Assessment of Evidence for COVID-19-Related Treatments: Updated 8/13/2020

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.


Selected entries were updated 8/13/20; 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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<tr>
<td>Baloxavir</td>
<td>8:18.92</td>
<td>Antiviral active against influenza viruses</td>
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<td></td>
<td>Antiviral</td>
<td>In vitro antiviral activity against SARS-CoV-2 demonstrated in one trial (^3)</td>
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<td>In vitro antiviral activity against various viruses, including coronaviruses (^{1,3,13,14})</td>
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<td>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 (^{1,4,32})</td>
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<td>Active in vitro against SARS-CoV-1 and MERS-CoV (^{2,3,5,9})</td>
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<td>Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in</td>
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\(^{1}\) Optimal dosage and duration of treatment not known \(^{25}\)  
\(^{2}\) Efficacy of in vitro EC\(_{50}\)/EC\(_{90}\) data and treatment duration not established \(^{35}\)  

**Antiviral Agents**

Updated 8-13-20. The current version of this document can be found on the ASHP COVID-19 Resource Center. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
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<th>Dosage*</th>
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<tr>
<td>patients with viral infections 13, 17, 36, 39</td>
<td></td>
<td>Known pharmacokinetics and toxicity profile based on use for other indications 13, 17</td>
<td>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 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>calculated lung concentrations; it is unclear whether this dosage regimen would provide any beneficial immunomodulatory effects. 57</td>
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<td>Double-blind, randomized, phase 2b study in Brazil (Borba et al; NCT04323527): 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. 35</td>
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<td>Additional data needed regarding toxicity profile when used in patients with COVID-19</td>
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<td>NIH COVID-19 Treatment Guidelines Panel recommends against use of chloroquine for the treatment of COVID-19, except in a clinical trial; the panel recommends against 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. 35</td>
<td></td>
<td>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</td>
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<td>IDSA recommends that chloroquine be used for the treatment of COVID-19 in the context of a clinical trial. 38 IDSA recommends that a combined regimen of chloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial. 38</td>
<td></td>
<td>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</td>
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<td>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: 13, 17, 36, 39 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 35, 36, 39 (See Hydroxychloroquine in this Evidence Table.)</td>
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<td>NIH panel states that 4-aminoquinolines (chloroquine, hydroxychloroquine)</td>
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<tr>
<td>Drug(s)</td>
<td>AHFS Class</td>
<td>Rationale</td>
<td>Trials or Clinical Experience</td>
<td>Dosage(^a)</td>
<td>Comments</td>
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<td>trials and experience with 4-aminoquinoline antimalarials in the management of COVID-19.</td>
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<td>Several clinical trials to evaluate chloroquine for the treatment of COVID-19 are registered at clinicaltrials.gov (some listed below):</td>
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<td>NCT04328493</td>
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<td>NCT04331600</td>
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<td>NCT04420247</td>
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<td>NCT04428268</td>
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<td>Several clinical trials to evaluate chloroquine for prevention of COVID-19 in the healthcare setting are registered at clinicaltrials.gov:</td>
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<td>NCT04303507</td>
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<td>NCT04333732</td>
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<td>NCT04343371</td>
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<td>should be used concomitantly with drugs that pose a moderate to high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, 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).</td>
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<td>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.</td>
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<td>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</td>
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<td>Drug(s)</td>
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<td>Rationale</td>
<td>Trials or Clinical Experience</td>
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<td>Favipiravir (Avigan®, Favilavir)</td>
<td>8:18.32</td>
<td>Antiviral</td>
<td>Only very limited clinical trial data available to date to evaluate use of favipiravir in the treatment of COVID-19</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 China.</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. Favoravir 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. 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. If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g.</td>
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**Updated 8/13/20**

**Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses.**

In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug. Licensed in Japan and China for treatment of influenza. Only very limited clinical trial data available to date to evaluate use of favipiravir in the treatment of COVID-19.

**Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): 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 (Arbidol®; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe to critical COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe to critical disease compared with the group receiving umifenovir. 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) 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 retrospective, observational, multicenter study in 63 adults with COVID-19 in Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and doses for 7–10 days) and higher improvement rate on chest CT imaging on day 14 (91 vs 62%) compared with the control group treated with umifenovir. 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 for 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 dose of 47.4 mg/kg on day 1 and doses for 7–10 days.

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 potential risks associated with the use authorized by the EUA. (See Hydroxychloroquine in this Evidence Table.)
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| HIV Protease Inhibitors | 8:18.08.08 HIV Protease Inhibitors | **Lopinavir (LPV):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells; evidence of in vitro activity against SARS-CoV-1 and MERS-CoV; some evidence of benefit in animal studies for treatment of MERS-CoV | 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 <45 mg/kg per day were negative predictors of early clinical improvement. | 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. 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. | **HIV Protease Inhibitors**

**Updated 7/30/20**

**Lopinavir (LPV):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells; evidence of in vitro activity against SARS-CoV-1 and MERS-CoV; some evidence of benefit in animal studies for treatment of MERS-CoV.

**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (Cao et al)** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale).

**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days.**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours).

**LPV/RTV:** Efficacy for the treatment of COVID-19, with or without other antivirals, not established.

**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.
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<th>Trials or Clinical Experience</th>
<th>Dosage*</th>
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<tbody>
<tr>
<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; human epithelial pulmonary cells (A549), and human monocytes</td>
<td>scale or hospital discharge, whichever came first. In ITT population, <strong>time to clinical improvement was not shorter with LPV/RTV compared with standard care</strong> (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group. The 28-day mortality rate was numerically lower in LPV/RTV group (19.2% vs 25% in ITT population; 16.7% vs 25% in modified ITT population). Some evidence that LPV/RTV initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. <strong>No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death. LPV/RTV stopped early in 13 pts because of adverse effects.</strong></td>
<td>LPV/RTV (COVID-19): LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days, with or without interferon (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ribavirin for up to 10 days; LPV/RTV (SARS): 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); LPV/RTV (MERS): 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>
<td>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>Darunavir (DRV):</td>
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<td>In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations in Caco-2 cells; in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells.</td>
<td>In one randomized open-label trial in adults with mild to moderate disease, all 10 pts treated with the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide had negative RT-PCR results 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>
<td>DRV (COVID-19): DRV 100 mg orally twice daily with cobicistat 100 mg orally twice daily with LPV 400 mg/RTV 100 mg, or equivalent twice daily, or with or without ribavirin (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ritonavir (500 mg orally twice daily).</td>
<td>NIH COVID-19 Treatment Guidelines Panel <strong>recommends against</strong> the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial. The panel states that, based on the pharmacodynamics of HIV protease inhibitors, there are concerns whether drug concentrations achieved with oral doses of the drugs are adequate to inhibit SARS-CoV-2 protease. In addition, clinical trials to date using LPV/RTV have not demonstrated a clinical benefit in patients with COVID-19.</td>
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<td>Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):</td>
<td></td>
<td>Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells.</td>
<td>In one randomized open-label trial in adults with mild to moderate disease, all 10 pts treated with the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide had negative RT-PCR results 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>
<td>DRV (COVID-19): DRV 100 mg orally twice daily with cobicistat 100 mg orally twice daily with LPV 400 mg/RTV 100 mg, or equivalent twice daily, or with or without ribavirin (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ritonavir (500 mg orally twice daily).</td>
<td>NIH COVID-19 Treatment Guidelines Panel <strong>recommends against</strong> the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial. The panel states that, based on the pharmacodynamics of HIV protease inhibitors, there are concerns whether drug concentrations achieved with oral doses of the drugs are adequate to inhibit SARS-CoV-2 protease. In addition, clinical trials to date using LPV/RTV have not demonstrated a clinical benefit in patients with COVID-19.</td>
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<td>IDSA recommends that LPV/RTV be used for the treatment of COVID-19 only in the context of a clinical trial.</td>
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<td>Drug(s)</td>
<td>AHFS Class</td>
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<td>moderate COVID-19 in Hong Kong (Hung et al; NCT04276688):</td>
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<td>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 scans were improving in 29% of pts treated with LPV/RTV alone vs 69% of pts treated with both drugs. (See Umifenovir in this Evidence Table.)</td>
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<td>LPV/RTV Clinical Experience (COVID-19):</td>
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<td>Only limited data on LPV/RTV used with or without interferon in pts with COVID-19 outside of clinical trials.</td>
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<td>LPV/RTV Clinical Experience (SARS and MERS):</td>
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<td>Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon.</td>
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<td>Darunavir and cobicistat (DRV/c) randomized, open-label trial in China (Chen et al):</td>
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<td>DRV/c</td>
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<td>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.</td>
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**LPV/RTV COVID-19 Clinical Trials:**
Some clinical trials registered at clinicaltrials.gov listed below:  
NCT04330690 (LPV/RTV vs hydroxychloroquine vs remdesivir)  
NCT04372628 (LPV/RTV vs placebo)  
NCT04403100 (LPV/RTV vs hydroxychloroquine vs LPV/RTV plus hydroxychloroquine vs placebo in pts with mild disease)  
NCT04315948 (LPV/RTV plus interferon β-1a vs LPV/RTV vs remdesivir [each regimen given with standard care] vs standard care)  
NCT04425382 (LPV/RTV vs DRV/cobicistat)  
NCT04455958 (LPV/RTV vs placebo)  

**Daranavir COVID-19 Clinical Trials:**
A few trials registered at clinicaltrials.gov:  
NCT04252274 (Open-label randomized trial to evaluate DRV/c)  
NCT04303299 (Open-label randomized trial includes treatment arms to evaluate DRV/RTV plus oseltamivir with or without hydroxychloroquine or DRV/RTV plus favipiravir followed by hydroxychloroquine)  
NCT04425382 (DRV/c vs LPV/RTV)
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<td>Hydroxychloroquine (Plaquenil®)</td>
<td>8:30.08</td>
<td><strong>Antimalarial (4-aminoquinoline derivative)</strong></td>
<td><strong>Clinical experience</strong> In treating pts with COVID-19: Majority of data to date involves use in pts with mild or moderate COVID-19; 7, 18, 31, 35, 47, 49 only limited clinical data on use in pts with severe and critical disease. 35 <strong>Hydroxychloroquine small pilot study conducted in China</strong>: 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; 18 both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV. 30 Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 13 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). 18 <strong>Hydroxychloroquine randomized, parallel-group study in adults in China</strong>: (ChiCTR2000029559): 31 pts with COVID-19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 5 days) and standard treatment (O₂, 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 &gt;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 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 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in</td>
<td>Optimal dosage and duration of treatment not known 26</td>
<td>Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established 10, 24, 39 No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19</td>
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hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group). **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, **data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported.**  

**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). 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 and standard of care and 56 treated with standard of care alone) had converted to negative for SARSCoV-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) was also similar in both groups. Adverse effects reported in 30% of those treated with hydroxychloroquine and 9% of those treated with standard of care alone. **Note:** Results indicate that use of hydroxychloroquine in pts with mild to moderate COVID-19 is effective for preventing SARS-CoV-2 infection when given before or after an exposure.  

**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.** 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.  

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. 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.  

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 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,
Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage\(^a\) | Comments
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m Moderate COVID-19 did not provide additional benefits compared with use of standard of care alone.\(^49\)

**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.\(^7\) *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) 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 day 13.**

**Hydroxychloroquine**

*Emergency use authorization (EUA) for hydroxychloroquine (now revoked):* Effective June 15, 2020, FDA has revoked the EUA for hydroxychloroquine and chloroquine \(^7\) 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.\(^24\) \(^57\) *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 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:

\(^a\) Including drug-induced cardiac effects.\(^35\) \(^36\) \(^38\) \(^39\) \(^41\) \(^44\)

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.\(^39\)

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### Drug(s)

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

**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 deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease.
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<td>Hydroxychloroquine with azithromycin uncontrolled, observational, retrospective analysis in France (Million et al):</td>
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<td>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.47</td>
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| 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. 48 **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. 45, 46

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 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). 46

Large, randomized, controlled, adaptive trial evaluating efficacy of 6 different treatments for prevention of death in hospitalized pts with COVID-19 compared with usual care alone (NCT04381936; RECOVERY): Study protocol included a treatment arm to evaluate efficacy of

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<td>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).</td>
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The investigators announced preliminary results for the hydroxychloroquine treatment arm. A total of 1542 pts were randomized to receive hydroxychloroquine with usual care and 3132 pts were randomized to usual care alone. Data for these pts indicate that hydroxychloroquine did not provide a significant difference in the primary end point of 28-day mortality (25.7% in those treated with hydroxychloroquine with usual care compared with 23.5% in those treated with usual care alone). In addition, there was no evidence of beneficial effects on duration of hospitalization or other outcomes. Note: Data regarding pt demographics and clinical characteristics (e.g., age, disease severity, comorbidities) and time from diagnosis to study enrollment have not been provided to date.

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...
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<td>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%). <strong>Note:</strong> 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. <a href="#">58</a></td>
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**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. [61](#) |

**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
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<td>(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&lt;sub&gt;10&lt;/sub&gt; 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).&lt;sup&gt;59&lt;/sup&gt;</td>
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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 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 \((n=6221)\), 16.4% in those treated with chloroquine alone \((n=1868)\), and 22.2% in those treated with chloroquine and a macrolide \((n=3783)\). **Note: This published study has now been retracted by the publisher at the request of 3 of the original authors.**

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<td>Concerns were raised with respect to the veracity of the data and analyses conducted by a global healthcare data collaborative. 51,52</td>
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**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 placebo); 66% were healthcare workers. Overall, 88% of participants reported high-risk exposures (occurred at a distance of <6 feet for >10 minutes while not wearing a face mask or eye shield) and the others reported moderate-risk exposures (occurred at a distance of <6 feet for >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 placebo (14.3%). 55 **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...**
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| Neuraminidase inhibitors (e.g., oseltamivir) | 8:18.28    | Antivirals active against influenza viruses  
Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in vitro cell culture  
Oseltamivir did not inhibit the replication of SARS-CoV-2 in infected Vero E6 cells in vitro | In a retrospective case series of 99 patients with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of patients 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.  
In a retrospective case series of 79 patients with COVID-19 who were negative for influenza A and B, early use of oseltamivir had  |

Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours.  
Dosages of oseltamivir from registered trials (either recruiting, or not yet recruiting) vary, but include 300 mg orally daily, 75 mg orally once or twice daily, and 4–6 mg/kg orally (frequency not specified).  |

No data to date support use in the treatment of COVID-19 |
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| Remdesivir    | 8:18.32    | Antiviral                      | 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 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. Note: Enrollment was terminated before the pre-specified．Optimal dosage and duration of remdesivir treatment not known 20, 25, 26
|               |            |                                | Emergency use authorization (EUA) remdesivir dosage and duration of treatment recommended for hospitalized adults and children weighing 40 kg or more: 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. 26
|               |            |                                | Emergency use authorization (EUA) remdesivir dosage and duration of treatment recommended for hospitalized children weighing 3.5 to less than 40 kg (using the 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 10 days. 26
|               |            |                                | Not commercially available in the US; most promising direct-acting antiviral (DAA) currently being investigated for COVID-19
|               |            |                                | Efficacy and safety of remdesivir for treatment of COVID-19 not established
|               |            |                                | The NIH COVID-19 Treatment Guidelines Panel issued guidelines regarding prioritizing use of remdesivir when supplies are limited: The panel recommends the drug be prioritized for use in hospitalized pts with COVID-19 who require supplemental oxygen, but are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, because efficacy in this pt population has been demonstrated. (For recommendations on treatment duration in such pts, see Dosage). The NIH panel states that they cannot make a recommendation either for or against initiating remdesivir in pts who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO because of uncertainty regarding whether initiating remdesivir in such pts confers clinical benefit. The panel states that these recommendations for prioritizing use of remdesivir are largely based on data from the phase 3 adaptive trial (NCT04280705; ACTT-1) in hospitalized adults with COVID-19 indicating that the benefit of remdesivir treatment was most apparent in pts who required supplemental oxygen. 26

Updated 8/13/20. The current version of this document can be found on the ASHP COVID-19 Resource Center. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
**Drug(s)**
- when given after animal already infected

**AHFS Class**
- 13

**Rationale**
- Pharmacokinetic data available from evaluations for Ebola

**Trials or Clinical Experience**
- 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 397 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 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 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.

**Dosage**
- 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.

**Comments**
- NIH COVID-19 Treatment Guidelines Panel-recommended duration of remdesivir treatment when supplies are limited: The NIH panel recommends that hospitalized pts who require supplemental oxygen, but are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, receive remdesivir for a duration of 5 days or until hospital discharge, whichever comes first. If the pt progresses 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.

- Phase 3 trial in adults and children ≥12 years of age with severe COVID-19 (NCT04292899; SIMPLE-Severe): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2); 100 mg IV on day 1, then 100 mg IV daily on days 2-10 (extension arms that include pts who are or are not receiving mechanical ventilation)

- Phase 3 trial in adults and children ≥12 years of age with moderate COVID-19 (NCT04292730; SIMPLE-Moderate): did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline. (See Trials or Clinical Experience.)

- NIH panel states that data are insufficient to recommend either for or against use of remdesivir for the treatment of mild or moderate COVID-19.

- Emergency use authorization (EUA) for remdesivir: FDA issued an EUA on May 1, 2020 that permits use of the drug for the treatment of COVID-19 only in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 who have severe disease (defined as oxygen saturation [SpO2] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) and requires that the drug be administered by a healthcare provider in an inpatient hospital setting via IV infusion at dosages recommended in the EUA.

- Distribution of remdesivir under this EUA is being directed by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state health departments. To request remdesivir for use under the EUA, healthcare providers should contact their state health department.

- The EUA 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).

- Concomitant use of remdesivir and chloroquine or hydroxychloroquine is not recommended; FDA warns that there is in vitro evidence that chloroquine antagonizes intracellular metabolic activation and antiviral activity of remdesivir.

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<td>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. 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 disease severity who received standard of care treatment (without remdesivir) during the same time period. More than 90% of pts in both groups were enrolled at North American trial sites and the rest were enrolled at European or Asian trial sites. Clinical recovery (improvement in clinical status based on a 7-point ordinal scale) and mortality rate for these 2 groups were compared. By day 14, recovery was reported in 74.4% of pts treated with remdesivir and 59% of pts in the retrospective cohort treated with standard of care and the mortality rate was 7.6 and 12.5%, respectively. 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 Moderate): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) Concomitant use of remdesivir and drugs that are strong inducers of cytochrome P-450 (CYP) isoenzymes (e.g., rifampin) is not recommended; remdesivir plasma concentration may be modestly reduced and the clinical relevance of such decreased concentrations is unknown. Although drug interaction studies have not been performed to date, remdesivir plasma concentrations are unlikely to be substantially altered by concomitant use with drugs that are weak to moderate inducers or strong inhibitors of CYP isoenzymes, P-glycoprotein (P-gp), or organic anion transport polypeptide (OATP).</td>
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<td>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 of 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. 34</td>
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<td>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 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 of care alone in adults with moderate COVID-19 (i.e., hospitalized with evidence of pulmonary infiltrates but without reduced oxygen levels); 32 protocol was subsequently modified to include pts 12 years of age or older and add an extension phase to include additional pts. 31</td>
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<td><strong>Manufacturer announced preliminary data</strong>&lt;br&gt;for the initial group of pts who received a 5-day regimen of remdesivir with standard of care (n=191), 10-day regimen of the drug with standard of care (n=194), or standard of care alone (n=200). At day 11, data indicate that 70, 65, or 61% of pts in the 5-day, 10-day, or standard of care alone group, respectively, had clinical improvement based on at least a 2-point improvement from baseline on a 7-point ordinal scale. When clinical improvement at day 11 was based on at least a 1-point improvement, data indicate a statistically significant improvement in clinical status in those treated with a 5-day regimen of remdesivir compared with standard of care alone (76% of pts in the 5-day group and 66% in the standard of care alone group had clinical improvement). Oxygen support of any kind was required in 11% of pts treated with standard of care alone compared with 6 or 7% of pts in the 5- or 10-day group, respectively. Although the differences were not statistically significant, at least a 1-point worsening of clinical status was reported in 11% of pts treated with standard of care alone compared with 3 or 6% of pts in the 5- or 10-day group, respectively. There were 4 deaths reported in the standard of care alone group compared with none in the 5-day group and 2 in the 10-day group. &lt;sup&gt;30&lt;/sup&gt;&lt;br&gt;&lt;br&gt;<strong>Note:</strong> Data regarding pt demographics and clinical characteristics at study enrollment (e.g., age, comorbidities, time to initiation of treatment after symptom onset) and information on any additional supportive treatment received not provided to date.</td>
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|         |            |           | study enrollment, time to initiation of treatment after symptom onset) were similar in both groups. Overall, 88.7% of pts had severe disease at study enrollment and the median time from symptom onset to randomization was 9 days (range: 6-13 days). Preliminary data analysis that included 1059 pts (538 randomized to remdesivir and 521 randomized to placebo) indicated **shorter median time to recovery in the remdesivir group (11 days) vs the placebo group (15 days)** and suggested that remdesivir treatment may have provided a survival benefit (Kaplan-Meier estimates of mortality by day 14 were 7.1% in the remdesivir group vs 11.9% in the placebo group). Based on preliminary subgroup analyses, the benefit of remdesivir was most apparent in the 421 pts who required supplemental oxygen but were not on mechanical ventilation or ECMO at baseline (recovery rate ratio 1.47). The recovery rate ratio in the subgroup of 272 pts on mechanical ventilation or ECMO at enrollment was 0.95. However, additional data analyses are needed and are ongoing regarding outcomes in these subgroups.  

**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. |
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- (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects. **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.

**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.  

**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
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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.

**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.

**Expanded access IND protocol (NCT04323761):** The manufacturer (Gilead) established a protocol for emergency access to remdesivir for the treatment of acute COVID-19 in hospitalized adults and children 12 years of age or older.

**Compassionate use access for pregnant women and children <18 years of age:** The manufacturer (Gilead) is accepting individual remdesivir compassionate use requests only for pregnant women and children <18 years of age with confirmed COVID-19 and severe manifestations of the disease. ([https://rdvcu.gilead.com/](https://rdvcu.gilead.com/))

**Compassionate use access (NCT04302766):** May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command.

**Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib (NCT04401579; ACTT2):** This iteration of NIAID’s Adaptive COVID-19 Treatment Trial (ACTT) is evaluating possible benefits of using baricitinib (a Janus kinase [JAK] inhibitor) in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and evidence of lung involvement.
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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>
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<td></td>
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<td>(abnormal chest x-rays, SpO₂ of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO). 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 oral baricitinib (4 mg once daily for the duration of hospitalization up to 14 days total) or placebo.²⁵ ³¹</td>
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<td><strong>Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with interferon beta-1a (NCT04492475; ACTT3):</strong> This iteration of NIAID’s Adaptive COVID-19 Treatment Trial (ACTT) will evaluate possible benefits of using interferon beta-1a in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection.³⁶ ³⁷ Inclusion criteria include evidence of lung involvement (radiographic infiltrates, SpO₂ 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 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.³⁶ ³⁷</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 will evaluate 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</td>
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<td>Drug(s)</td>
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| Umifenovir (Arbidol\(^b\)) | 8:18.92 | Antiviral | Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses \(^4\)
Although data limited, in vitro activity against SARS-CoV-1 \(^4\) and SARS-CoV-2 \(^5\) reported
Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza \(^4\) | **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 \(^8\)
**Retrospective cohort study** in 33 adults with COVID-19 in China suggests more favorable outcome with LPV/RTV plus umifenovir vs LPV/RTV alone: 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 12/16 pts (75%) treated with LPV/RTV plus umifenovir vs 6/17 pts (35%) treated with LPV/RTV alone; at 14 days, undetectable in 15/16 pts (94%) treated with both drugs vs 9/17 pts (53%) treated with LPV/RTV alone. At 7 days, chest CT scans were improving in 11/16 pts (69%) treated with both drugs vs 5/17 pts (29%) treated with LPV/RTV alone \(^1\)
**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) \(^9\)
**Open-label, prospective, randomized, multicenter study** in 236 adults with | **Dosage recommended for treatment of COVID-19 in China:** Adults, 200 mg orally 3 times daily for no more than 10 days \(^5,7\)
**Dosage used or being investigated in COVID-19 clinical trials:** 200 mg orally 3 times daily for duration of 7-10 days or longer \(^2,3,6,8\) | Not commercially available in the US
Included in some guidelines for treatment of COVID-19 \(^7\)
Efficacy for the treatment of COVID-19 not established |
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<td>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. ⁶ (See Favipiravir in this Evidence Table.)</td>
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<td>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. ⁶ (See Favipiravir in this Evidence Table.)</td>
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<td>Randomized, single-center, partially blind ed trial in China (NCT0425885) 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. ²,¹⁰ 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.¹⁰</td>
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<td>Randomized, single-center, partially blind ed trial in China (NCT0425885) 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. ²,¹⁰ 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.¹⁰</td>
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<td>NCT04260594 (not yet recruiting): Randomized, open-label trial evaluating efficacy and safety of umifenovir in conjunction with standard of care in adults with COVID-19 ³</td>
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## SUPPORTING AGENTS

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| Anakinra (Kineret®) Updated 7/2/20 | 92:36 Disease-modifying Anti-rheumatic Drug | Recombinant human interleukin-1 (IL-1) receptor antagonist ¹ | Currently no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19 ² | Various dosage regimens are being studied ³,⁴,⁵  
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 ³  
Some studies under way in Europe are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge ³  
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 ⁵,⁶  
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 ⁷  
(Note: Anakinra is approved only for subcutaneous administration in the U.S.) ¹,⁵ | 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 ⁷ |
| | | 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 ⁶,⁷,⁸  
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 2 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 ⁵,⁷,⁸  
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 ⁸  
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 with non-invasive ventilation outside of the ICU at a |  

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<tr>
<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><strong>IV ascorbic acid:</strong> 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 NCT04264533 NCT04323514 NCT04363216</td>
<td><strong>IV ascorbic acid:</strong> 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</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</td>
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**Updated 7/30/20**

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 3 Numerous other clinical trials evaluating anakinra in the treatment of COVID-19 are planned or under way, mainly in Europe 3

**Updated 8-13-20. The current version of this document can be found on the ASHP COVID-19 Resource Center.**

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<tr>
<td>Azithromycin</td>
<td>8:12.12</td>
<td>Macrolides</td>
<td>Adjunctive therapy in certain respiratory viral infections: Although contradictory results reported, some evidence of beneficial immunomodulatory and ant-inflammatory effects when used in pts with some viral infections (e.g., influenza). However, in a retrospective cohort study in critically ill pts with laboratory-confirmed MERS, there was no statistically significant effect.</td>
<td>Adjunctive treatment in certain viral infections: 500 mg once daily has been used.</td>
<td>Current data are insufficient to establish pros and cons of adjunctive use of azithromycin in the management of COVID-19, including use for empiric antibacterial coverage for suspected secondary bacterial pneumonia. Empiric coverage for bacterial pathogens is not required and is not recommended.</td>
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**Drug(s):**

- **NCT04401150 (LOVIT-COVID)**
- **NCT04395768**

**Oral ascorbic acid:**

Randomized, open-label study (NCT04342728; COVIDATo2) 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 oral ascorbic acid treatment registered, including NCT04395768.

- Included at lower dosages as an active or placebo-equivalent comparator (control) in other COVID-19 prevention or treatment studies.
- Included as a component of some hydroxychloroquine-based combination regimens being studied for prevention or treatment of COVID-19.

**Other infections:**

- Sepsis: Meta-analysis of several small studies suggested beneficial effects from IV ascorbic acid; however, primary end points not improved in CITRIS-ALI study (NCT02106975) in patients with sepsis and ARDS or in VITAMINS study (NCT03333278) in patients with septic shock; additional studies under way.
- Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia.
- 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.

**Dosage:**

- **Oral ascorbic acid:**
  - NCT04342728: Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses.
  - NCT04395768 (outpatients): Ascorbic acid 1 g orally 3 times daily for 7 days following initial 200-mg/kg IV dose.

**Note:** May interfere with laboratory tests based on oxidation-reduction reactions (e.g., blood and urine glucose testing, nitrite and bilirubin concentrations, leukocyte counts). High circulating vitamin C concentrations may affect accuracy of point-of-care glucometers. Manufacturer states to delay oxidation-reduction reaction-based tests until 24 hours after infusion, if possible.

**Inconclusive. Studies of ascorbic acid in patients with sepsis or ARDS have shown variable efficacy and limited safety concerns.**

NIH COVID-19 Treatment Guidelines Panel also states that there are insufficient data to recommend either for or against use of ascorbic acid for the treatment of COVID-19 in noncritically ill patients. The panel states that there is no compelling reason to use ascorbic acid in this setting since patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation.
Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage\(^a\) | Comments
--- | --- | --- | --- | --- | ---
\[\text{Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated.}\] & \[\text{Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza).}\] & \[\text{difference in 90-day mortality rates or clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not.}\] & \[\text{Adjunctive therapy in certain respiratory conditions: Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS).}\] & \[\text{Clinical experience in pts with COVID-19: Has been used for antibacterial coverage in hospitalized pts with COVID-19.}\] & \[\text{Recommended in all pts with confirmed COVID-19-related pneumonia. If bacterial pneumonia or sepsis is strongly suspected or confirmed, empiric antibacterial treatment should be administered.}\]

\[\text{Use in conjunction with hydroxychloroquine in pts with COVID-19: Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), open-label uncontrolled study in France (11 pts), uncontrolled observational study in France (80 pts), and larger uncontrolled observational study in France (1061 pts). Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.)}\] & \[\text{Use in conjunction with hydroxychloroquine in hospitalized pts with COVID-19: Data from 2 retrospective studies that analyzed outcome data for hospitalized pts in New York treated with hydroxychloroquine with or without azithromycin indicate that use of the 4-aminoquinoline antimalarial with or without azithromycin is not associated with decreased in-hospital mortality.}\] & \[\text{Multiple clinical trials to evaluate azithromycin alone or azithromycin with hydroxychloroquine or chloroquine for} \] &
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<tr>
<td>Baricitinib</td>
<td>92:36</td>
<td>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</td>
<td>Currently no known published controlled clinical trial evidence supporting efficacy or safety in patients with COVID-19. 1-3</td>
<td>Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1. 1, 3-5</td>
<td>not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. 20, 22, 25, 28, 33</td>
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<td>(Olumiant®)</td>
<td>Disease-modifying Anti-rheumatic Drug</td>
<td>Inhibits JAK1 and JAK2-mediated cytokine release; may combat cytokine release syndrome (CRS) in severely ill patients. 1-5</td>
<td>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. 13, 14</td>
<td>Dosage information not yet available (see Trials or Clinical Experience)</td>
<td>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</td>
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<td>Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a</td>
<td>Baricitinib was well tolerated with no serious adverse events reported. 13 At week 1 and week 2, patients who received baricitinib had significant improvement in respiratory function parameters and none of the patients required ICU support. 13</td>
<td>NIH COVID-19 Treatment Guidelines Panel recommends dosage adjustment if baricitinib is administered concurrently with a strong OAT3 inhibitor 11</td>
<td>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.)</td>
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<td>treatment of COVID-19 are registered at clinicaltrials.gov (some listed below): 29</td>
<td>Baricitinib is included in the second phase of NIAID’s Adaptive COVID-19 Treatment Trial (ACTT 2; NCT04401579). 5, 12, 15, 17</td>
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<td>NCT04329832</td>
<td>Inclusion criteria: Laboratory-confirmed COVID-19 infection and evidence of lung injury. 5, 12, 15, 17</td>
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<td>NCT04332107</td>
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<td>Colchicine</td>
<td>92:16 Antigout Agents</td>
<td>possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19</td>
<td>involvement (abnormal chest X-rays, SpO₂ of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO); Patients randomized to receive treatment with remdesivir with or without baricitinib. Remdesivir administered as one 200-mg IV dose on day 1 followed by 100 mg IV daily for the duration of hospitalization (up to 10-day treatment course). Baricitinib administered as a 4-mg oral dose administered once daily for the duration of hospitalization (up to 14-day treatment course).</td>
<td>Adaptive phase 2/3 clinical trial: Open-label study planned to evaluate safety and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232)</td>
<td>Safety and efficacy for treatment of COVID-19 not established</td>
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<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</td>
<td>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>May combat the hyper-inflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines ²</td>
<td>indication for and duration of colchicine use were unknown ¹⁵</td>
<td>Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days ¹</td>
<td>Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19 ²</td>
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<td>NLRP3 inflammasome activation results in release of interleukins, including IL-1β ³,⁵,⁶,⁹,¹¹</td>
<td>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 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. ¹⁶</td>
<td>Consider possible need for colchicine dosage adjustment; ⁷ manufacturer-recommended dosages for labeled indications depend on patient’s age, renal and hepatic function, and concomitant use of interacting drugs, including protease inhibitors (e.g., lopinavir/ritonavir), other moderate or potent CYP3A4 inhibitors, and P-glycoprotein (P-gp) inhibitors ⁵</td>
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<td>In experimental models of acute respiratory distress syndrome/acute lung injury (ARDS/ALI), the NLRP3 inflammasome had a major role in the development of lung injury ³,¹¹</td>
<td>Potential to limit COVID-19-related myocardial damage also has been hypothesized ² ² based on the drug’s mechanisms of action and promising results of ongoing research on colchicine in various cardiac conditions ¹,⁶,¹⁰</td>
<td>Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated ⁵</td>
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<td>SARS-CoV-1 envelope (E) protein, a viroporin involved in replication and virulence, activates the NLRP3 inflammasome in vitro in Vero E6 cells by forming calcium-permeable ion channels, leading to increased IL-1β production ³,¹²,¹³</td>
<td>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 peak C-reactive protein concentration. Small number of clinical events limited the statistical robustness of the results. ¹⁷</td>
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¹⁵ 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 temperature <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. ¹⁶

¹⁷ Phase 3, randomized, double-blind, placebo-controlled study (NCT04322682; COL-CORONA) initiated in adults ≥40 years of age. Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days ¹

² Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19 ²

⁷ Consider possible need for colchicine dosage adjustment; ⁷ manufacturer-recommended dosages for labeled indications depend on patient’s age, renal and hepatic function, and concomitant use of interacting drugs, including protease inhibitors (e.g., lopinavir/ritonavir), other moderate or potent CYP3A4 inhibitors, and P-glycoprotein (P-gp) inhibitors ⁵

⁵ Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated ⁵
### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage | Comments
--- | --- | --- | --- | --- | ---
Corticosteroids (systemic) | 68:04 Adrenals | Potent 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 | 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

Evidence suggests that cytokine storm, a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), is a contributing factor in COVID-19-associated mortality. Immunosuppression from corticosteroids has been proposed as a treatment option for such hyperinflammation.

May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low

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).

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.

Dexamethasone randomized, controlled, unblinded study in hospitalized patients with ARDS (DEXA-ARDS): The effects of dexamethasone in conjunction with conventional care were evaluated in hospitalized patients with moderate-to-severe ARDS receiving lung-protective mechanical ventilation. Treatment with IV dexamethasone at a dosage of 20 mg once daily on days 1-5, followed by 10 mg once daily on days 6-10 resulted in reduced duration of mechanical ventilation and reduced overall mortality (i.e., 15% increase in 60-day survival) compared with conventional

The NIH COVID-19 Treatment Guidelines Panel recommends an IV or oral Dexamethasone dosage of 6 mg daily for up to 10 days 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: Hydrocortisone 160 mg, Methylprednisolone 32 mg, or Prednisone 40 mg. Based on half-life and duration of action, frequency of administration varies among these corticosteroids. Dexamethasone is long-acting and administered once daily. Methylprednisolone and Prednisone are intermediate-acting and administered once daily or in 2 divided doses daily. Hydrocortisone is short-acting and administered in 2-4 divided doses daily.

Regimens used in China were typically methylprednisolone 40-80 mg IV

Data on the use of corticosteroids in COVID-19 are limited. The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19.

NIH, CDC, WHO, IDSA, and other experts have issued guidelines for the use of corticosteroids in patients with COVID-19 based on the currently available information. Recommendations are made according to the severity of illness, indications, and underlying medical conditions and should be considered on a case-by-case basis.

Non-critical patients: Corticosteroids generally should not be used in the treatment of early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding.

Critically ill patients: The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and...
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<td>treatment alone. 27 Based on results of this study, a randomized controlled open-label trial (NCT04325061; DEXA-COVID19) has been initiated to specifically evaluate the use of IV dexamethasone at the same dosage of 20 mg once daily on days 1-5, followed by 10 mg once daily on days 6-10 in patients with ARDS due to COVID-19. 21</td>
<td>daily for a course of 3-6 days. Some experts suggest that equivalent dosages of dexamethasone (i.e., 7-15 mg daily, typically 10 mg daily) may have an advantage of producing less fluid retention, since dexamethasone has less mineralocorticoid activity. 8 This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial. 6,11 However, lower dosages of dexamethasone (i.e., 6 mg once daily for 10 days) were used in the RECOVERY trial. 32,33</td>
<td>respiratory failure (without ARDS). 12 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. 12</td>
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<td>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 invasive 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 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 &gt;7 days compared with those having more recent symptom onset. Dexamethasone treatment also suggested for cytokine storm. 6 (See Comments column.)</td>
<td>Methylprednisolone: Dosage used in the retrospective study (Wang et al) was 1-2 mg/kg daily IV for 5-7 days. 13</td>
<td>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) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. The panel recommends against the use of dexamethasone in COVID-19 patients who do not require supplemental oxygen. ** The NIH guideline panel states that it is not known at this time whether other corticosteroids will have a similar benefit as dexamethasone. However, if dexamethasone is not available, the panel recommends using alternative corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone). 24</td>
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|  |  |  | Corticosteroid dosages used in patients included in the retrospective, observational study (Keller et al) not provided. 36 |  | IDSA suggests the use of corticosteroids over no corticosteroid therapy in hospitalized patients with severe COVID-19 (i.e., defined as patients with SpO2 ≤94% on room air and those who require supplemental oxygen, mechanical ventilation, or ECMO). 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 COVID-19 without hypoxemia requiring supplemental oxygen. 25 | Findings from observational studies suggest that for patients with COVID-19 pneumonia who progress to ARDS,
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<td>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. 24, 32, 33</td>
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<td><strong>Note:</strong> 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.</td>
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**Methylprednisolone retrospective, observational, single-center study:** In 201 patients with confirmed COVID-19 pneumonia who developed ARDS, methylprednisolone appeared to reduce the risk of death. 6

Among patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46%) patients died, while of those who did not receive methylprednisolone, 21 of 34 (61.8%) died. 6

**Methylprednisolone retrospective, observational, single-center study (Wang et al):** In 46 patients with confirmed severe COVID-19 pneumonia that progressed to acute respiratory failure, use of methylprednisolone was associated with improvement in clinical symptoms (i.e., fever, hypoxia) and a shortened disease course. 13

Death occurred in 3 patients during hospitalization; 2 of these patients received methylprednisolone. 13

**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. 23

**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, methylprednisolone) treatment may be beneficial. However, results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Confirmation from randomized controlled studies is needed. 6, 13

**Cytokine storm:** There is no well-established or evidence-based treatment for cytokine storm in patients with COVID-19. 8 However, some experts suggest that use of more potent immunosuppression with corticosteroids may be beneficial in such patients. 8 These experts suggest higher dosages of corticosteroids (e.g., IV methylprednisolone 60-125 mg every 6 hours for up to 3 days) followed by tapering of the dose when inflammatory markers (e.g., C-reactive protein levels) begin to decrease. 8 The decision to use corticosteroids in patients with early signs of cytokine storm should be balanced with the known adverse effects. 24

**Septic shock:** The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different than the effects seen in those with ARDS. 12 The Surviving Sepsis Campaign and NIH suggest the use of low-dose corticosteroid therapy (e.g., hydrocortisone 200 mg daily as an IV infusion or intermittent doses) over no corticosteroid therapy in adults with COVID-19 and refractory shock. 12, 24

Randomized controlled studies evaluating use of corticosteroids (e.g., hydrocortisone, dexamethasone, methylprednisolone, prednisolone) in septic shock suggest a small, but uncertain mortality reduction. 3, 4 Clinicians considering corticosteroids for such patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding. 1 If corticosteroids are prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia. 1, 4
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<td>hydrocortisone, methylprednisolone, prednisone</td>
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<td>Patients receiving corticosteroid therapy for chronic conditions: NIH states 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. (See Corticosteroids [inhaled] in this Evidence Table for recommendations for use of inhaled corticosteroids in COVID-19 patients with asthma or COPD.)</td>
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<td>Rheumatology experts, including members of the American College of Rheumatology COVID-19 Clinical Guidance Task Force, state that abrupt discontinuance 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.</td>
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<td>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. 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. These guidelines also apply to patients who are receiving prolonged therapy (&gt;3 months) with corticosteroids for underlying inflammatory conditions, including asthma, allergy, and rheumatoid arthritis. In such conditions, the patients should be monitored closely for signs of adrenal insufficiency and the corticosteroid dose should be adjusted accordingly.</td>
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Dexamethasone, hydrocortisone, or prednisone for treatment of COVID-19 pneumonia: Registered clinical trials that have been initiated or underway include:

- NCT04327401
- NCT04344288
- NCT04344730
- NCT04348305
- NCT04359511
- NCT04360876
- NCT04395105

Note: The limitations of the observational study design should be considered when interpreting these results. Further study is needed to determine the role of CRP levels in guiding the use of corticosteroid treatment in patients with COVID-19.

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. |
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| Methylprednisolone | | | **Methylprednisolone studies for treatment of COVID-19 pneumonia or ARDS:** Registered clinical trials that have been initiated or underway include: 22  
NCT03852537  
NCT04263402  
NCT04273321  
NCT04323592  
NCT04329650  
NCT04343729  
NCT04374071 | | | patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral 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, 26  
Additional study is needed to determine the optimum corticosteroid stress dosage regimens in patients with COVID-19. 19, 26  
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  
**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 |

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| Corticosteroids (inhaled) | Added 7/23/20 | Inhaled corticosteroids may mitigate local inflammation and inhibit virus proliferation. | There are currently no published studies specifically evaluating use of inhaled corticosteroids in patients with COVID-19. 
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. 
Clinical trials evaluating the use of inhaled corticosteroids (e.g., budesonide, ciclesonide) in patients with COVID-19 are being planned or underway, including the following trials registered at clinicaltrials.gov: NCT04330586, NCT04355637, NCT04377711, NCT04381364, NCT04416399, NCT04435795 | 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. | 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. 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 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. |
| Inhaled prostacyclins (e.g., epoprostenol, iloprost) | Updated 7/16/20 | Selective pulmonary vasodilators; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19 | There are currently no published studies specifically evaluating use of inhaled prostacyclins in COVID-19 patients. 
In patients with ARDS, inhaled prostacyclins have been shown to substantially reduce mean pulmonary artery pressure and | Various dosages of inhaled epoprostenol have been used in patients with ARDS: Dosages up to 50 ng/kg per minute (titrated to response) have been used in clinical studies. 
To provide a clinically important increase in PaO₂ and reduction in | 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 |

1, 4, 6, 9, 10

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<td>Interferons</td>
<td>8:18.20</td>
<td>Interferons (IFNs) modulate immune responses to some viral infections; 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 to compensate for possibly insufficient endogenous IFN production 1, 3, 4, 7, 18</td>
<td>Only limited clinical trial data available to date specifically evaluating efficacy of IFNs for treatment of COVID-19; for information on additional studies including IFN alfa or IFN beta 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: NCT04315948 (IFN beta-1a) NCT04492475 (IFN beta-1a) NCT04324463 (IFN beta) NCT04343768 (IFN beta-1a, IFN beta-1b) NCT04385095 (SNG001 [inhaled IFN beta-1a]) Open-label, randomized study in Hong Kong in hospitalized adults with COVID-19, mainly mild disease (NCT04276688): Combination regimen of LPV/RTV, ribavirin, and sub-Q IFN beta-1b (IFN beta-1b was omitted to avoid proinflammatory effects when treatment was initiated 7-14 days after symptom onset) was associated with shorter median time from treatment initiation to negative RT-PCR result in nasopharyngeal swab (7 vs 12 days), earlier resolution of symptoms (4 vs 8 days), and shorter hospital stay (9 vs 14 days) compared to these studies suggest that the most effective and safe dosage appears to be 20-30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients 9 Dosage of inhaled iloprost in the phase 2, open-label study (NCT04445246) that has been initiated in patients with suspected or confirmed COVID-19 is 20 mcg every 8 hours for 5 days (delivered by nebulization) 13</td>
<td>Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established 12 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., &lt;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. 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</td>
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<td>IFN alfa and IFN beta are active in vitro against SARS-CoV-2 in Vero cells at clinically relevant concentrations; in vitro study suggests SARS-CoV-2 is more sensitive than SARS-CoV-1 to IFN alfa. However, lack of clinical benefit observed with use of type 1 IFNs, generally in combination with ribavirin, for treatment of SARS and MERS. IV IFN beta-1a did not reduce ventilator dependence or mortality in a placebo-controlled trial in patients with acute respiratory distress syndrome (ARDS)</td>
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<td>Type 3 IFNs (IFN lambda) are thought to provide important immunologic defense against respiratory viral infections and may have less potential than type 1 IFNs to produce systemic inflammatory response, including inflammatory effects on respiratory tract; IFN lambda receptor is expressed mainly on epithelial (including respiratory epithelial) cells and neutrophils, and is distinct from the ubiquitous type 1 IFN receptor; despite different receptors and expression patterns, type 1 and type 3 IFNs activate similar signaling cascades; unknown whether limited receptor distribution might also affect efficacy</td>
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<td>with control (LPV/RTV). In the subset of patients initiating treatment 7 or more days after symptom onset (i.e., those not treated with IFN beta-1b), there was no significant difference in time to negative RT-PCR result, time to resolution of symptoms, or duration of hospital stay between the combination regimen (LPV/RTV and ribavirin) and control (LPV/RTV). IFN beta-1b (8 million units on alternate days) was administered for 1, 2, or 3 doses when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset (median of 2 IFN beta-1b doses given); 52 of 86 patients (60%) randomized to combination regimen received all 3 drugs, and 41 patients received control LPV/RTV. 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 atazanavir/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 vs 8.3 days); durations of hospital stay, ICU stay, and mechanical ventilation also did not differ between the groups. Discharge rate on day 14 (67% vs 44%) was higher and 28-day overall mortality rate (19 vs 44%) was significantly lower with IFN beta-1a compared with control; early initiation of IFN beta-1a (&lt;10 days after symptom onset), but not late initiation of the drug (≥20 days after symptom onset), was associated with reduced mortality. NOTE: Total of 92 patients were randomized; results are based on the 42 IFN beta-1a-treated patients and 39 control patients who completed the study. Percentage of patients with RT-PCR-confirmed disease not reported to date. Patients were recruited from general, intermediate, and ICU wards; 45% of the IFN beta-1a-treated patients and 59% of the control patients were admitted to ICU; 36 and 44%, 3, and 6 in conjunction with 14-day regimen of LPV/RTV</td>
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<tr>
<td>Peginterferon lambda-1a: For treatment of COVID-19 in adults (NCT04344600): Two 180-mcg sub-Q doses of peginterferon lambda-1a given 1 week apart</td>
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*Interferon alfa via atomization inhalation is included in Chinese guidelines as a possible option for treatment of COVID-19.
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<tr>
<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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<tbody>
<tr>
<td>Nitric oxide (inhaled)</td>
<td>48:48 Vasodilating Agent</td>
<td>Selective pulmonary vasodilator with bronchodilatory 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&lt;sup&gt;2, 3, 9, 11, 14&lt;/sup&gt; Also has been shown to have antiviral effects. In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronaviruses&lt;sup&gt;1, 11&lt;/sup&gt;</td>
<td>There are currently no published studies specifically evaluating use of inhaled nitric oxide in COVID-19 patients&lt;sup&gt;10&lt;/sup&gt; One case report described possible benefit in a SARS-CoV-2-positive outpatient who also had idiopathic pulmonary arterial hypertension&lt;sup&gt;15&lt;/sup&gt; Randomized controlled studies of inhaled nitric oxide in ARDS patients generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment)&lt;sup&gt;4, 5, 6&lt;/sup&gt; Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway, including the NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign recommend against the routine use of inhaled nitric oxide in mechanically ventilated COVID-19 patients with ARDS; however, a trial of inhaled pulmonary vasodilator as rescue therapy may be considered in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment&lt;sup&gt;10, 12&lt;/sup&gt;</td>
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Aerosolized IFN alfa (not commercially available in U.S.) has been used in China in children and adults for treatment of COVID-19<sup>13, 14, 15</sup> 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<sup>®</sup>) (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.<sup>15</sup>

Sub-Q peginterferon lambda-1a (not commercially available in U.S.) is being evaluated for treatment (e.g., NCT04354259, NCT04388709) and postexposure prophylaxis (e.g., NCT04344600) of SARS-CoV-2 infection<sup>5</sup><sup>10</sup>

In the Chen et al. study in severe SARS patients, inhaled nitric oxide therapy was given for 23 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)<sup>2</sup>

Various dosing protocols using different methods of delivery are being evaluated in ongoing studies in COVID-19 patients<sup>3</sup>
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<th>Drug(s)</th>
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<th>Trials or Clinical Experience</th>
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<tr>
<td>Ruxolitinib (Jakafi®)</td>
<td>Antineoplastic Agents</td>
<td>syndrome coronavirus (SARS-CoV-1) (^1), (^14) In a small pilot study (Chen et al.) conducted during the SARS outbreak, treatment with inhaled nitric oxide was found to reverse pulmonary hypertension, improve severe hypoxia, and shorten the duration of ventilatory support in critically ill SARS patients (^2), (^3) Genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential benefit in patients with COVID-19 (^1), (^14) following trials: NCT04388683, NCT04383002, NCT04421508, NCT04397692, NCT04398290, NCT04338828, NCT04305457, NCT04306393, NCT04312243</td>
<td>Various dosages are being evaluated (^3), (^6), (^10) Phase 3 study (NCT04362137): Ruxolitinib 5 mg twice daily for 14 days with possible extension to 28 days (^10) Phase 3 study (NCT04377620): Ruxolitinib 5 or 15 mg twice daily (approximately every 12 hours) (^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 second patient; these cases differed in the timing of ruxolitinib initiation and the severity of COVID-19 illness (^11)</td>
<td>Janus kinase (JAK) 1 and 2 inhibitor; may potentially combat cytokine release syndrome (CRS) in severely ill patients (^5), (^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 infectivity by disrupting regulators of endocytosis (e.g., AP2-associated protein kinase 1 [AAK1]). (^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 (^5), (^7)</td>
<td>Limited published clinical trial evidence regarding efficacy and safety in patients with COVID-19 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 inflammation (CIS ≥10, without sepsis) were evaluated for 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. (^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...</td>
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<td>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.</td>
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<td>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 control patients 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.</td>
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<td>Phase 3 randomized, double-blind, placebo-controlled clinical trial (NCT04362137; RUXCOVID) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.)</td>
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<td>Sarilumab (Kevzara®)</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>
<td>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).</td>
<td>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)</td>
<td>NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of sarilumab in the treatment of COVID-19. No new safety findings observed with use in COVID-19 patients.</td>
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<td>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 <a href="mailto:medinfo@incyte.com">medinfo@incyte.com</a>).</td>
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<td>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 <a href="mailto:medinfo@incyte.com">medinfo@incyte.com</a>).</td>
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<td>Other clinical trials also registered, including: NCT04338958 NCT04348695 NCT04403243 NCT04477993</td>
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severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab rapidly lowered C-reactive protein (CRP) levels, meeting the primary end point. Baseline IL-6 levels were elevated in all treatment arms; higher levels were observed in critical patients compared with severe patients. At the time of data analysis, of the 226 critical patients, 32% in the sarilumab 400-mg group had died or were on a ventilator, compared with 46% in the 200-mg group and 55% in the placebo group. Comparing mortality alone, 23% of those in the sarilumab 400-mg group died compared with 36% in the 200-mg group and 27% in the placebo group. In contrast to the positive outcomes among critical patients, negative trends for most outcomes were observed in severe patients.  

A second manufacturer-sponsored phase 3 clinical trial is under way in countries outside the U.S. (Italy, Spain, Germany, France, Canada, Russia, Israel, and Japan). Approximately 400 patients hospitalized with COVID-19 are expected to be enrolled; initial results expected in the third quarter of 2020.  

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.  

Multiple clinical trials to evaluate sarilumab for treatment of COVID-19 are registered at clinicaltrials.gov.
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<tr>
<td>Siltuximab (Sylvant&lt;sup&gt;®&lt;/sup&gt;)&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;Added 5/13/20</td>
<td>10:00 Antineoplastic agents</td>
<td>Recombinant chimeric monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients&lt;sup&gt;1,5&lt;/sup&gt;</td>
<td><strong>Italy:</strong> Early (non-peer-reviewed) findings from an observational case-control study of the first 21 patients with COVID-19 and pneumonia/acute respiratory distress syndrome (ARDS) who participated in a compassionate use program (SISCO study; NCT04322188) in one hospital and were followed for up to 7 days showed reduced and normalized C-reactive protein (CRP) levels (a marker of systemic inflammation) by day 5 in all 16 siltuximab-treated patients with sufficient available data. An interim analysis revealed that the condition of 33% of the siltuximab-treated patients improved and no clinically relevant change in condition was reported in 43% of patients while 24% of patients worsened, including one patient who died and another with a cerebrovascular event. This cohort study with patients treated with standard therapy is ongoing.&lt;sup&gt;4,6&lt;/sup&gt;&lt;br&gt;Other clinical trials evaluating siltuximab in the treatment of COVID-19 currently are recruiting in Belgium (NCT04330638)&lt;sup&gt;7&lt;/sup&gt; and Spain (NCT04329650)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>In the SISCO study in Italy, patients received an initial dose of siltuximab 11 mg/kg by IV infusion over 1 hour; a second dose could be administered at the physician’s discretion (5 of the first 21 patients received a second dose after 2-3 days)&lt;sup&gt;4&lt;/sup&gt;&lt;br&gt;Other clinical studies under way are evaluating a single siltuximab dose of 11 mg/kg by IV infusion&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>Efficacy and safety of siltuximab in the treatment of COVID-19 not established; additional study needed</td>
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<td>Sirolimus (Rapamune&lt;sup&gt;®&lt;/sup&gt;)&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;&lt;br&gt;Updated 8/6/20</td>
<td>92:44 Immunosuppressive agent; mammalian target of rapamycin (mTOR) inhibitor</td>
<td>mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus&lt;sup&gt;1,2,5&lt;/sup&gt;&lt;br&gt;In vitro studies demonstrated inhibitory activity against MERS-CoV infection&lt;sup&gt;7&lt;/sup&gt;&lt;br&gt;Limited experience in patients with H1N1 pneumonia suggests possible benefit; in one study, treatment with sirolimus 2 mg daily in conjunction with corticosteroids for 14 days was associated with improved patient outcomes (e.g., shortened duration of mechanical ventilation, improved hypoxia and multi-organ function)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Clinical trials evaluating sirolimus for the treatment of COVID-19 are planned or underway including the following trials:&lt;sup&gt;4&lt;/sup&gt;&lt;br&gt;NCT04341675 (SCOPE)&lt;br&gt;NCT04374903 (COVID19-HOPE)&lt;br&gt;NCT04371640&lt;br&gt;NCT04461340&lt;br&gt;NCT04482712 (RAPA-CARDS)</td>
<td>Various dosing regimens are being evaluated in registered trials&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Although possible clinical application, current data not specific to COVID-19; additional study needed&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>Tocilizumab</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. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients&lt;sup&gt;1-3, 6, 9,10, 14&lt;/sup&gt;</td>
<td>Case reports and observational and open studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world&lt;sup&gt;1-3, 5, 10, 12, 15, 17&lt;/sup&gt; 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)&lt;sup&gt;3&lt;/sup&gt; 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.&lt;sup&gt;10&lt;/sup&gt; 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.</td>
<td>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&lt;sup&gt;5, 17&lt;/sup&gt; The subcutaneous formulation of tocilizumab is not intended for IV use&lt;sup&gt;9&lt;/sup&gt; IV infusion: China recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg&lt;sup&gt;2&lt;/sup&gt; US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA): Will evaluate an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose may be given if symptoms worsen or show no improvement&lt;sup&gt;8&lt;/sup&gt;</td>
<td>In China, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels&lt;sup&gt;2&lt;/sup&gt; NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of tocilizumab in the treatment of COVID-19&lt;sup&gt;9&lt;/sup&gt; The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study&lt;sup&gt;14&lt;/sup&gt;</td>
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Updated 6/25/20

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<td><strong>Italy</strong>: A prospective, open, single-arm, multicenter study evaluated the 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 PaO\textsubscript{2}/FiO\textsubscript{2} ratio improved between admission and Day 7. Overall mortality was 11%. Tocilizumab appeared to be well tolerated.\textsuperscript{17}</td>
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<td>Zhang et al. from China reported on a patient with COVID-19 and multiple myeloma who appeared to be successfully treated with tocilizumab\textsuperscript{13}</td>
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<td>Currently, there are no well-controlled published studies on the efficacy and safety of tocilizumab for the treatment of COVID-19; however, numerous clinical trials are planned or underway globally\textsuperscript{1, 5, 7, 8}</td>
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<td><strong>France</strong>: An open-label, phase 2, randomized clinical trial (CORIMUNO-TOCI, NCT04331808) is under way at Assistance Publique – Hôpitaux de Paris hospitals in Paris. Interim results from this study have been released in a press release (non-peer-reviewed). Sixty-five out of 129 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 64 patients were randomized to receive standard of care alone. A significantly lower proportion of the patients in the tocilizumab arm attained the primary outcome of need for ventilation or death at day 14. Results of this study will be submitted for publication in a peer-reviewed journal\textsuperscript{15, 16}</td>
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<td><strong>China</strong>: Randomized, multicenter, controlled clinical trial evaluating efficacy &amp; safety in 188 patients with COVID-19 underway through 5/10/20. Results not yet available</td>
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<td>Vitamin D</td>
<td>88:16 Vitamin D</td>
<td>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, 13</td>
<td>No known published controlled clinical trial evidence supporting efficacy of vitamin D supplementation for treatment or prevention of COVID-19.</td>
<td>Various dosages of vitamin D are being evaluated for prevention or treatment of COVID-19. 5</td>
<td>Efficacy of vitamin D supplementation in the prevention or treatment of COVID-19 has not been established. 1, 2, 3 Some experts recommend maintaining recommended levels of vitamin D intake during the COVID-19 pandemic to maintain bone and muscle health and avoid deficiency. 2, 3, 14</td>
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Vitamin D deficiency is associated with increased autoimmunity and increased susceptibility to infection. 10, 11 In observational studies, low vitamin D concentrations have been associated with increased risk of community-acquired pneumonia in older adults and upper respiratory viral infections in children. 1, 8, 9 Vitamin D deficiency is common in the U.S., particularly


US/Global randomized, placebo-controlled trial: Manufacturer (Roche) conducting a randomized, double-blind, placebo-controlled phase 3 trial (COVACTA; NCT04320615) in collaboration with the US Health and Human Services’ Biomedical Advanced Research and Development Authority (BARDA); the study will evaluate safety and efficacy of tocilizumab in combination with standard of care compared with placebo. Expected to enroll about 330 patients globally, including in the U.S., beginning in April 2020 7, 8

Prevention of respiratory infections: Efficacy of vitamin D supplementation for prevention of influenza or other respiratory infections is unclear. 10 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

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. 5

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

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<th>Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Zinc</td>
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<td>Trace mineral involved in immune function, including antibody and white blood cell production; an important cofactor for many enzymes; may improve wound healing&lt;sup&gt;2&lt;/sup&gt;</td>
<td>540,000 international units (IU; units) of vitamin D&lt;sub&gt;3&lt;/sub&gt;; patients in VITdAL-ICU also received oral maintenance doses (90,000 units monthly for 5 months).&lt;sup&gt;6, 7&lt;/sup&gt; <strong>Ongoing COVID-19 trials:</strong> Clinical trials are evaluating effects of vitamin D supplementation on COVID-19-associated clinical outcomes, including NCT04344041, NCT04386850, NCT04407286, NCT04482673, and NCT04435119.&lt;sup&gt;4&lt;/sup&gt; Clinical trials also are evaluating efficacy of vitamin D supplementation for prevention of COVID-19, including NCT04386850, NCT04483635, and NCT04482673.&lt;sup&gt;4&lt;/sup&gt; Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day.&lt;sup&gt;4, 7&lt;/sup&gt; Appropriate dosage regimens 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.&lt;sup&gt;2, 6, 9, 10&lt;/sup&gt;</td>
<td>Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day.&lt;sup&gt;4, 7&lt;/sup&gt; Appropriate dosage regimens 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.&lt;sup&gt;2, 6, 9, 10&lt;/sup&gt;</td>
<td>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.&lt;sup&gt;3&lt;/sup&gt;</td>
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<td><strong>Drug(s)</strong></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).&lt;sup&gt;1-7&lt;/sup&gt; High-dose zinc supplementation reduced the duration but not severity of common cold symptoms compared with placebo in a meta-analysis.&lt;sup&gt;1,7&lt;/sup&gt; Zinc enhances cytotoxicity and induces apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine): chloroquine can enhance intracellular zinc uptake in vitro.&lt;sup&gt;9&lt;/sup&gt; Elderly patients and patients with certain concurrent medical conditions are at higher risk of zinc deficiency.&lt;sup&gt;2,3,8&lt;/sup&gt;</td>
<td>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.&lt;sup&gt;10&lt;/sup&gt;</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.&lt;sup&gt;3,6,8&lt;/sup&gt;</td>
<td>Zinc concentrations are difficult to measure accurately since it is distributed as a component of various proteins and amino acids.&lt;sup&gt;9&lt;/sup&gt; Adverse effects may include nausea (possibly dose dependent), vomiting, and changes in taste.&lt;sup&gt;1,6,7,8&lt;/sup&gt; 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.&lt;sup&gt;9&lt;/sup&gt; 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.&lt;sup&gt;6,8&lt;/sup&gt; Potential for interactions with iron and copper, certain antibiotics (e.g., quinolones, tetracyclines), and other medications.&lt;sup&gt;8&lt;/sup&gt;</td>
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### Drug(s)

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| ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) | 24:32 Renin-Angiotensin-Aldosterone System Inhibitor | **Hypothetical harm**: Human pathogenic coronaviruses bind to their target cells through angiotensin-convertase 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.  

**Hypothetical benefit**: ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding. | Data are lacking; no evidence of harm or benefit with regards to 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).  

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: Study included data obtained from a regional healthcare database in the Lombardy region of Italy for 6272 case pts with confirmed severe COVID-19. | American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend to continue treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents. 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; recommends against use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial.  

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 7/30/20*
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<td>COVID-19 acute respiratory syndrome from Feb 21 to Mar 11, 2020 who were matched to 30,759 controls based on sex, age, and place of residence. Information about use of selected drugs and clinical profiles was obtained from regional healthcare databases. Use of ACE inhibitors or ARBs was more frequent in patients with COVID-19 than among controls because of their higher prevalence of cardiovascular disease. Percentage of patients receiving ACE inhibitors was 23.9% for case pts and 21.4% for controls. Percentage of patients receiving ARBs was 22.2% and 19.2% for case and control pts, respectively. The authors concluded that there was no evidence that treatment with ACE inhibitors or ARBs significantly affected the risk of COVID-19 or altered the course of infection or resulted in more severe disease.</td>
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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. 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. |

Clinical trial underway: Initiation of losartan in adults with COVID-19 requiring hospitalization; primary outcome measure: | | |
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<td><strong>Anticoagulants</strong>&lt;br&gt;&lt;br&gt;Updated 7/2/20</td>
<td>20:12.04 Anti-coagulants</td>
<td>Patients with COVID-19, particularly those with severe disease, may develop a hypercoagulable state, which has been associated with poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).&lt;sup&gt;1-6, 14, 16, 28, 29&lt;/sup&gt;</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]).&lt;sup&gt;4, 19&lt;/sup&gt; Observational data derived from a large US cohort of hospitalized patients with COVID-19 suggest possible benefit of therapeutic-dose anticoagulation; however, the study had important limitations (e.g., indications for anticoagulation initiation and details on patient characteristics not reported).&lt;sup&gt;28, 31&lt;/sup&gt; Several clinical trials have been initiated or currently underway to evaluate anticoagulant strategies in patients with COVID-19, including the following: NCT04373707, NCT04372589, NCT04345848, NCT04412304, NCT04416048, NCT04444700, NCT04401293, NCT04393805&lt;sup&gt;12&lt;/sup&gt;</td>
<td>See Comments column for available dosage-related information.</td>
<td>Additional study is needed to understand the anticoagulant needs of COVID-19 patients.&lt;sup&gt;9, 11, 27, 29&lt;/sup&gt; VTE risk should be assessed in all patients on an individual basis.&lt;sup&gt;4, 5, 10, 17, 18, 27, 28, 32&lt;/sup&gt; Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy.&lt;sup&gt;4, 5, 9, 25, 27, 28, 30, 32&lt;/sup&gt; The NIH COVID-19 Treatment Guidelines Panel recommends VTE prophylaxis according to the usual standard of care in all hospitalized adults with COVID-19 unless contraindicated.&lt;sup&gt;28&lt;/sup&gt; WHO recommends pharmacologic prophylaxis (e.g., LMWH) according to local and international standards for prevention of VTE in adults and adolescents hospitalized with COVID-19 unless contraindicated.&lt;sup&gt;28&lt;/sup&gt; The International Society for Thrombosis and Haemostasis and American Society of Hematology recommend that all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, severe thrombocytopenia, fibrinogen &lt;0.5 g/L).&lt;sup&gt;4, 5&lt;/sup&gt;</td>
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<td>Anticoagulant therapy</td>
<td>therapy is given to reduce the risk of thrombotic complications and improve clinical outcomes.</td>
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<td>LMWH or UFH may be preferred over oral anticoagulants in critically ill hospitalized patients with COVID-19 because of their shorter half-lives, ability to be administered parenterally, and fewer drug-drug interactions. 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. Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, some clinicians have used (or suggested the use of) higher prophylactic doses or even therapeutic doses of anticoagulants to prevent thromboembolic complications in such patients; however, prospective studies are needed to evaluate these approaches. Pending additional data, use of higher-intensity nonstandard VTE prophylaxis or therapeutic-dose anticoagulation should ideally be done in the context of a clinical trial. 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. NIH and other experts state that the current data are insufficient to recommend for or against the use of therapeutic anticoagulation in COVID-19 patients in the absence of confirmed or suspected thrombosis. The efficacy of intermediate or full-dose therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is currently being evaluated. Patients who are already on anticoagulant therapy for an existing condition.</td>
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<td><strong>COVID-19 Convalescent Plasma</strong>&lt;br&gt;<strong>Updated 8/13/20</strong></td>
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<td><strong>Study with retrospectively matched control in US (Liu et al):</strong> 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</td>
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<td>(e.g., VTE, atrial fibrillation) should continue to receive such treatment unless significant bleeding occurs or other contraindications are present. 4, 28</td>
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<td>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</td>
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<td>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. 3, 6, 7, 30, 32, 33</td>
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<td>Bleeding appears to be infrequent in COVID-19 patients. 5, 30 However, standard risk factors for bleeding should be individually assessed to balance risk of thrombosis with risk of bleeding. 4, 32</td>
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<td>Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. 11, 25</td>
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<td>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. 25</td>
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<td>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. 30</td>
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<td>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. 1,5,9 Theoretically,</td>
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## Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage\(^a\) | Comments
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 |  |  | decrease mortality,\(^8,14\) 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.\(^1,2,6-8\) 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). No significant transfusion-related morbidity or mortality was observed in patients receiving convalescent plasma.\(^32\) Uncontrolled pilot study in China (Duan et al): 10 adults with severe COVID-19 received a single transfusion of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody titers of 1:640 or greater) with standard care; all patients received antiviral therapy (e.g., umifenovir [Arbidol\(^a\)], ribavirin, oseltamivir, peramivir, interferon α) and 6 patients also received methylprednisolone. The median time from onset of symptoms to transfusion of convalescent plasma was 16.5 days. COVID-19 symptoms (fever, cough, shortness of breath, chest pain) improved in all patients within 1-3 days after the transfusion and all patients showed radiologic improvement in pulmonary lesions. Titters of neutralizing antibody increased in 5 patients after the transfusion, but remained the same in 4 patients. Prior to the transfusion, RT-PCR tests for SARS-CoV-2 RNA were positive in 7 patients and negative in 3 patients; after transfusion, SARS-CoV-2 RNA was undetectable in 5 patients on day 2, 3 patients on day 3, and 1 patient on day 6.\(^7\) Uncontrolled case series in China (Shen et al): 5 critically ill adults with rapidly progressing severe COVID-19 and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation who had high viral loads despite antiviral treatment received 2 transfusions of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody end point dilution titers of 80-480 depending on the donor); patients continued to receive antiviral treatments (e.g., LPV/RTV, favipiravir, umifenovir [Arbidol\(^a\)], darunavir, interferon α-1b) and methylprednisolone. Patients received the convalescent plasma transfusions 10-22 days after hospital admission. Following the transfusions, body temperature normalized within 3 days in 4/5 patients, sequential convalescent plasma should be more effective if given during the early course of the disease.\(^1,2,16,17,20,24\) Optimal timing of donor plasma collection in relation to recovery from COVID-19, most appropriate methods of antibody testing, and minimum titers of SARS-CoV-2 antibody in convalescent plasma that may be associated with clinical benefits in pts with COVID-19 not determined.\(^1,5\) Logistics of obtaining, processing, storing, and distributing COVID-19 convalescent plasma evolving.\(^1,5,11,14,15\) FDA does not collect COVID-19 convalescent plasma and does not provide such plasma; healthcare providers and acute care facilities obtain COVID-19 convalescent plasma from FDA-registered establishments.\(^11\) Analysis of key safety indicators in 20,000 adults who participated in a US FDA Expanded Access Program (NCT04338360) suggests that IV transfusion of COVID-19 convalescent plasma is safe in hospitalized patients with COVID-19;\(^31\) however, potential risks associated with COVID-19 convalescent plasma therapy (e.g., inadvertent transmission of other infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], antibody-dependent enhancement of infection) and steps to mitigate such risks not fully determined and require further evaluation.\(^1,5,9,23,24,25\) FDA issued a guidance for industry to provide recommendations to healthcare providers and investigators regarding administration and study of investigational COVID-19 convalescent plasma. This guidance document includes recommendations regarding pathways for access to COVID-19 convalescent plasma, patient eligibility to receive such plasma, collection of such plasma (including donor eligibility and
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<td>organ failure assessment (SOFA) scores improved in all patients (decreased from initial scores of 2-10 to 1-4 on day 12), titers of SARS-CoV-2 IgG, IgM, and neutralizing antibody increased in all patients, and viral loads decreased and became negative within 12 days. 10</td>
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<td>Retrospective observational study in China (Zeng et al): 6 critically ill adults with COVID-19 were treated with convalescent plasma at a median of 21.5 days after first detection of viral shedding. Although viral clearance was observed in all patients following transfusion, death occurred in 5 of 6 patients. 16</td>
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<td>Uncontrolled descriptive study in China (Ye et al): 6 adults with COVID-19 received convalescent plasma at a relatively late stage of the disease (most patients received 2 or 3 plasma transfusions); various laboratory, radiologic, and clinical improvements were reported. 18</td>
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<td><strong>Uncontrolled case series in China (Chen et al; non-peer-reviewed):</strong> 16 adults with COVID-19 as determined by a SARS-CoV-2 nucleic acid amplification (NAA) test and rapidly progressive, severe, or life-threatening disease received ABO-compatible COVID-19 convalescent plasma (up to 2-3 IV transfusions; each transfusion 200 – 400 mL); no minimum titer of neutralizing antibody was specified for the convalescent plasma. Patients also received multiple other treatments (e.g., antivirals, antibacterials, traditional Chinese medicine). The average time from symptom onset to plasma transfusion was 23 days. Prior to convalescent plasma transfusion, 10/16 patients had consistently positive SARS-CoV-2 results. Time to SARS-CoV-2 negativity following convalescent plasma transfusion was 2-8 days in 8/10 patients, including 5 critically ill patients and 3 with severe COVID-19 disease. SARS-CoV-2 positivity persisted in 2 critically ill patients; these patients died on day 3 and day 6 post-transfusion. 19</td>
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<td>qualifications), product labeling, and recordkeeping. 11</td>
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<td>There are no convalescent blood products currently licensed by the FDA. 25 COVID-19 convalescent plasma is regulated as an investigational product. 11 FDA states that there are 3 available pathways for administering or studying the use of such plasma:</td>
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<td>1). Clinical Trials: Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional investigational new drug (IND) regulatory pathway. 11</td>
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<td>2). Expanded Access IND: For patients with serious or immediately life-threatening COVID-19 who are not eligible or are unable to participate in randomized clinical trials, an expanded access IND can be used. A National Expanded Access Treatment Protocol has been established to facilitate access through participation of acute care facilities under an IND that is already in place. 11 Information on a protocol that is currently in place is available at <a href="https://www.uscovidplasma.org">https://www.uscovidplasma.org</a>. 12</td>
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<td>3). Single Patient Emergency IND (eIND): Licensed physicians seeking to administer COVID-19 convalescent plasma to individual patients with serious or life-threatening disease may request an eIND from the FDA. Consult the FDA guidance document for specific information on applying for an eIND. 11</td>
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<td>Donor eligibility: FDA guidance suggests that COVID-19 convalescent plasma be collected from individuals with laboratory-confirmed evidence of COVID-19 infection and 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</td>
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<td>Antibody titers in donor plasma: If measurement of antibody titers is available, FDA recommends a neutralizing antibody titer of at least 1:160 (a titer of</td>
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<td>Uncontrolled case series in US (Salazar et al): 25 adults with severe and/or life-threatening COVID-19 disease received convalescent plasma in addition to multiple other treatments (e.g., antivirals, anti-inflammatory agents). The median time from symptom onset to plasma transfusion was 10 days and 24/25 patients received a single transfusion. Convalescent plasma was well tolerated and no transfusion-related adverse events were reported. At day 7 post-transfusion, 9 patients (36%) had clinical improvement (defined as at least a 1-point improvement based on a 6-point ordinal scale); by day 14 post-transfusion, 19 patients (76%) had clinical improvement or were discharged. The contribution of convalescent plasma to clinical improvement in these patients is unclear since there was no control group and patients also received other treatments.</td>
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<td><strong>Cochrane systematic review:</strong> Analysis of 8 published studies (7 case series, 1 prospective single-arm intervention study) evaluating convalescent plasma in adults with COVID-19 (total of 32 study participants) found very low confidence in the efficacy and safety of this treatment approach. There was a high risk of bias within and across the studies (all were uncontrolled, nonrandomized, and included a small number of participants) and great variability in terms of dose and timing of convalescent plasma administration, donor and recipient characteristics, and outcomes evaluated.</td>
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<td><strong>Systematic review (Joyner et al; non-peer-reviewed):</strong> 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 &lt;0.001). Note: There were several limitations to this analysis including aggregating mortality data</td>
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1:80 may be considered acceptable if an alternative matched unit of plasma is not available). **Patient eligibility:** For healthcare providers seeking an eIND for the treatment of patients with severe or life-threatening disease, consideration should be given to following the patient eligibility criteria used in the National Expanded Access Treatment Protocol [https://www.uscovidplasma.org](https://www.uscovidplasma.org). According to the protocol, **severe** disease is defined as one or more of the following: shortness of breath, respiratory frequency 30/minute or greater, blood oxygen saturation 93% or lower, PaO₂/FiO₂ ratio less than 300, lung infiltrates greater than 50% within 24-48 hours, and **life-threatening disease** is defined as one or more of the following: respiratory failure, septic shock, multiple organ dysfunction or failure. **
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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>
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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 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.  
Convalescent plasma therapy was well tolerated by the majority of patients; 2 cases of transfusion-associated adverse events were reported. There was a signal of possible benefit in the subgroup of patients with severe COVID-19 disease. 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. 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.  

**Expanded access IND protocol (Joyner et al):** Analysis of key safety indicators in 20,000 adults hospitalized with laboratory-confirmed SARS-CoV-2 infection who had, or were considered at high risk of progression to, severe or life-threatening COVID-19 who participated in a US FDA Expanded Access Program (NCT04338360) suggests that IV transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. Patients received ABO-compatible COVID-19 convalescent plasma (approximately 200 – 500 mL) IV according to institutional transfusion guidelines; no minimum titer of neutralizing antibody was specified for the convalescent plasma. Within the first 4 hours after transfusion, 146 serious adverse events (i.e., transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI],
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<td>severe allergic transfusion reaction) were reported (incidence of &lt;1% of all transfusions with a mortality rate of 0.3%); however, only 13/146 serious adverse events were judged by the treating clinician as related to convalescent plasma transfusion. 31 Within 7 days after transfusion, 1136 other serious adverse events 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. 31</td>
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<td>Open-label, prospective study (non-peer-reviewed) (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 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</td>
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<td>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., immuno-suppressed, end-stage renal disease).&lt;sup&gt;33&lt;/sup&gt;</td>
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<td><strong>Although there is some evidence suggesting possible benefits of convalescent plasma in patients with COVID-19, available data to date are largely from case reports or series; confirmation from additional randomized controlled studies is required.</strong>&lt;sup&gt;1,20-23,27-29&lt;/sup&gt;</td>
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<td><strong>Multiple clinical trials have been initiated globally to evaluate use of COVID-19 convalescent plasma in various settings (e.g., postexposure prophylaxis, treatment of different stages of the disease).</strong>&lt;sup&gt;19,22&lt;/sup&gt; Some trials are listed below. For additional trials, see clinicaltrials.gov:</td>
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<td>Famotidine</td>
<td>56:28.12</td>
<td>Histamine H$_2$ Antagonists</td>
<td>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.(^1)(^4)</td>
<td>Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19</td>
<td>Safety and efficacy for treatment of COVID-19 not established **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.(^9)</td>
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**Anecdotal observations:**
Observations based on retrospective medical record review indicated that many Chinese COVID-19 survivors had received famotidine for chronic heartburn; mortality rate appeared to be lower in hospitalized COVID-19 patients receiving famotidine than in patients not receiving the drug (14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors.\(^3\)

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 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.\(^8\)

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.\(^5\)

Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage;\(^6\) the study excludes patients with creatinine clearance (Cr$_{\text{cr}}$) \(\leq 50\) mL/minute, including dialysis patients;\(^5\) renally impaired patients may be at increased risk of adverse CNS effects since drug half-life is closely related to Cr$_{\text{cr}}$.\(^6\)

<p>| NCT04397757 (US) | NCT04412486 (US) | NCT04392232 (US) | NCT04353206 (US) | NCT04421404 (US) | NCT04360486 (US ARMY) | NCT04347681 | NCT04346446 | NCT0435523 | NCT04342182 | NCT04352751 | NCT04375098 | NCT04357106 | NCT04327349 | NCT04292340 |</p>
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<tr>
<td>Famotidine</td>
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<td>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 (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 H₂ 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).</td>
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<p>| HMG-CoA Reductase Inhibitors (statins) | 24:06 Antilipemic Agents | In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects, which may prevent acute lung injury. Statins affect ACE2 as part of their function in reducing endothelial dysfunction. | | |
| Updated 7/16/20 | | Data from randomized controlled trials are lacking on the use of statins in patients with COVID-19. <strong>Retrospective cohort study</strong> in 13,981 patients 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 patients who received statins during hospitalization compared with patients who did not receive statins. Among propensity-score-matched patients (861 patients in the statin group vs. 3444 matched patients in the no-statin group), the risk of 28-day all-cause mortality was 42% lower in patients who received statins during hospitalization compared with those who did not receive statins. In addition, lower incidence of NIH COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy; <strong>2</strong> recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. <strong>3</strong> Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections. <strong>3</strong> In patients with active COVID-19 who may develop severe rhabdomyolysis, it may be advisable to withhold statin therapy for a short period of time. | | |</p>
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<td>Immune Globulin</td>
<td>80:04 Immune Globulin</td>
<td>Commercially available immune globulin (IGIV, IVIG, γ-globulin) is derived from pooled plasma and contains many antibodies normally present in adult human blood; used for replacement therapy in patients with primary humoral immunodeficiency who are unable to produce</td>
<td>invasive mechanical ventilation was observed in the statin-treated patients. The authors note that patients in the statin group were older and had a higher prevalence of comorbidities and more severe symptoms at baseline; matched non-statin patients therefore had more severe baseline symptoms and comorbidities than unmatched patients, which could account for the increased mortality in the non-statin group after propensity score matching.</td>
<td>Most statins are substrates for the CYP450 system; potential for drug interactions. Clinicians should ensure that their high-risk primary prevention (for ASCVD) patients are on guideline-directed statin therapy.</td>
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<td>Retrospective cohort study in 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 patients receiving statin therapy remained asymptomatic compared with 22% of the 123 patients not receiving statins. Preliminary findings have shown mixed results with other respiratory illnesses; some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients hospitalized with influenza and/or pneumonia.</td>
<td>IGIV dosage of 0.3-0.5 g/kg daily for 3-5 days has been used or is being investigated in patients with COVID-19. Role of commercially available immune globulin (IGIV, IVIG, γ-globulin) and investigational SARS-CoV-2 immune globulin in the treatment of COVID-19 unclear. The NIH COVID-19 Treatment Guidelines Panel recommends against the use of commercially available IGIV (i.e., non-SARS-CoV-2-specific IGIV) for the treatment of COVID-19 except in the context of clinical deterioration reported to</td>
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<td>Clinical trials evaluating statin use in COVID-19: Multiple trials registered at clinicaltrials.gov (some listed below):</td>
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<td>IGIV has been used in the treatment of SARS. Benefits were unclear because of patient comorbidities, differences in stage of illness, and effect of other treatments; IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients.</td>
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<td>IGIV experience: IGIV has been used in the treatment of SARS. Benefits were unclear because of patient comorbidities, differences in stage of illness, and effect of other treatments; IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients.</td>
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<td>COVID-19 case reports in China (Cao et al): Treatment with IGIV at the early stage of clinical deterioration was reported to</td>
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<td>IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients.</td>
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Updated 8-13-20. The current version of this document can be found on the ASHP COVID-19 Resource Center. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
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<td>sufficient IgG antibodies and also used to provide passive immunity to certain viral infections in other individuals.</td>
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<td>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.</td>
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<td>of a clinical trial and states that current IGIV preparations are not likely to contain SARS-CoV-2 antibodies. 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.</td>
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<td>Investigational SARS-CoV-2 immune globulin is a concentrated immune globulin preparation containing specific antibody derived from the plasma of individuals who have recovered from COVID-19.</td>
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<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.</td>
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<td>NIH states that there are insufficient data to recommend for or against the use of investigational SARS-CoV-2 immune globulin for the treatment of COVID-19.</td>
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<td>Immune globulin preparations containing antibodies specific to SARS-CoV-2 may theoretically help suppress the virus and modulate the immune response to COVID-19 infection.</td>
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<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.</td>
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<td>The Surviving Sepsis Campaign COVID-19 subcommittee suggests that IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, currently available IGIV preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis, septic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury).</td>
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<td>Commercially available preparations of immune globulin (IGIV, IVIG, γ-globulin) may contain antibodies against some previously circulating coronaviruses. 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.</td>
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<td>Retrospective study in China: 58 cases of severe or critical COVID-19 illness in ICU patients were reviewed. Patients received IGIV in addition to other treatments (e.g., antiviral and anti-inflammatory agents). A statistically significant difference in 28-day mortality was observed between patients who received IGIV within 48 hours of admission compared with those who received IGIV after 48 hours (23 vs 57%). Treatment with IGIV within 48 hours also was associated with reduced duration of hospitalization and reduced ICU length of stay and need for mechanical ventilation.</td>
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<td>Several clinical studies have been initiated to evaluate efficacy and safety of IGIV or SARS-CoV-2 immune globulin in patients with COVID-19, including the following trials:</td>
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<td>Efficacy data not available from controlled clinical studies to date.</td>
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<sup>a</sup> IGIV is not precluded for potential indications.
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| Ivermectin | 8:08 Anthelmintic | In vitro activity against some human and animal viruses<sup>1</sup>  
In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug<sup>1</sup> | Currently no known published data from randomized, controlled clinical trials regarding efficacy or safety in the treatment of COVID-19  
**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.  
**Retrospective observational evaluation of COVID-19 pts treated with ivermectin (not peer reviewed):** Outcome data for 173 pts with confirmed COVID-19 who received at least one dose of oral ivermectin (0.2 mg/kg) at any time during hospitalization, at the discretion of the treating physician, in addition to usual care were compared with outcome data for 107 pts who received usual care. The primary outcome measure was all-cause in-hospital mortality. The investigators reported that overall mortality was lower in the ivermectin group (15%) than in the group not treated with ivermectin (25.2%); there was no difference in duration of hospitalization between the | No data to date to support use in the treatment of COVID-19  
Ivermectin plasma concentrations attained with dosages recommended for treatment of parasitic infections are substantially lower than concentrations associated with in vitro inhibition of SARS-CoV-2;<sup>7,9</sup> pharmacokinetic modeling predicts that plasma concentrations attained with dosages up to 10 times higher than usual dosage also are substantially lower than concentrations associated with in vitro inhibition of the virus<sup>9</sup>  
FDA issued a warning concerning possible inappropriate use of ivermectin products intended for animals as an attempt to self-medicate for the treatment of COVID-19<sup>8</sup> |
<table>
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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>Nebulized drugs</td>
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<tr>
<td>Updated 7/16/20</td>
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**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. 1, 2, 4, 5

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. 3

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. 1, 4

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. 2, 5

There is a lack of published information and guidance on the optimal administration of aerosolized drugs in the treatment of patients with COVID-19. The safe and effective delivery of aerosol therapy to such patients may require modifications in dosage, frequency, and delivery techniques. 5

WHO states there is insufficient evidence to classify nebulizer therapy as an aerosol-generating procedure associated with COVID-19 transmission and that further study is needed. 6
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<tbody>
<tr>
<td>Niclosamide</td>
<td>8:08</td>
<td>Broad antiviral activity</td>
<td>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19</td>
<td>Protocol in one ongoing trial (NCT04372082) specifies a niclosamide dosage of 2 g on day 1, then 500 mg twice daily for 10 days for treatment of COVID-19 in adults</td>
<td>Not commercially available in the US No data to date support use in treatment of COVID-19</td>
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<tr>
<td>Updated 7/16/20</td>
<td>Anthelmintic</td>
<td>In vitro evidence of activity against SARS-CoV and MERS-CoV 1,2</td>
<td>In drug repurposing screens, was found to inhibit replication and antigen synthesis of SARS-CoV; did not interfere with virion’s attachment into cells 1,2</td>
<td>Protocol in one ongoing trial (NCT04399356) specifies a niclosamide dosage of 2 g once daily for 7 days for treatment of mild to moderate COVID-19 in adults</td>
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<td>Randomized, open-label, controlled trial in France (NCT04372082- HYdILIC)</td>
<td>Evaluate niclosamide in adults with SARS-CoV-2 infection (asymptomatic or onset of symptoms less than 8 days previously) and comorbidities 3</td>
<td>Protocol in one ongoing trial (NCT04436458) specifies a 3-times daily niclosamide regimen (dose unspecified) for 14 days for treatment of moderate COVID-19 in adults 3</td>
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<td>to evaluate niclosamide in adults with mild to moderate COVID-19 3</td>
<td>Randomized, double-blind placebo-controlled trial in Boston, (NCT04399356) to evaluate niclosamide in adults with moderate COVID-19 3</td>
<td>Protocol in one ongoing trial (NCT04436458) specifies a niclosamide dosage of 2 g once daily for 7 days for treatment of moderate COVID-19 in adults with GI signs and symptoms 3</td>
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<td>Randomized, double-blind placebo-controlled trial (NCT04436458) to evaluate niclosamide in adults with moderate COVID-19 3</td>
<td>Randomized, double-blind placebo-controlled trial (NCT04436458) to evaluate niclosamide in adults with moderate COVID-19 3</td>
<td>Protocol in one ongoing trial (NCT04343248, NCT04359680) specifying a niclosamide dosage of 500 mg or 600 mg two, three, or four times daily for 5-14 days for 1 g twice daily for 14 days for treatment of COVID-19 in adults</td>
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<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 6,7,8</td>
<td>Protocol in many registered trials generally specify these dosages for post-exposure prophylaxis, 6 NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for post-exposure prophylaxis against SARS-CoV-2, except in a clinical trial 11</td>
<td>Protocol in two ongoing trials sponsored by the manufacturer (NCT04343248, NCT04359680) evaluating 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>
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<tr>
<td>Niclosamide</td>
<td>8:30.92</td>
<td>Antiprotozoal</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 6,7,8</td>
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<td>Updated 8/13/20</td>
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<td>In vitro activity against various viruses, including coronaviruses 4,5</td>
<td>Experience in treating influenza: In a randomized, placebo-controlled study in 624 otherwise healthy adult and adolescent patients with acute uncomplicated influenza, treatment with nitazoxanide reduced duration of symptoms by approximately 1 day 6</td>
<td>Protocol in many registered trials generally specify these dosages for post-exposure prophylaxis, 6 NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for post-exposure prophylaxis against SARS-CoV-2, except in a clinical trial 11</td>
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<td>Structurally similar to niclosamide 4,5</td>
<td>Experience in treating influenza-like illness: In two studies for the treatment of influenza-like illness symptoms associated with viral respiratory infection in 186 adults and pediatric pts, treatment with nitazoxanide reduced duration of symptoms (4 days versus ≥7 days with placebo). 7 In another study in 260 adults and pediatric pts hospitalized with influenza-like illness (≥50% with pneumonia at presentation), treatment with nitazoxanide did not reduce the duration of hospital stay (primary end point) or duration of symptoms 7</td>
<td>Protocol in two ongoing trials sponsored by the manufacturer (NCT04343248, NCT04359680) evaluating 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>
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<td>In vitro evidence of activity against SARS-CoV-2 7</td>
<td>In vitro activity against MERS-CoV 4</td>
<td>Protocol in many registered trials generally specify these dosages for post-exposure prophylaxis, 6 NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for post-exposure prophylaxis against SARS-CoV-2, except in a clinical trial 11</td>
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<td>In vitro activity against MERS-CoV 4</td>
<td>Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice 4</td>
<td>Protocol in many registered trials generally specify these dosages for post-exposure prophylaxis, 6 NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for post-exposure prophylaxis against SARS-CoV-2, except in a clinical trial 11</td>
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<td>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>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>Protocol in many registered trials generally specify these dosages for post-exposure prophylaxis, 6 NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for post-exposure prophylaxis against SARS-CoV-2, except in a clinical trial 11</td>
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<td>Nonsteroidal Anti-inflammatory Agents (NSAIAs)</td>
<td>28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)</td>
<td>Updated 6/18/20</td>
<td><strong>COVID-19</strong>: Randomized, double-blind, placebo-controlled proof-of-concept trials initiated to evaluate nitazoxanide for treatment of hospitalized pts with noncritical COVID-19 (<a href="https://clinicaltrials.gov/ct2/show/NCT04423861">NCT04423861</a>) and pts with moderate COVID-19 (<a href="https://clinicaltrials.gov/ct2/show/NCT04348409">NCT04348409</a>) 8</td>
<td>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 fasted state and 700 mg 4 times daily, 900 mg 3 times daily, and 1400 mg twice daily in the fed state are capable of maintaining plasma and lung nitrozoxanide (major metabolite of nitazoxanide) exposures exceeding the EC₉₀ for SARS-CoV-2 9</td>
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<td><strong>Two randomized, double-blind, placebo-controlled clinical trials</strong> have been initiated by the manufacturer (Romark) to evaluate efficacy and safety for postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers (<a href="https://clinicaltrials.gov/ct2/show/NCT04359680">NCT04359680</a>) or elderly residents of long-term care facilities (<a href="https://clinicaltrials.gov/ct2/show/NCT04343248">NCT04343248</a>) 8</td>
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<td><strong>Multiple other clinical trials planned or initiated</strong> to evaluate nitazoxanide in combination with other drugs (e.g., hydroxychloroquine, ivermectin) or alone for treatment of COVID-19 8</td>
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<td><strong>Ibuprofen</strong>: Speculative link between ibuprofen and increased ACE2 expression leading to worse outcomes in COVID-19 patients, and should NOT be used in patients with COVID-19 1</td>
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<td><strong>Indomethacin</strong>: In vitro antiviral activity in SARS-CoV-2 pseudovirus-infected Vero E6 cells; 7 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 6, 7 (interferes with viral RNA synthesis) 6, 8</td>
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<td>On 3/19/20, FDA issued a statement that it is not aware of scientific evidence connecting the use of NSAIAs, such as ibuprofen, with worsening COVID-19 symptoms. FDA stated that it is investigating this issue further and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that by reducing inflammation, and possibly fever, these drugs may diminish the utility of diagnostic signs in detecting infections. <a href="https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19">https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19</a>. Therefore, currently no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19. However, some experts have recommended preferentially using acetaminophen for treatment of fever.</td>
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</table>

NIH COVID-19 Treatment Guidelines Panel states that patients who are receiving NSAIAs for other conditions should continue receiving the drugs; states antipyretic strategy (e.g., use of acetaminophen or NSAIAs) should be no different between patients with or without COVID-19. The Surviving Sepsis Campaign COVID-19 guidelines state that until more evidence is available, use of acetaminophen over no treatment for fever control is suggested (weak recommendation).
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<tbody>
<tr>
<td>Tissue Plasminogen Activator (t-PA; alteplase)</td>
<td>20:12.20 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).</td>
<td>Results of a small phase 1 study suggested possible benefit of plasminogen activators in the treatment of ARDS. 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 withurokinase or streptokinase; such therapy improved PaO₂ and also appeared to improve survival. In a case series of 5 COVID-19 patients who had severe hypoxemia, declining respiratory status, and increasing oxygen requirements, administration of t-PA (alteplase) at an initial IV bolus dose of 25 mg over 2 hours followed by a continuous IV infusion of 25 mg over the next 22 hours appeared to improve oxygen requirements in all patients and prevent progression to mechanical ventilation in 3 of the patients. **Other case series have described the use of t-PA in COVID-19 patients with severe respiratory failure or ARDS who were rapidly deteriorating and were either already on mechanical ventilation or likely to require intubation. Following IV infusion of t-PA (dosages varied), the majority of patients responded with rapid improvement in oxygenation. However, multiple confounding factors limit interpretation of findings from these case reports. An open-label, randomized trial (NCT04357730) is being conducted to evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure. An open-label, nonrandomized pilot study (NCT04356833) is being conducted to evaluate an inhaled formulation of t-PA (via nebulization) in patients with ARDS due to COVID-19; the inhaled formulation of t-PA is investigational at this time.</td>
<td>Two dosage regimens of t-PA (alteplase) are being evaluated in the open-label systemic fibrinolytic therapy trial (NCT04357730): 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) and 100 mg (administered as a 10-mg IV bolus dose followed by IV administration of the remaining 90 mg over a total time of 2 hours); a heparin infusion will be initiated immediately following completion of the alteplase infusion. Other dosage regimens have been evaluated in patients with COVID-19, including an initial t-PA (alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg of t-PA 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>Two 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]). Several institutions (Beth Israel Deaconess, University of Colorado Anschutz Medical Campus, Denver Health) are currently testing this approach under the FDA compassionate use program. Preliminary findings from the first few cases reported an initial, but transient improvement in PaO₂/FiO₂ (P/F) ratio. 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. 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.</td>
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*a See US prescribing information for additional information on dosage and administration of drugs commercially available in the US for other labeled indications.
REFERENCES

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)

Anakirina:

Anticoagulants

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Ascorbic acid:

Azithromycin:

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Baloxavir:


Barticinib:


Chloroquine and Hydroxychloroquine:

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Colchicine:

Corticosteroids (systemic) and Corticosteroids (inhaled):


COVID-19 Convalescent Plasma:


Favipiravir:

Favipiravir:


HMG-CoA Reductase Inhibitors (statins)


Immune Globulin:


Inhaled Prostaglycerins:

Interferons:


Ivermectin:


Nebulized drugs:


Neuraminidase Inhibitors (e.g., oseltamivir):

Nicolosamide:

Nitazoxanide:

Nitric Oxide (inhaled):


NSAIAs, including ibuprofen:


Remdesivir:


**Ruxolitinib**


Sarilumab:
- Sanofi Genzyme, Cambridge, MA: Personal communication.

Siltuximab:
- Janssen Biotech, Inc. Sylvant® (siltuximab) injection, for intravenous use prescribing information. Horsham, PA; 2018 May.

Sirolimus:

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Tissue Plasminogen Activator (t-PA; alteplase):


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Tocilizumab:

Umifenovir:

Vitamin D:
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