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Public access to AHFS Drug Information® (https://www.ahfscdi.com/login) is available for the next 60 days with the username "ahfs@ashp.org" and password "covid-19." ASHP's patient medication information is available at http://www.safemedication.com/.

Select entries were updated on 4/03/2020; these can be identified by the date that appears in the Drug(s) column.

### ANTIVIRAL AGENTS

<table>
<thead>
<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>Baloxavir</td>
<td>8:18.92</td>
<td>Antiviral active against influenza viruses</td>
<td>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 China: Two randomized clinical trials registered, but not yet recruiting. Chinese Clinical Trial Registry links: <a href="https://www.chictr.org.cn/show.aspx?id=2000029544">ChiCTR2000029544</a> <a href="https://www.chictr.org.cn/show.aspx?id=2000029548">ChiCTR2000029548</a></td>
<td>Protocol in one registered Chinese trial (2000029548) specifies a baloxavir marboxil dosage of 80 mg orally on day 1, 80 mg orally on day 4, and 80 mg orally on day 7 as needed, not to exceed 3 total doses.</td>
<td>No data to date support use in the treatment of COVID-19</td>
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<tr>
<td>Chloroquine Phosphate</td>
<td>8:30.08</td>
<td>Antimalarial</td>
<td>In vitro activity against various viruses, including coronaviruses; 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; active in vitro against SARS-CoV-1 and MERS-CoV</td>
<td>Only limited clinical trial data available to date to evaluate use of chloroquine for treatment or prevention of COVID-19 Multiple clinical trials initiated in China and other countries to evaluate various chloroquine dosages for treatment of pts with COVID-19.</td>
<td>Optimal dosage and duration of treatment not known. Consider: 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base. Various dosages recommended or being investigated for treatment of COVID-19. Oral chloroquine phosphate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or when there is no access to a clinical trial. Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration.</td>
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Updated 4/03/2020

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<th>Drug(s)</th>
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<td>Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections 1-3, 13, 15-16</td>
<td>Emergency use authorization (EUA) for chloroquine: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible 24, 25</td>
<td>participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation 25</td>
<td>Chloroquine suggested as possible option and included in some guidelines for treatment of COVID-19</td>
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<td>Known pharmacokinetics and toxicity profile</td>
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<td>Favipiravir (Avigan(^a), Favilavir)</td>
<td>8:18.92 Antiviral</td>
<td>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses 1-5</td>
<td>Only very limited clinical trial data available to date to evaluate use of favipiravir in the treatment of COVID-19</td>
<td>Oral favipiravir: 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7-10 days 6</td>
<td>Efficacy and safety of favipiravir for treatment of COVID-19 not established</td>
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<td>In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug 1,5</td>
<td>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(^a); 200 mg 3 times daily for 7-10 days). Stratified by disease</td>
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<td>Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dose and duration</td>
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<tr>
<td>Hydroxychloroquine (Plaquenil®)</td>
<td>8:30.08</td>
<td>Antimalarial</td>
<td>Only limited clinical trial data available to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19</td>
<td>Optimal dosage and duration of treatment not known</td>
<td>Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established</td>
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<td><strong>Updated 4/3/20</strong></td>
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<td>Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19</td>
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<td>Data needed regarding toxicity profile when used in patients with COVID-19</td>
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<td>Hydroxychloroquine</td>
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<td>Known pharmacokinetics and toxicity profile Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects;&lt;sup&gt;13, 14&lt;/sup&gt; may have more favorable dose-related toxicity profile than chloroquine,&lt;sup&gt;13-16&lt;/sup&gt; but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs&lt;sup&gt;15, 20&lt;/sup&gt;</td>
<td>end point was negative conversion in pharyngeal swabs on day 7. Negative conversion reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).&lt;sup&gt;18&lt;/sup&gt;</td>
<td><strong>Oral hydroxychloroquine sulfate:</strong> 400 mg once or twice daily for 5-10 days&lt;sup&gt;10, 18&lt;/sup&gt;</td>
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<td>Hydroxychloroquine with Azithromycin: Preliminary data from an ongoing study in France 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 (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.&lt;sup&gt;7&lt;/sup&gt; 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 was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented. Although it provides some evidence of the effects of hydroxychloroquine</td>
<td><strong>Oral hydroxychloroquine sulfate:</strong> 600 mg twice daily on day 1, then 400 mg daily on days 2-5&lt;sup&gt;20&lt;/sup&gt;</td>
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<td>Hydroxychloroquine with Azithromycin: Preliminary data from an ongoing study in France 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 (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.&lt;sup&gt;7&lt;/sup&gt; 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 was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented. Although it provides some evidence of the effects of hydroxychloroquine</td>
<td><strong>Oral hydroxychloroquine sulfate:</strong> 100-200 mg twice daily for 5-14 days&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Hydroxychloroquine with Azithromycin: Preliminary data from an ongoing study in France 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 (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.&lt;sup&gt;7&lt;/sup&gt; 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 was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented. Although it provides some evidence of the effects of hydroxychloroquine</td>
<td><strong>Oral hydroxychloroquine sulfate:</strong> 200 mg 3 times daily for 10 days&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>in pts with COVID-19, additional data needed before any conclusions can be made regarding possible benefits of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.)</td>
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<td><strong>Efficacy measures</strong>: Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. RT-PCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined.</td>
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<td><strong>Emergency use authorization (EUA) for hydroxychloroquine</strong>: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. To request the drug, healthcare providers should contact local or state health departments; distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting). FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID-19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks. Consult the EUA, EUA fact sheet for healthcare providers, and EUA fact sheet for patients and parent/caregivers for additional information.</td>
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<td>Lopinavir and Ritonavir (LPV/RTV; Kaletra(a))</td>
<td>8:18.08.08 HIV Protease Inhibitor</td>
<td>Antiretroviral with in vitro activity against SARS-CoV and MERS-CoV(1, 2, 9, 11); some evidence of benefit in animal studies for treatment of MERS-CoV(2, 7, 9, 11); Published data currently lacking on in vitro activity against SARS-CoV-2(9)</td>
<td>Various clinical trials are being initiated in the US and elsewhere to evaluate hydroxychloroquine for prevention of COVID-19 in the healthcare setting or in household contacts of pts with the disease: 10 NCT04328961 NCT04303507 NCT04318444 NCT04318015 NCT04330144</td>
<td>COVID-19: LPV 400 mg/RTV 100 mg orally twice daily for 14 days(3)</td>
<td>Efficacy for treatment of COVID-19 not definitely established Additional study needed to evaluate possible clinical benefits of early use of LPV/RTV in COVID-19 Additional study needed to evaluate benefits of concomitant use of LPV/RTV with other antivirals for COVID-19; usually used in conjunction with other antivirals (e.g., ribavirin with or without an interferon) for SARS and MERS</td>
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<td>Lopinavir and Ritonavir (LPV/RTV; Kaletra(a)) Updated 3/24/20</td>
<td>8:18.08.08 HIV Protease Inhibitor</td>
<td>Antiretroviral with in vitro activity against SARS-CoV and MERS-CoV(1, 2, 9, 11); some evidence of benefit in animal studies for treatment of MERS-CoV(2, 7, 9, 11); Published data currently lacking on in vitro activity against SARS-CoV-2(9)</td>
<td>COVID-19 Randomized, open-label trial in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard of care (99 pts) vs standard of care alone (100 pts). Primary end point: time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, time to clinical improvement was not shorter with LPV/RTV compared with standard of care (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 of 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. 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.(3) COVID-19 Retrospective cohort study in adults evaluated use of LPV/RTV with or without Arbidol (influenza antiviral not licensed in US). Primary end point was negative conversion rate of coronavirus and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in</td>
<td>COVID-19: LPV 400 mg/RTV 100 mg orally twice daily for 14 days(3)</td>
<td>Efficacy for treatment of COVID-19 not definitely established Additional study needed to evaluate possible clinical benefits of early use of LPV/RTV in COVID-19 Additional study needed to evaluate benefits of concomitant use of LPV/RTV with other antivirals for COVID-19; usually used in conjunction with other antivirals (e.g., ribavirin with or without an interferon) for SARS and MERS</td>
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<td>Neuraminidase inhibitors (e.g., oseltamivir)</td>
<td>8:18.28</td>
<td>Antivirals active against influenza viruses</td>
<td>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.</td>
<td>Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours.</td>
<td>No data to date support use in the treatment of COVID-19</td>
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<td>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).</td>
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| Remdesivir   | 8:18.92   | Broad-spectrum antiviral with activity against coronaviruses              | Phase 3 randomized, open-label trial (NCT04292899) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- and 10-day regimens of Remdesivir in conjunction with standard of care in pts with severe COVID-19 10 | Phase 3 trial protocol (severe COVID-19): 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) 10 | Not commercially available; most promising antiviral currently being investigated for COVID-19  
Safety and efficacy not established; additional data needed |
|              | Antivirals, Miscellaneous | Previously tested for SARS, MERS, and Ebola                              | Phase 3 randomized, open-label trial (NCT04292730) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- or 10-day regimens of remdesivir in conjunction with standard of care in pts with moderate COVID-19 compared with standard of care alone 11 | Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) 11 |                                                     |
|              |           | In vitro evidence of activity against SARS-CoV-2 3                       | Phase 2 randomized, placebo-controlled trial (NCT04280705) sponsored by NIAID initiated to evaluate safety and efficacy of remdesivir in hospitalized pts with labor-atory-confirmed COVID-19 13 | NIAID study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total 13 |                                                     |
|              |           | In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected 18 | Various clinical trials initiated in China and other countries                                |                                                                                       |                                                     |
|              |           | Pharmacokinetic data available from evaluations for Ebola                |                                                                                                 |                                                                                       |                                                     |

**Updated 3/24/20**

**AHFS Class:**

- 8:18.92 Antivirals, Miscellaneous

**Rationale:**

- Broad-spectrum antiviral with activity against coronaviruses
- Previously tested for SARS, MERS, and Ebola
- In vitro evidence of activity against SARS-CoV-2 3
- In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected 18
- Pharmacokinetic data available from evaluations for Ebola

**Trials or Clinical Experience:**

- Phase 3 randomized, open-label trial (NCT04292899) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- and 10-day regimens of Remdesivir in conjunction with standard of care in pts with severe COVID-19 10
- Phase 3 randomized, open-label trial (NCT04292730) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- or 10-day regimens of remdesivir in conjunction with standard of care in pts with moderate COVID-19 compared with standard of care alone 11
- Phase 2 randomized, placebo-controlled trial (NCT04280705) sponsored by NIAID initiated to evaluate safety and efficacy of remdesivir in hospitalized pts with laboratory-confirmed COVID-19 13
- Various clinical trials initiated in China and other countries

**Dosagea:**

- Phase 3 trial protocol (severe COVID-19): 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) 10
- Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) 11
- NIAID study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total 13

**Comments:**

- Not commercially available; most promising antiviral currently being investigated for COVID-19
- Safety and efficacy not established; additional data needed
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<td><strong>Umifenovir (Arbidol®)</strong> Added 4/3/20</td>
<td>8:18.92 Antiviral</td>
<td>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses. Although data limited, in vitro activity against SARS-CoV-1 and SARS-CoV-2 reported. Licensed in China and Russia for prophylaxis and treatment of influenza.</td>
<td><strong>Retrospective cohort study</strong> 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.</td>
<td><strong>Dosage recommended for treatment of COVID-19 in China:</strong> Adults, 200 mg orally 3 times daily for no more than 10 days. <strong>Dosage used or being investigated in COVID-19 clinical trials:</strong> 200 mg orally 3 times daily for duration of 7-10 days or longer.</td>
<td>Not commercially available in the US. Included in some guidelines for treatment of COVID-19. Published data to support use in treatment of COVID-19 currently are limited.</td>
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| Open-label, prospective, randomized, multicenter study | in 236 adults with COVID-19 in China (ChiCTR200030254): When favipiravir was compared with umifenovir, clinical recovery rate was greater in those treated with favipiravir than in those treated with umifenovir. (See Favipiravir in this Evidence Table.) |  |
| Clinical trials initiated in China: NCT04252885: Randomized, single-center, open-label trial evaluating efficacy of umifenovir in conjunction with standard of care vs LPV/RTV in conjunction with standard of care in adults with COVID-19 | NCT04260594: Randomized, open-label trial evaluating efficacy and safety of umifenovir in conjunction with standard of care in adults with COVID-19 |  |
## SUPPORTING AGENTS

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>AHFS Class</th>
<th>Rationale</th>
<th>Trials or Clinical Experience</th>
<th>Dosage*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td>92:36</td>
<td>Recombinant human interleukin-1 (IL-1) receptor antagonist; 1 may potentially combat cytokine release syndrome (CRS) symptoms in severely ill patients 2, 3, 4</td>
<td>Currently no known published clinical trial evidence supporting efficacy or safety of anakinra in treating COVID-19</td>
<td>Phase 3 trial protocol (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days 3</td>
<td>No data to date support use in the treatment of COVID-19</td>
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<tr>
<td><strong>Added 4/1/20</strong></td>
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<td></td>
<td>Encouraging preliminary results reported in China with another disease-modifying antirheumatic drug, tocilizumab 5, 6</td>
<td>(Note: Anakinra is approved only for subcutaneous administration in the U.S.) 1</td>
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<td><strong>Italy:</strong> Phase 3 randomized, open-label, multicenter trial (NCT04324021) to be 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 (estimated start date 3/20)</td>
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<tr>
<td>Ascorbic acid</td>
<td>88:12</td>
<td>Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress 3, 5, 7</td>
<td>Phase 2 randomized, placebo-controlled trial (NCT04264533) initiated in China to evaluate high-dose IV ascorbic acid in ICU patients with severe COVID-19-associated pneumonia 1</td>
<td>Phase 2 trial protocol (NCT04264533): Ascorbic acid 12 g IV every 12 hours for 7 days (12 g of drug diluted in sterile water for injection to total volume of 50 mL and infused IV at rate of 12 mL/hour) 1</td>
<td>Current data not specific to COVID-19; additional study needed 6</td>
</tr>
<tr>
<td><strong>Updated 4/3/20</strong></td>
<td></td>
<td>Presence of infection may decrease vitamin C concentrations 2, 3</td>
<td>COVID-19 patients may be eligible for enrollment in some ongoing sepsis studies 1</td>
<td>Uncontrolled, noncomparative trial (NCT04323514; currently recruiting) in patients hospitalized with COVID-19 pneumonia: 10-g dose by IV infusion 1</td>
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<td><strong>Other infections:</strong> 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 receiving high-dose IV ascorbic acid; additional studies under way 4, 6, 8, 9</td>
<td>Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia 2, 3</td>
<td>Uncontrolled, noncomparative trial (NCT04323514; currently recruiting) in patients hospitalized with COVID-19 pneumonia: 10-g dose by IV infusion 1</td>
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<td></td>
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<td>Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia 2, 3</td>
<td>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 2, 3</td>
<td>Various dosages of IV ascorbic acid used in sepsis studies; 50 mg/kg every 6 hours for 4 days used in CITRIS-ALI study 4, 6, 9</td>
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*Updated 04-03-2020*
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<tr>
<th>Drug(s)</th>
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<tbody>
<tr>
<td><strong>Azithromycin</strong>&lt;br&gt;Added 3/24/20</td>
<td>8:12.12 Macrolides</td>
<td>Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika)¹ ³ ⁵&lt;br&gt;No data to date on in vitro activity against coronaviruses, including SARS-CoV-2&lt;br&gt;Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated² ⁶ ⁸ ¹¹-¹⁴ ¹⁷&lt;br&gt;Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza)¹⁰ ¹³&lt;br&gt;Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the management of certain respiratory conditions (e.g., bronchiectasis, bronchiolitis, cystic fibrosis, COPD exacerbations, ARDS)¹⁵ ¹⁶</td>
<td><strong>Adjunctive therapy in certain respiratory viral infections:</strong> Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza).¹⁰ ¹² ¹³&lt;br&gt;However, in a retrospective cohort study in critically ill pts with laboratory-confirmed MERS, there was no statistically significant difference in 90-day mortality rates or clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not.¹²</td>
<td><strong>Adjunctive treatment in certain viral infections:</strong> 500 mg once daily has been used¹⁵</td>
<td>Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19&lt;br&gt;Additional data needed before any conclusions can be made regarding possible benefits of using a combined regimen of hydroxychloroquine and azithromycin in pts with COVID-19&lt;br&gt;Because both azithromycin and hydroxychloroquine are associated with QT prolongation, caution is advised if considering use of both drugs in pts who have chronic medical conditions (e.g., renal failure, hepatic disease) or are receiving other drugs that cause arrhythmias¹⁶</td>
</tr>
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<td><strong>Clinical experience in pts with COVID-19:</strong>&lt;br&gt;Has been used for antibacterial coverage in hospitalized pts with COVID-19¹⁵</td>
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<td><strong>Use in conjunction with hydroxychloroquine in pts with COVID-19:</strong> In a small nonrandomized study evaluating use of hydroxychloroquine, 6 study pts received azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) in addition to the 10-day regimen of hydroxychloroquine.⁷ Although preliminary results indicated that all 6 of these pts had negative PCR results in nasopharyngeal samples at day 6 (a higher percentage than those receiving hydroxychloroquine alone), data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.)</td>
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<td>Corticosteroids</td>
<td>68:04</td>
<td>Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia.</td>
<td>Observational studies: Evidence suggests that corticosteroids in patients with SARS and MERS showed no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes).</td>
<td></td>
<td>WHO and CDC recommend that corticosteroids not be routinely used in patients with COVID-19 for treatment of viral pneumonia or ARDS unless indicated for another reason (e.g., asthma or COPD exacerbation, septic shock).</td>
</tr>
</tbody>
</table>
### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage$^a$ | Comments
--- | --- | --- | --- | --- | ---
Epoprostenol (inhaled) | 48:48 | Vasodilating Agent | Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19. | Various dosages of inhaled epoprostenol have been used in ARDS studies. | Additional studies are needed to evaluate the potential role of inhaled epoprostenol in the treatment of ARDS.

**Added 4/3/20**

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

No studies evaluating use specifically in COVID-19 patients. Experience in patients with ARDS indicates that inhaled epoprostenol can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients; however, data demonstrating clinical benefit are lacking.

Dosages up to 50 ng/kg per minute have been used (titrated to response). To provide a clinically important increase in PaO$_2$ and reduction in pulmonary artery pressure, data from 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.

(Notes: Epoprostenol is labeled only for IV administration in the US.)

Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®) | 68:04 | Adrenal | Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia. | Dosage used in this retrospective study not provided. Based on expert consensus statement from Chinese Thoracic Society, dosage of methylprednisolone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent). Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days. | Findings suggest that for patients with COVID-19 pneumonia who progressed to ARDS, methylprednisolone treatment may be beneficial. Results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Randomized controlled studies are needed.

Retrospective, observational, single-center study: In 201 patients with confirmed COVID-19 pneumonia who developed ARDS, methylprednisolone appeared to reduce the risk of death. 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.

Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days.
<table>
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<th>Trials or Clinical Experience</th>
<th>Dosage*</th>
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<tbody>
<tr>
<td>Nitric oxide (inhaled)</td>
<td>48:48</td>
<td>Vaso-dilating Agent</td>
<td>Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19. In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and COVID-19 suggests potential effectiveness for COVID-19.</td>
<td>Inhaled nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) in a pilot study in SARS-CoV patients.</td>
<td>Therapeutic guidelines for the treatment of ARDS state that inhaled nitric oxide may be considered in patients with severe hypoxemia not responsive to conventional ventilation strategies; however, routine use not recommended. The Surviving Sepsis Campaign suggests a trial of inhaled pulmonary vasodilator therapy as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if rapid improvement in oxygenation is not observed, treatment should be tapered off. Clinical trials evaluating inhaled nitric oxide for treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243). On March 20th, 2020, Bellerophon Therapeutics announced that the FDA granted emergency expanded access allowing its inhaled nitric oxide delivery system (INOpulse®) to be immediately used for...</td>
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<tr>
<td>Updated 4/3/20</td>
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<td>No studies evaluating use specifically in COVID-19 patients. In a small pilot study conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support. 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).</td>
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<tr>
<td>Sarilumab (Kefzara®)</td>
<td>92:36</td>
<td>Disease-modifying Anti-rheumatic Drug</td>
<td>Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients.</td>
<td>Not available (see Trials or Clinical Experience)</td>
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<tr>
<td>Updated 3/27/20</td>
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<td>Currently no known published clinical trial evidence supporting efficacy or safety against Coronavirus. However, based on encouraging results in China with a similar drug, tocilizumab, a U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently under way.</td>
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<tr>
<td>Drug(s)</td>
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<td>Dosage&lt;sup&gt;a&lt;/sup&gt;</td>
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| Sirolimus 3/20/20       | 92:44 Immunosuppressive agent (mTOR inhibitor) | mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus<sup>1, 2, 5</sup> | In vitro studies demonstrated inhibitory activity against MERS-CoV infection<sup>2</sup>  
In an open-label prospective randomized study in 38 patients with confirmed H1N1 pneumonia, 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 multiorgan function)<sup>3</sup>  
Currently a registered clinical trial (NCT03901001 not yet recruiting) designed to evaluate adjunctive use of sirolimus and oseltamivir in patients hospitalized with influenza<sup>4, 6</sup> | Dosage of sirolimus in the open-label trial was 2 mg daily orally, administered in conjunction with oral prednisolone 20 mg daily for 14 days; patients also received oseltamivir 75 mg twice daily for 10 days<sup>3</sup> | Although possible clinical application, current data not specific to 2019-nCoV/SARS-CoV2; additional study needed<sup>5</sup> |
| Tocilizumab (Actemra®)  | 92:36 Disease-modifying Anti-rheumatic Drug | Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients<sup>1, 2, 3, 6</sup> | Case study/series describing use of tocilizumab in patients with COVID-19 reported from various areas of the world<sup>1, 3</sup>  
In preliminary data from a non-peer-reviewed, single-arm Chinese trial 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)<sup>3</sup>  
Currently no other known clinical trial evidence supporting efficacy and safety of tocilizumab against Coronavirus<sup>1</sup>  
**China**: Randomized, multicenter, controlled clinical trial evaluating efficacy & safety in 188 patients with COVID-19 under way through 5/10/20. Results not yet available. Chinese Clinical Trial Registry link: http://www.chictr.org.cn/showprojen.aspx?proj=49409  
**US/Global randomized, placebo-controlled trial (manufacturer sponsored)**: 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<sup>8</sup>  
**In China**, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels<sup>2</sup>  
Published data to support use currently are limited<sup>1, 7</sup> | 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<sup>2</sup> |
### Drug(s) | AHFS Class | Rationale | Trials or Clinical Experience | Dosage\(^a\) | Comments
--- | --- | --- | --- | --- | ---
**Trials or Clinical Experience**
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.\(^7,8\)

**Multiple other clinical trials planned or initiated** using tocilizumab in COVID-19 patients in China and Europe.\(^5\)

### OTHER

**Drug(s)** | AHFS Class | Rationale | Trials or Clinical Experience | Dosage\(^a\) | Comments
--- | --- | --- | --- | --- | ---
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) | 24:32 Renin-Angiotensin-Aldosterone System Inhibitor | Hypothetical harm: Human pathogenic corona-viruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2).\(^1,4,5\) Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs.\(^1,4,8\) Increased expression of ACE2 may potentially facilitate COVID-19 infections.\(^5\)

**Hypothetical benefit:** ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.\(^1,2,6\)

Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection.\(^1,2,3\)

Clinical trial underway: Initiation of losartan in adult patients with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009)\(^7\)

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.\(^2,3\)

Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.\(^1,4\)

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.\(^8\)

Ibuprofen | 28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA) | 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\(^1\)

None; anecdotal\(^1\)

A letter published in The Lancet Respir Med [1] stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2. No sources have been cited for this.
<table>
<thead>
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|         |            |           |                              |        | A statement attributed to WHO spokes-
|         |            |           |                              |        | person Christian Lindmeier recommend-
|         |            |           |                              |        | ing paracetamol and avoiding ibuprofen
|         |            |           |                              |        | as a self-medication was widely circulat-
|         |            |           |                              |        | ed in the media; however, such a posi-
|         |            |           |                              |        | tion could not be found on the WHO
|         |            |           |                              |        | website or other official sources. WHO
|         |            |           |                              |        | has stated "after a rapid review of the
|         |            |           |                              |        | literature, is not aware of published
|         |            |           |                              |        | clinical or population-based data on this
|         |            |           |                              |        | topic." As of 3/18/20 (via Twitter) "WHO
|         |            |           |                              |        | does not recommend against the use of
|         |            |           |                              |        | ibuprofen." [https://twitter.com/WHO/status/1240409217997189128](https://twitter.com/WHO/status/1240409217997189128)
|         |            |           |                              |        | In addition, there have been unsubstan-
|         |            |           |                              |        | tiated reports of younger, healthy pa-
|         |            |           |                              |        | tients who took ibuprofen and suffered
|         |            |           |                              |        | severe outcomes with COVID-19. Official
|         |            |           |                              |        | case reports are lacking.
|         |            |           |                              |        | On March 19, 2020, FDA issued a state-
|         |            |           |                              |        | ment that it is not aware of scientific
|         |            |           |                              |        | evidence connecting the use of NSAIA,
|         |            |           |                              |        | 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 de-
|         |            |           |                              |        | Therefore, currently no compelling
|         |            |           |                              |        | evidence to support an association
|         |            |           |                              |        | between ibuprofen and negative out-
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<tr>
<td>Indomethacin</td>
<td>28:08.04</td>
<td>Nonsteroidal Anti-inflammatory Agents (NSAIA)</td>
<td>Possible antiviral activity against other coronavirus(es) SARS-CoV &amp; CanineCoV (interferes with viral RNA synthesis)</td>
<td>Speculative; one in vitro &amp; animal model study with other coronaviruses SARS-CoV &amp; CanineCoV</td>
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<td>Nebulized drugs</td>
<td>Added 3/27/20</td>
<td>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.</td>
<td>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.</td>
<td>American College of Allergy, Asthma &amp; 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.</td>
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<tr>
<td>Niclosamide</td>
<td>8:08</td>
<td>Anthelmintic</td>
<td>Broad antiviral activity against SARS-CoV and MERS-CoV</td>
<td>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19</td>
<td>No data to date support use in treatment of COVID-19</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Added 4/1/20</td>
<td>Antiprotozoal</td>
<td>In vitro activity against various viruses, including coronaviruses</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</td>
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*Dosages investigated for other viral infections in clinical trials: Adults and adolescents (≥12 years of age): 500 to 600 mg orally twice daily for 5 days.*
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<td></td>
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<td>Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice</td>
<td><strong>Other infections</strong> <em>(influenza-like illness)</em>: In two phase 2 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). In another phase 2 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</td>
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* See US prescribing information for additional information on dosage and administration of drugs commercially available in the US for other labeled indications.
ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)


Anakinra:


Ascorbic acid:


Azithromycin:


Baloxavir:

Chloroquine and Hydroxychloroquine:


**Corticosteroids, including methylprednisolone:**


Updated 04-03-2020


**Epoprostenol:**


Favipiravir

Ibuprofen:

Indomethacin:

Lopinavir and Ritonavir:


**Nebulized drugs:**


**Neuraminidase Inhibitors (e.g., oseltamivir):**


**Niclosamide:**


Updated 04-03-2020

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Nitazoxanide:


Nitric Oxide (inhaled):


Updated 04-03-2020

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Remdesivir:
11. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment. NCT04292730. (https://ClinicalTrials.gov/ct2/show/NCT04292730)
12. Expanded access remdesivir (RDV; GS-5734). (https://ClinicalTrials.gov/ct2/show/NCT04302766)

Sarilumab:

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**Sirolimus:**

**Tocilizumab:**

**Umifenovir:**