in either the unmatched or matched cohorts (median of 7 days for both groups). There also was no significant difference in extubation rates between groups in either the unmatched or matched cohorts. <strong>Note:</strong> The effect of ivermectin on viral load was not evaluated and the impact of confounding factors in these patients (e.g., time from diagnosis to initiation of treatment, differences in drugs used for standard care and variances in clinical benefits of such drugs) is not known.</td>
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### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage<sup>a</sup> | Comments
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Nebulized drugs | **Updated 2/11/21** | **Potential harm:** Concern that use of nebulized drugs (e.g., albuterol) for the management of respiratory conditions in patients with COVID-19 infection may distribute the virus into the air and expose close contacts. | | | American College of Allergy, Asthma & Immunology (ACAAI) recommends that nebulized albuterol should be administered in a location that minimizes exposure to close contacts who do not have COVID-19 infection. In the home, choose a location where air is not recirculated (e.g., porch, patio, or garage) or areas where surfaces can be cleaned easily or may not need cleaning. In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose or dry powder inhalers in patients who are awake and who can perform specific breathing techniques because of the risk of the virus becoming airborne when treating patients infected with COVID-19. There is a lack of published information and guidance on the optimal

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1 days in the 5-day ivermectin group, 11.5 days in the ivermectin with doxycycline group, and 12.7 days in the placebo group. There was no significant difference between groups in remission of fever and cough.  

**Randomized, double-blind, placebo-controlled pilot study to evaluate ivermectin for reduction of SARS-CoV-2 transmission** (Chaccour et al): Twelve adults with nonsevere COVID-19 who had no risk factors and symptom onset within the last 72 hours were randomized 1:1 to receive ivermectin (single dose of 400 mcg/kg) or placebo. The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7. Results indicated no difference in the proportion of PCR-positive patients between the ivermectin group and placebo group at day 7 (100% of pts in both groups still had positive PCR).  

Various clinical trials evaluating ivermectin used alone or in conjunction with other drugs for the treatment or prevention of COVID-19 are registered at clinicaltrials.gov.

**Nebulizer treatment used in clinical practice to treat influenza and other respiratory infections is thought to generate droplets or aerosols.** In one study, nebulized saline delivered droplets in the small- and medium-size aerosol/droplet range. These results may have infection control implications for airborne infections, including severe acute respiratory syndrome and pandemic influenza infection.
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| Niclosamide | 8:08 Anthelmintic | Broad antiviral activity | In vitro evidence of activity against SARS-CoV-1 and MERS-CoV; inhibited replication and antigen synthesis of SARS-CoV-1 in vitro, but did not interfere with attachment to and entry into cells. | Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 | Protocol in one ongoing trial (NCT04399356) specifies a niclosamide dosage of 2 g orally once daily for 7 days for treatment of mild to moderate COVID-19 in adults. Protocol in one ongoing trial (NCT04603924) specifies a niclosamide dosage of 1 g orally twice daily for 7 days for treatment of moderate COVID-19 in hospitalized adults. Protocols in two ongoing trials (NCT04436458, NCT04542434) specify a 3-times-daily niclosamide regimen (e.g., 400 mg of niclosamide orally 3 times daily) for 14 days for treatment of moderate COVID-19 in adults with GI signs and symptoms. | ** CDC states that it is unclear whether the potential association between nebulizer therapy and increased risk of transmission of COVID-19 infection is related to the aerosol-generating procedure or to increased contact between those administering the nebulized therapy and infected patients. ** If clinicians need to be present during nebulizer use among patients who have symptoms or a diagnosis of COVID-19, recommended infection control precautions (e.g., social distancing, use of negative-pressure rooms, discarding or disinfecting personal protective equipment after each use) should be followed when aerosol-generating procedures are performed.

Although suggested as a potential treatment for COVID-19 based on broad antiviral activity, including activity against coronaviruses, no data to date support the use of niclosamide in the treatment of COVID-19. Not commercially available in the US. |
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<tr>
<td>Nitazoxanide</td>
<td>8:30.92</td>
<td>Antiprotozoal</td>
<td>In vitro activity against various viruses, including coronaviruses $^{4,5}$ Structurally similar to niclosamide $^{4,5}$ In vitro evidence of activity against SARS-CoV-2 $^{1,14}$ In vitro activity against MERS-CoV $^{4}$ Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice $^{4}$ Some in vitro evidence of potential synergism between nitazoxanide and remdesivir and between nitazoxanide and umifenovir against SARS-CoV-2; additional data needed $^{10}$</td>
<td>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19</td>
<td>Dosages investigated for treatment of influenza and influenza-like illness or being investigated for other viral infections: Adults and adolescents (≥12 years of age); 500 or 600 mg orally twice daily for 5 days $^{5,7,8}$ Protocols in many registered trials generally specify a nitazoxanide dosage of 500 or 600 mg twice, three, or four times daily for 5-14 days or 1 g twice daily for 7 or 14 days for treatment of COVID-19 in adults $^{5}$ Protocol in two ongoing trials sponsored by the manufacturer (NCT04359680, NCT04343248) evaluating preexposure and/or postexposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks in adults; another study (NCT04435314) specifies a dosage of 600 mg 3 times daily for 7 days for postexposure prophylaxis in adults $^{8}$</td>
</tr>
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Protocol in one ongoing trial (NCT04558021) specifies a niclosamide dosage of 200 mg (as an oral suspension) orally 3 times daily for 5 days for the treatment of COVID-19 in adults $^{3}$ | | | | | |

**Updated 1/14/21**

COVID-19: Randomized, double-blind, placebo-controlled trials initiated to evaluate nitazoxanide for treatment of hospitalized pts with noncritical COVID-19 (NCT04423861) and pts with moderate COVID-19 (NCT04348409) $^{8}$

Randomized, double-blind, placebo-controlled trial in adults with mild COVID-19 (Rocco et al; NCT04552483): Total of 392 outpatients were randomized 1:1 to receive nitazoxanide (500 mg 3 times daily) or placebo for 5 days; median time from symptom onset to first dose was 5 days. Percentage of pts experiencing complete resolution of symptoms (i.e., dry cough, fever, fatigue) at 5 days did not differ between pts treated with nitazoxanide or placebo. Nitazoxanide significantly reduced SARS-CoV-2 viral load at 5 days compared with placebo. $^{13}$

Dosage used in a case series of 41 pts with COVID-19 (20 pregnant women, 5 hospitalized internal medicine pts, 16 ambulatory pts) was 500 mg every 6 hours. $^{12}$

Results of a physiologically based pharmacokinetic model predict that nitazoxanide dosages of 1200 mg 4 times daily, 1600 mg 3 times daily, and 2900 mg twice daily in the fastest phase 1a trials or clinical experience $^{11}$

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### Nonsteroidal Anti-inflammatory Agents (NSAIAs)

**Updated 2/11/21**

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<th>Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
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<tr>
<td>Ibuprofen</td>
<td>28:08.04</td>
<td>Nonsteroidal Anti-inflammatory Agent (NSAIA)</td>
<td><strong>Two randomized, double-blind, placebo-controlled clinical trials</strong> were initiated by the manufacturer (Romark) to evaluate efficacy and safety for preexposure and postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers and others at increased risk of SARS-CoV-2 infection (NCT04359680) or postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (NCT04343248)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>state and 700 mg 4 times daily, 900 mg 3 times daily, and 1400 mg twice daily in the fed state</td>
<td><strong>Concerns that anti-inflammatory drugs such as ibuprofen may worsen COVID-19 circulated widely in the early months of the pandemic.</strong>&lt;sup&gt;5, 12, 14&lt;/sup&gt; These reports were based largely on a letter published in The Lancet Respir Med stating that increased expression of ACE2 could facilitate infection with COVID-19 and that ibuprofen can increase ACE2. In addition, there were unconfirmed reports of younger, healthy patients who had used ibuprofen to treat early symptoms of COVID-19 and later experienced severe outcomes. <strong>A statement attributed to the WHO recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position by the WHO has not been substantiated.</strong> WHO subsequently performed a rapid review of the literature and concluded that there was no evidence at that time of severe adverse events or effects on acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIAs.&lt;sup&gt;9&lt;/sup&gt; FDA has stated that it is not aware of scientific evidence connecting the use of NSAIAs, such as ibuprofen, with worsening COVID-19 symptoms and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that results from large cohort studies have not found associations between NSAIA use and increased risk of COVID-19 incidence or severity.&lt;sup&gt;14-17&lt;/sup&gt; In a <em>national registry-based cohort study</em> in Denmark, NSAIA use was <em>not</em> associated with increased 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in individuals who tested positive for SARS-CoV-2. In this study, of the 9236 individuals who had a positive PCR test for SARS-CoV-2, 2.7% had used NSAIAs (defined as individuals having filled a prescription for an NSAIA within 30 days prior to a positive SARS-CoV-2 test) based on national community pharmacy records. The authors note that in Denmark, NSAIAs are available only by prescription with the exception of low-dose ibuprofen (200 mg) sold over the counter (OTC) in packages of no more than 20 tablets, and such OTC purchases of ibuprofen constituted 15% of total ibuprofen sales and a smaller proportion of total NSAIA sales. This definition of NSAIA use was a major limitation of the study.&lt;sup&gt;14&lt;/sup&gt; NSAIA use was <em>not</em> associated with increased incidence of COVID-19 (suspected or confirmed) or all-cause mortality in a UK database-based study comparing 13,202 pts with osteoarthritis who were prescribed NSAIAs with 12,457 propensity-matched pts who were prescribed comparator analgesics (acetaminophen and codeine/dihydrocodeine).&lt;sup&gt;16&lt;/sup&gt;</td>
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**Indomethacin:** In vitro antiviral activity in SARS-CoV-2 pseudovirus-infected Vero E6 cells;<sup>7</sup> also has in vitro activity against other coronaviruses: SARS-CoV-1 (in Vero E6 and human pulmonary epithelial [A549] cells) and canine coronavirus; also has in vivo activity against canine coronavirus in dogs,<sup>6, 7</sup> interferes with viral RNA synthesis,<sup>6, 8</sup> stating that ibuprofen can increase ACE2. Increased expression of ACE2 could facilitate infection with COVID-19 and that ibuprofen can increase ACE2. In addition, there were unconfirmed reports of younger, healthy patients who had used ibuprofen to treat early symptoms of COVID-19 and later experienced severe outcomes. A statement attributed to the WHO recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position by the WHO has not been substantiated. WHO subsequently performed a rapid review of the literature and concluded that there was no evidence at that time of severe adverse events or effects on acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIAs. FDA has stated that it is not aware of scientific evidence connecting the use of NSAIAs, such as ibuprofen, with worsening COVID-19 symptoms and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that

**Results from large cohort studies have not found associations between NSAIA use and increased risk of COVID-19 incidence or severity.**<sup>14-17</sup>
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<tr>
<td>Thrombolytic Agents (t-PA [alteplase], tenecteplase)</td>
<td>20:12.20</td>
<td>Thrombolytic agents</td>
<td>A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which has been shown to contribute to poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).&lt;sup&gt;1&lt;/sup&gt; Coagulation abnormalities observed include prothrombotic disseminated intravascular coagulation</td>
<td>Results of a small phase 1 study suggested possible benefit of plasminogen activators in the treatment of ARDS.&lt;sup&gt;1,3&lt;/sup&gt; In this study, 20 patients with ARDS secondary to trauma and/or sepsis who failed to respond to standard ventilator therapy and were not expected to survive were treated with urokinase or streptokinase; such therapy improved PaO&lt;sub&gt;2&lt;/sub&gt; and also appeared to improve survival. &lt;sup&gt;1-3&lt;/sup&gt; There is some evidence suggesting that t-PA (alteplase) may decrease dead-space ventilation in patients with COVID-19-associated ARDS, but whether this leads to improved clinical outcomes is not known.</td>
<td><strong>In addition, 2 other large UK database-based cohort studies did not find an association between NSAIA use and increased risk of COVID-19-related death in the general population or in pts with rheumatoid arthritis or osteoarthritis. These studies defined current NSAIA users as individuals with a prescription for an NSAIA within 4 months prior to study entry and compared 536,423 current NSAIA users with 1,927,284 NSAIA nonusers from the general population; among pts with rheumatoid arthritis or osteoarthritis, 175,495 current NSAIA users were compared with 1,533,286 NSAIA nonusers. In multivariate analyses, an increased risk of COVID-19-related death was not observed in NSAIA users.</strong>&lt;sup&gt;17&lt;/sup&gt; <strong>Ibuprofen:</strong> In a retrospective cohort study of 403 hospitalized patients with COVID-19 at a single center in Israel, use of ibuprofen (1 week prior to diagnosis or during the course of disease) was not associated with increased mortality or the need for respiratory support compared with acetaminophen or no antipyretic drug.**&lt;sup&gt;15&lt;/sup&gt; <strong>Indomethacin:</strong> In vitro studies and animal models only; currently no published studies evaluating use specifically in COVID-19 patients</td>
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**t-PA (alteplase):** Dosage regimen being evaluated in the registered NCT04357730 trial is 50 mg (administered as a 10-mg IV bolus followed by IV infusion of the remaining 40 mg over a total time of 2 hours); IV infusion of heparin will be initiated immediately following the alteplase infusion. Repeat doses of alteplase 50 mg may be given according to protocol. <sup>12</sup> Other t-PA (alteplase) dosage regimens evaluated in patients with COVID-19 include an initial t-PA dose of 100 mg over 2 hours, followed by 50 mg over 2 hours every 12 hours, and also appeared to improve survival. <sup>1-3</sup> | **t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who are not responding to or do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).**<sup>1,13,14,22,29</sup> Several institutions (e.g., Beth Israel Deaconess, University of Colorado, Denver Health) are currently testing this approach with t-PA (alteplase).<sup>9</sup> Preliminary findings from the first few cases reported an initial, but transient improvement in PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio. <sup>9</sup> |

*Updated 1/28/21*

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<td>(DIC), elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis.</td>
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<td>Various case reports or case series describing the use of t-PA in severe COVID-19 patients have been published.</td>
<td>(alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg; however, the optimum dose, route of administration, and duration of treatment remain to be determined.</td>
<td>The NIH COVID-19 Treatment Guidelines Panel states that current data are insufficient to recommend for or against the use of thrombolytic agents in hospitalized COVID-19 patients outside the setting of a clinical trial; patients who develop catheter thrombosis or other indications for thrombolytic therapy should be treated according to the usual standard of care in patients without COVID-19.</td>
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<td>A consistent finding in patients with ARDS (regardless of the cause) is fibrin deposition and microthrombi formation in the alveoli and pulmonary vasculature.</td>
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<td>Many patients are found to have increased dead-space ventilation, a clinical feature of pulmonary embolism and diffuse pulmonary microemboli.</td>
<td>Dysregulation of the clotting system in ARDS is a result of both enhanced activation of coagulation and suppression of fibrinolysis.</td>
<td>In another case series, t-PA (doses varied) was administered concomitantly with heparin anticoagulation in 5 critically ill mechanically ventilated COVID-19 patients with apparent thrombotic coagulopathy and ARDS. Although respiratory status in all 5 patients improved following t-PA administration, sustained improvement was observed in only 3 of the patients.</td>
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<td>Thrombolytic therapy may restore microvascular patency and limit progression of ARDS in patients with COVID-19.</td>
<td>Fibrinolysis shutdown, as evidenced by complete failure of clot lysis on thromboelastography, has been observed in critically ill patients with COVID-19.</td>
<td>In these case reports, multiple confounding factors (including the use of various other treatments) were present, limiting interpretation of findings.</td>
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<td>Several randomized controlled studies evaluating IV alteplase in patients with ARDS due to COVID-19 are registered at clinicaltrials.gov.</td>
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<td>A phase 3 randomized, double-blind, placebo-controlled study (NCT04453371; AtTAC) has been initiated to evaluate t-PA (alteplase) IV infusion in patients with ARDS due to COVID-19.</td>
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<td>An open-label, nonrandomized pilot study (NCT04356833) is being conducted to evaluate an inhaled formulation of t-PA (via nebulization).</td>
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The Anticoagulation Forum recommends against the use of thrombolytic agents in COVID-19 patients outside the setting of a clinical trial unless there is another clinical indication (e.g., STEMI, acute ischemic stroke, high-risk [massive] PE with hemodynamic compromise); in general, thrombolytic therapy is not recommended in the vast majority of patients with PE given limited efficacy data in patients who are hemodynamically stable.

The American Society of Hematology states that treatment of the underlying pathology is paramount in COVID-19 patients with coagulopathies; supportive care should be individualized and standard risk factors for bleeding should be considered.
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<tr>
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<td>nebulization) in patients with ARDS due to COVID-19; 12 the inhaled formulation of t-PA is investigational at this time 15</td>
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<td>Several randomized, double-blind, placebo-controlled trials evaluating low-dose IV bolus tenecteplase in conjunction with anticoagulation for the treatment of COVID-19-associated respiratory failure are registered at clinicaltrials.gov.12</td>
<td></td>
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</tr>
</tbody>
</table>

See US prescribing information for additional information on dosage and administration of drugs commercially available in the US for other labeled indications.
ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)


Anakinra:


Anticoagulants


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58. Atallah B, Sadik ZG, Salem N et al. The impact of protocol 
57. Lopes RD, Fanaroff AC. Anticoagulation in COVID 
55. Dobesh PP, Trujillo TC. Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID 
54. Bai C, Chotirmall SH, Rello J et al. Updated guidance on the management of COVID 
Azithromycin:

Ascorbic acid:

Azithromycin:

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Baloxavir:


Chloroquine and Hydroxychloroquine:


Baricitinib:


39. US Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. April 24, 2020. Available at https://www.fda.gov/media/137250/download.


Colchicine:


Corticosteroids (systemic) and Corticosteroids (inhaled):


### COVID-19 Convalescent Plasma:


Favipiravir


Famotidine:


Favipiravir:


HMG-CoA Reductase Inhibitors (statins)


Frost FJ, Petersen H, Tollestrup K et al. Influenza and COPD mortality protection is pleiotropic, dose-dependent effects of statins. Chest. 2007; 130:1006-12. PMID: 17426203 DOI: 10.1378/chest.06-097


De Spiegheler A, Bronselaer A, Teo JT et al. The effects of ARBs, ACEIs and statins on clinical outcomes of COVID-19 infection among nursing home residents. J Am Med Dir Assoc. 2020; 21(7) 909-914.e2. PMCID: PMC7294267 DOI: 10.1016/j.jamda.2020.06.018


Immune Globulin:
Inhaled Prostacyclins:


Interferons:


Ivermectin:


Nebulizers:


Neuraminidase Inhibitors (e.g., oseltamivir):


Niclosamide:


Nitazoxanide:


Nitric Oxide (inhaled):


Updated 02-11-2021. The current version of this document can be found on the ASHP COVID-19 Resource Center.

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NSAIs, including ibuprofen:


Remdesivir:


**Ruxolitinib**


Sarilumab:

SARS-CoV-2-Specific Monoclonal Antibodies


Siltuximab:

Sirolimus:

Thrombolytic Agents (t-PA [alteplase], tenecteplase):


Tocilizumab:


Umifenovir:


Vitamin D:


**Zinc:**


The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.