
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. 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 5/4/2020; these can be identified by the date that appears in the Drug(s) column.

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Updated 5-04-20. The current version of this document can be found on the ASHP COVID-19 Resource Center.
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<th>Drug(s)</th>
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<tr>
<td>Baloxavir</td>
<td>8:18.92</td>
<td>Antiviral</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 ²: <a href="https://www.chictr.org.cn/trial/ChiCTR-TRC-2000029544">ChiCTR2000029544</a> <a href="https://www.chictr.org.cn/trial/ChiCTR-TRC-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. ¹</td>
<td>No data to date support use in the treatment of COVID-19</td>
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<td>Chloroquine Phosphate</td>
<td>8:30.08</td>
<td>Antimalarial</td>
<td>In vitro activity against various viruses, including coronaviruses ¹⁻³, ¹³, ¹⁴ 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, ¹² Active in vitro against SARS-CoV-1 and MERS-CoV²⁻³, ⁵⁺⁻⁹ Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections ¹⁻³, ¹³, ¹⁵⁻¹⁶ Known pharmacokinetics and toxicity profile Only limited clinical trial data available to date to evaluate use of chloroquine for treatment or prevention of COVID-19 Clinical experience in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 ⁴⁻⁶ Double-blind randomized phase 2b study in Brazil (Borba et al) to evaluate two different chloroquine dosages as adjunctive therapy in hospitalized adults with severe COVID-19 (NCT04323527): The first 81 enrolled 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. 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 trial.</td>
<td>Optimal dosage and duration of treatment not known ²⁰, ²⁵ Consider: 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base ¹⁷ 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 participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation ²⁵. Oral chloroquine phosphate: 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 Oral chloroquine phosphate: Initial dose of 600 mg (of chloroquine) followed by 300 mg (of chloroquine) 12 hours later on day 1, then 300 mg (of chloroquine) twice daily on days 2-5 ⁴</td>
<td>Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established ¹⁰, ²⁴, ³⁹ Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. ¹¹ NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of chloroquine for the treatment of COVID-19. ³⁵ IDSA recommends that chloroquine be used for the treatment of COVID-19 in the context of a clinical trial. ³⁸ NIH COVID-19 Treatment Guidelines Panel does not recommend the use of chloroquine.</td>
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<td>Drug(s)</td>
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<td>high-dose group (18.9%) than in the lower-dose group (11.1%). The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data were insufficient to evaluate efficacy. Study continuing using only the lower dosage. 37</td>
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<td>any agents, including chloroquine, for preexposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection outside of clinical trials. 35</td>
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Multiple clinical trials to evaluate chloroquine for the treatment of COVID-19 are registered at clinicaltrials.gov (some listed below): 37, 10
NCT04323527
NCT04328493
NCT04331600
NCT04333628
NCT04353336
NCT04360759
NCT04362332

Several clinical trials to evaluate chloroquine for prevention of COVID-19 in the healthcare setting are registered at clinicaltrials.gov: 38
NCT04303507
NCT04333732
NCT04349371

Because chloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; 36, 39 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. 35, 36, 39

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

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 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. 29 To mitigate risks of this
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<td>Favipiravir (Avigan®, Favilavir)</td>
<td>8:18.92 Antiviral</td>
<td>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td><strong>Only very limited clinical trial data available</strong> 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 days was used in one open-label COVID-19 study&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Not commercially available in the US</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&lt;sup&gt;1,5,16&lt;/sup&gt;</td>
<td><strong>Open-label, prospective, randomized, multicenter study</strong> 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 COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe disease compared with the group receiving umifenovir.&lt;sup&gt;6&lt;/sup&gt;</td>
<td>A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days was used in one open-label COVID-19 study&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Efficacy and safety of favipiravir for treatment of COVID-19 not established</td>
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<td>Licensed in Japan and China for treatment of influenza&lt;sup&gt;1,4,6&lt;/sup&gt;</td>
<td><strong>In a small, open-label, nonrandomized study</strong> in patients with non-severe COVID-19 in China (ChiCTR2000029600), favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (n=35) was associated with decreased median time to viral clearance (4 vs 11 days) and higher improvement rate on median time to viral clearance (4 vs 11 days).</td>
<td>Protocol in one ongoing trial (NCT04336904) for treatment of moderate COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 600 mg three times daily thereafter for up to 14 days&lt;sup&gt;7&lt;/sup&gt;</td>
<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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<td>Protocol in one ongoing trial (NCT04346628) for treatment of mild COVID-19 specifies a favipiravir dosage of 1800 mg on day 1, then 800 mg twice daily on days 2–10&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Protocol in one ongoing trial (NCT04349241) for treatment of non-severe COVID-19 specifies a favipiravir dosage of 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10&lt;sup&gt;7&lt;/sup&gt;</td>
<td>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.&lt;sup&gt;14&lt;/sup&gt;</td>
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<td>Protocol in one ongoing trial (NCT04349241) for treatment of non-severe COVID-19 specifies a favipiravir dosage of 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Protocol in one ongoing trial (NCT04358549) for treatment of COVID-19 specifies a favipiravir dosage of 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10&lt;sup&gt;7&lt;/sup&gt;</td>
<td>If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g&lt;sup&gt;17,18&lt;/sup&gt;</td>
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<td>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.&lt;sup&gt;15&lt;/sup&gt;</td>
<td>COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14&lt;sup&gt;7&lt;/sup&gt;</td>
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<td><strong>Italy:</strong> Randomized, placebo-controlled multicenter trial (&lt;span&gt;NCT04336904&lt;/span&gt;) to evaluate efficacy and safety of favipiravir in pts with moderate COVID-19 (started 3/25/20; estimated completion date 7/20)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2,&lt;sup&gt;1,5,13&lt;/sup&gt; it has been suggested that high favipiravir dosages, like those used in the treatment of Ebola virus disease, should be considered for the treatment of COVID-19.&lt;sup&gt;11&lt;/sup&gt; One such favipiravir regimen used in the treatment of Ebola virus disease includes a loading dosage of 6000 mg (doses of 2400 mg, 2400 mg, and 1200 mg given 8 hours apart on day 1), then a maintenance dosage of 1200 mg every 12 hours on days 2–10.&lt;sup&gt;12,13&lt;/sup&gt;</td>
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<td><strong>US:</strong> Randomized, controlled open-label proof-of-concept trial (&lt;span&gt;NCT04358549&lt;/span&gt;) of favipiravir for the treatment of COVID-19&lt;sup&gt;7&lt;/sup&gt;</td>
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<td><strong>US:</strong> Randomized, open-label trial (&lt;span&gt;NCT04346628&lt;/span&gt;) to evaluate efficacy of favipiravir in pts with mild, uncomplicated COVID-19&lt;sup&gt;7&lt;/sup&gt;</td>
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<td><strong>Multiple clinical trials initiated</strong> in pts with COVID-19 in China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents:</td>
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<td>&lt;sup&gt;7,9&lt;/sup&gt;</td>
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<tbody>
<tr>
<td>HIV Protease Inhibitors</td>
<td>8.18.08.08 HIV Protease Inhibitors</td>
<td><strong>Lopinavir (LPV):</strong> In vitro activity against SARS-CoV-2 in Vero E6 cells; also has in vitro activity against SARS-CoV-1 and MERS-CoV; some evidence of benefit in animal studies for treatment of MERS-CoV.</td>
<td><strong>Inhibitors HIV Protease</strong> Drug(s) <strong>- 04</strong></td>
<td>LPV/RTV (COVID-19): LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days.</td>
<td>LPV/RTV: Efficacy for the treatment of COVID-19, with or without other antivirals, not definitely established.</td>
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<td>Atazanavir (ATV):</td>
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<td><strong>ATV</strong> alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells; human epithelial pulmonary cells (AS49); and human monocytes.</td>
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<td>Darunavir: No data to date to support use in the treatment of COVID-19. Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/cobicistat for treatment of COVID-19 and initial unpublished results from a study in China indicated that a 5-day regimen of DRV/cobicistat was not effective for treatment of COVID-19.</td>
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<td><strong>Darunavir (DRV):</strong> 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>
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<td>NIH COVID-19 Treatment Guidelines Panel recommends against the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial.</td>
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<td>Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):</td>
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<td><strong>Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):</strong> In vitro activity against SARS-CoV-2 in Vero E6 cells.</td>
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<td>IDSA recommends that LPV/RTV be used for COVID-19 only in the context of a clinical trial.</td>
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<td><strong>Lopinavir and Ritonavir (LPV/RTV; Kaletra®):</strong> randomized, open-label trial in China 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 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.</strong> LPV/RTV stopped early in 13 pts because of adverse effects.</td>
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<td><strong>LPV/RTV (COVID-19):</strong> LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days.</td>
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<td><strong>LPV/RTV (COVID-19):</strong> LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours).</td>
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<td><strong>LPV/RTV (COVID-19):</strong> 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.</td>
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<td><strong>LPV/RTV (SARS):</strong> LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours).</td>
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<td><strong>LPV/RTV (MERS):</strong> 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 β1b (0.25 mg/mL sub-Q on alternate days) for 14 days.</td>
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<td><strong>LPV/RTV Clinical Experience (COVID-19): Only limited data on LPV/RTV used with or without umifenovir in this Evidence Table.</strong></td>
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Updated 5-04-20. 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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<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>
</table>
| Hydroxychloroquine (Plaquenil®) | 8:30.08 Antimalarial | In vitro activity against various viruses, including coronaviruses 5, 8, 12-14  
In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed 8, 12  
Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections 1, 4, 11, 15, 16 | without interferon in pts with COVID-19 outside of clinical trials. 5, 12, 14, 16  
**LPV/RTV Clinical Experience (SARS and MERS)**: Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon. 1, 8, 9, 10, 11  
**LPV/RTV COVID-19 Clinical Trials at clinicaltrials.gov**:  
NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease) 15  
NCT04276688 (LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone) 15  
NCT04328012 (LPV/RTV vs hydroxychloroquine vs losartan vs placebo) 15  
**Darunavir COVID-19 Clinical Trials**:  
NCT04252274: Open-label randomized trial in China to evaluate DRV/cobicistat 15  
NTC04303299: Open-label randomized trial in Thailand to evaluate DRV/RTV in conjunction with other antivirals 15  
ChiCTR2000029541: Open-label randomized trial in China to evaluate DRV/cobicistat vs LPV/RTV 20  
**Hydroxychloroquine small pilot study conducted in China**:  
15 treatment-naïve 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 7 in 13 pts | **Optimal dosage and duration of treatment not known** 20, 26  
**Various dosages recommended or being investigated** for treatment of COVID-19  
**Oral hydroxychloroquine sulfate 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 participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation 26  
**Oral hydroxychloroquine sulfate**: 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 8, 20 | **Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established** 10, 24, 39  
Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19  
Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration  
Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.)
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<tr>
<td>unknown pharmacokinetics and toxicity profile Hydroxy analog of chloroquine with similar mechanisms of action and adverse effects; may have more favorable dose-related toxicity profile than chloroquine, but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs</td>
<td>Hydroxychloroquine randomized, parallel-group study in adults in China (ChiCTR2000029559): 31 pts with COVID-19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 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 hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group).</td>
<td>Oral hydroxychloroquine sulfate: 400 mg once or twice daily for 5-10 days</td>
<td>Additional data needed regarding toxicity profile when used in patients with COVID-19 Hydroxychloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against use of hydroxychloroquine for the treatment of COVID-19. IDSA recommends that hydroxychloroquine be used for the treatment of COVID-19 in the context of a clinical trial. NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial. IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial. NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for prevention of SARS-CoV-2 infection outside of clinical trials. Because hydroxychloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects</td>
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*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 trials.
TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, 32 data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported. 31

**Hydroxychloroquine 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 (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 was 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 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

**Emergency use authorization (EUA) for hydroxychloroquine:** 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, 26 To request the drug, healthcare providers should contact local or state health departments; 26 distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. 29 To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch). 24, 26 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. 24 Consult the EUA, 24 EUA fact sheet for healthcare providers, 28 and EUA fact sheet for patients and parent/caregivers 28 for additional information.
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<td>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 discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. 33 Note: In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.</td>
<td>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 (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. 34 Note: Almost all pts were considered low risk for clinical...</td>
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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.

**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.\(^\text{40}\) **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.

**Efficacy measures:** Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in
nasopharyngeal samples at day 6 or 7.\textsuperscript{7,16} RT-PCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19;\textsuperscript{19,21} 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.\textsuperscript{52,23}

Multiple clinical trials to evaluate hydroxychloroquine for treatment of COVID-19 are registered at clinicaltrials.gov (some listed below):\textsuperscript{10}

- NCT04329923
- NCT04332991
- NCT04334967
- NCT04335552
- NCT04341727
- NCT04345692
- NCT04350450
- NCT04351620
- NCT04353037
- NCT04362332

Multiple clinical trials to evaluate hydroxychloroquine for prevention of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed below):\textsuperscript{10}

- NCT04303507
- NCT04318015
- NCT04318444
- NCT04328961
- NCT04330144
- NCT04331834
- NCT04333225
- NCT04341441
- NCT04352946
- NCT04359537
- NCT04363450
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| Neuraminidase inhibitors (e.g., oseltamivir) 3/20/20 | 8:18.28    | Antivirals active against influenza viruses   | 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.  
While oseltamivir is noted to have been widely used for confirmed or suspected COVID-19 cases in hospitals in China, there has been no exact evidence to date that oseltamivir is effective in the treatment of COVID-19. Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture.  
Clinicaltrials.gov trials for COVID-19 that include oseltamivir:  
NCT04303299 (not yet recruiting)  
NCT04261270 (recruiting)  
NCT04255017 (recruiting)  
Optimal dosage and duration of treatment not known  
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); 200 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 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)  
Drug(s) AHFS Class Rationale Trials or Clinical Experience Dosagea Comments                                                                 |
| Remdesivir Updated 5/4/20 | 8:18.32    | Antiviral                                      | Various clinical trials initiated in US, China, and other countries  
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.  
Optimal dosage and duration of treatment not known  
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); 200 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 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)  
Not commercially available; most promising direct-acting antiviral (DAA) currently being investigated for COVID-19  
Efficacy and safety of remdesivir for treatment of COVID-19 not established  
NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of remdesivir for the treatment of 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 |
**Drug(s)**

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<td>lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control 19</td>
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<td>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</td>
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<td>Pharmacokinetic data available from evaluations for Ebola</td>
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<td><strong>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%).</strong> 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. <strong>Note:</strong> Enrollment was terminated before the pre-specified number of pts was attained (lack of available pts); trial was insufficiently powered to detect assumed differences in clinical outcome.</td>
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<td>**Phase 3 randomized, open-label trial in hospitalized adults with severe COVID-19 (NCT04292899) sponsored by the manufacturer (Gilead): Initial study protocol 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 once daily for total of 5 or 10 days) in conjunction with standard of care in pts not receiving mechanical ventilation; protocol subsequently modified to add extension arms to evaluate safety and efficacy of 10-day regimen of remdesivir in conjunction with standard of care in pts who are or are not receiving mechanical ventilation. 10 Manufacturer announced that data available 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)</td>
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<td><strong>NIADD adaptive study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total 13</strong></td>
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<td>Compassionate use access protocol: 200 mg IV on day 1, then 100 mg IV on days 2-10 16</td>
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<td><strong>Emergency use authorization (EUA) dosage recommended for adults and children weighing 40 kg or more:</strong> Loading dose of 200 mg by IV infusion on day 1, followed by 100 mg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 100 mg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts not requiring mechanical ventilation and/or ECMO). 26</td>
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<td><strong>Emergency use authorization (EUA) dosage recommended for children weighing 3.5 to less than 40 kg:</strong> 5 mg/kg by IV infusion on day 1, followed by 2.5 mg/kg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 2.5 mg/kg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts not requiring mechanical ventilation and/or ECMO). 26</td>
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<td><strong>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. 25, 26</strong> Distribution of remdesivir under this EUA is controlled by the US government for use consistent with the terms and conditions of the EUA. The manufacturer (Gilead) will supply remdesivir to authorized distributors, or directly to a US government agency, who will distribute the drug to hospitals and other healthcare facilities as directed by the US government, in collaboration with state and local government authorities, as needed. 25 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). 25, 26 Consult the EUA, 25 EUA fact sheet for healthcare providers, 26 and EUA fact sheet for patients and parent/caregivers 27 for additional information.</td>
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indicate similar clinical improvement with both treatment durations. **Time to clinical improvement for 50% of pts was 10 days in the 5-day treatment group vs 11 days in the 10-day treatment group.** At day 14, 129/200 pts (64.5%) in the 5-day group and 106/197 pts (53.8%) in the 10-day group achieved clinical recovery. Pts who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms.  

**Note:** Data regarding this initial pt population (e.g., disease severity and comorbidities at study enrollment, additional supportive treatment received) not provided to date.

**Phase 3 randomized, open-label trial in pts with moderate COVID-19 (NCT04292730)** sponsored by the manufacturer (Gilead) is evaluating safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care compared with standard of care alone.

**Phase 3 adaptive, randomized, placebo-controlled trial (NCT04280705) in hospitalized adults sponsored by NIAID:** Pts received remdesivir (200 mg IV on day 1, then 100 mg once daily for duration of hospitalization up to 10 days total) or placebo. **Sponsor announced** that preliminary data analysis (total of 1063 pts) indicated **shorter median time to recovery in remdesivir group (11 days) vs placebo group (15 days)** and suggested that remdesivir treatment may have provided a survival benefit (mortality rate 8% in remdesivir group vs 11.6% in placebo group).  

**Note:** Data regarding the pt population (e.g., disease severity and comorbidities at study enrollment, time to initiation of treatment after symptom onset, additional supportive treatment received) not provided to date.
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<th>Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
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<tr>
<td>Expanded access IND protocol (NCT04323761):</td>
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<td>The manufacturer (Gilead) has established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19.</td>
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<td>Compassionate use access:</td>
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<td>The manufacturer (Gilead) is transitioning from individual compassionate use requests to an expanded access program for emergency access to the drug for severely ill pts with confirmed COVID-19. New individual compassionate use requests cannot be accepted, with the possible exception of requests for pregnant women and children &lt;18 years of age with confirmed infections and severe manifestations of the disease.</td>
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<tr>
<td>Compassionate use access (NCT04302766):</td>
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<td>May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command.</td>
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<td>Data from the manufacturer’s compassionate use program:</td>
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<td>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</td>
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<sup>a</sup>Drug: AHFS Class, Rationale, Trials or Clinical Experience, Dosage, Comments.
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<tr>
<td>Umifenovir (Arbidol®)</td>
<td>8:18.92</td>
<td>Antiviral</td>
<td><strong>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses</strong>&lt;sup&gt;4&lt;/sup&gt; <strong>and SARS-CoV-2</strong>&lt;sup&gt;5&lt;/sup&gt; reported</td>
<td><strong>Retrospective cohort study</strong> 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&lt;sup&gt;8&lt;/sup&gt; <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&lt;sup&gt;1&lt;/sup&gt;</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&lt;sup&gt;5,7&lt;/sup&gt; <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&lt;sup&gt;2,3,6,8&lt;/sup&gt;</td>
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<td>Anakinra</td>
<td>92:36 Disease-modifying Anti-rheumatic Drug</td>
<td>Recombinant human interleukin-1 (IL-1) receptor antagonist; may potentially combat cytokine release syndrome (CRS) symptoms in severely ill patients</td>
<td>Currently no known published clinical trial evidence supporting efficacy or safety of anakinra in treating COVID-19</td>
<td>Various dosage regimens are being studied</td>
<td>Insufficient clinical data to recommend either for or against use in the treatment of COVID-19. Safety profile well established in patients with sepsis and has been studied extensively in pediatric patients with rheumatologic conditions.</td>
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**Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 in China ([ChiCTR200030254](https://www.chictr.org/index.aspx?tid=000030254)): 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.

**SUPPORTING AGENTS**

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**Italy**: Phase 3 randomized, open-label, multicenter trial (NCT04324021) initiated by the manufacturer (Swedish Orphan Biotech) 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. 

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.

Some studies under way in Greece and Belgium are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge.

(Note: Anakinra is approved only for subcutaneous administration in the U.S.)
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<tbody>
<tr>
<td><strong>Ascorbic acid</strong></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 (^3,5,7)</td>
<td>Other noncomparative, open-label trials are recruiting in Greece (NCT04356366, NCT04339712) and Belgium (NCT04330638) (^1)</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>
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<td>Current data not specific to COVID-19; additional study needed (^6)</td>
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<tr>
<td><strong>Azithromycin</strong></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)</td>
<td>No data to date on in vitro activity against coronaviruses, including SARS-CoV-2</td>
<td>Adjunctive therapy in certain respiratory viral infections: 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) 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>Adjunctive treatment in certain viral infections: 500 mg once daily has been used (^13) COVID-19: 500 mg on day 1, then 250 mg daily on days 2-5 in conjunction with 10-day regimen of hydroxychloroquine has been used (^7,18,19)</td>
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<td>Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19</td>
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<td>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</td>
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Updated 4/8/20. 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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<tr>
<td>Baricitinib (Olumiant®)</td>
<td>92:36</td>
<td>Janus kinase (JAK) 1 and 2 inhibitor; disrupts regulators of endocytosis</td>
<td>Currently no known published clinical trial evidence supporting efficacy or safety in patients</td>
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<td>Disease</td>
<td>AP2-associated protein kinase 1 [AAK1] and cyclin G-associated kinase</td>
<td>with COVID-19</td>
<td>Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to</td>
<td>NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial.</td>
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<td>- modifying Anti-rheumatic Drug</td>
<td>[GAK]), which may help reduce viral entry and inflammation; also may interfere with intracellular virus particle assembly</td>
<td>evidence supporting efficacy or safety in patients with COVID-19</td>
<td>inhibit AAK1</td>
<td>IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial.</td>
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<td>Inhibits JAK1 and JAK2-mediated cytokine release; may combat cytokine</td>
<td>Baricitinib to be included as an arm in NIAID’s Adaptive COVID-19 Treatment Trial 3</td>
<td>Dosage information not yet available</td>
<td>Because both azithromycin and hydroxychloroquine are associated with QT prolongation, caution is advised if considering use of both drugs in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias;</td>
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<td>release syndrome (CRS) in</td>
<td>Adaptive phase 2/3 clinical trial: Open-label study planned to evaluate safety and</td>
<td>(see Trials or Clinical Experience)</td>
<td>20 diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects</td>
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<td>effects, including effects on proinflammatory cytokines; precise</td>
<td>efficacy and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232)</td>
<td></td>
<td>4 TheraCare recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit</td>
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<td></td>
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<td>mechanisms of such effects not fully elucidated 2, 6, 8, 9, 11-14, 17</td>
<td>7</td>
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<tr>
<td>Colchicine</td>
<td>92:16 Antigout Agents</td>
<td><strong>severely ill patients</strong>&lt;sup&gt;1,2,4,5&lt;/sup&gt; 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&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Minimal anecdotal experience and no clinical trial data reported to date in COVID-19&lt;sup&gt;4&lt;/sup&gt; <strong>Phase 3, randomized, double-blind, placebo-controlled study</strong> (NCT04322682; COL-CORONA) initiated in adults 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&lt;sup&gt;1&lt;/sup&gt; Other registered randomized, open-label, parallel-group studies (not yet recruiting) will evaluate effects of colchicine plus standard treatment vs standard treatment alone on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in adults with COVID-19: NCT04326790, NCT04322565, NCT04328480, NCT04350320, NCT04355143&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days&lt;sup&gt;1&lt;/sup&gt; Consider possible need for colchicine dosage adjustment;&lt;sup&gt;4&lt;/sup&gt; 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&lt;sup&gt;5&lt;/sup&gt; Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Safety and efficacy for treatment of COVID-19 not established</td>
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**Added 4/24/20**

Colchicine exerts broad anti-inflammatory and immunomodulatory effects through multiple mechanisms, including inhibition of NOD-like receptor protein 3 (NLRP3) inflammasome assembly and disruption of cytoskeletal functions through inhibition of microtubule polymerization<sup>2,3,5,6</sup> May combat the hyperinflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines<sup>7</sup> NLRP3 inflammasome activation results in release of interleukins, including IL-1β<sup>3,5,8,11</sup> 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<sup>1,11</sup>
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<td>Corticosteroids (general)</td>
<td>68:04 Adrenals</td>
<td>Potential to limit COVID-19-related myocardial damage also has been hypothesized based on the drug's mechanisms of action and promising results of ongoing research on colchicine in various cardiac conditions. 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. <strong>Observational studies:</strong> Evidence suggests that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). Uncontrolled observational data from the recent COVID-19 outbreak in China suggest a possible treatment benefit of methylprednisolone in COVID-19 patients with acute respiratory distress syndrome (ARDS). (See Methylprednisolone in this Evidence Table.) Pending results of randomized controlled clinical studies specifically evaluating corticosteroids for COVID-19, indirect evidence from studies in patients with community-acquired pneumonia, ARDS, and other viral infections has been used to inform treatment decisions for COVID-19 patients. In general, low to moderate dosages of corticosteroids are recommended in intubated patients with ARDS. Regimens used in China were typically methylprednisolone 40-80 mg IV 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. This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial. Higher dosages have been suggested for cytokine storm. (See Comments column.)</td>
<td>In general, low to moderate dosages of corticosteroids are recommended in intubated patients with ARDS. Regimens used in China were typically methylprednisolone 40-80 mg IV 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. This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial. Higher dosages have been suggested for cytokine storm. (See Comments column.)</td>
<td>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. <strong>General recommendations:</strong> WHO, CDC, NIH, and IDSA generally recommend against the routine use of corticosteroids for the treatment of COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock). <strong>Non-critical patients:</strong> Corticosteroids generally should not be used in the treatment of early or mild disease since...</td>
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<td>by sepsis (possible complication of infection with COVID-19) and increase BP when low</td>
<td>evidence is low to moderate in quality and most studies were performed prior to the prelung protection strategy era.</td>
<td>the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding.</td>
<td><strong>Trials or Clinical Experience</strong>&lt;br&gt;In a recent multicenter, unblinded, randomized controlled study (DEXA-ARDS trial), 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 treatment alone. Based on results of this study, a clinical trial (NCT04325061) has been initiated to specifically evaluate the use of dexamethasone in patients with ARDS due to COVID-19. Other clinical trials have been initiated in various countries to evaluate use of IV corticosteroids (e.g., dexamethasone, hydrocortisone), oral corticosteroids (e.g., prednisone), or inhaled corticosteroids (e.g., budesonide) for treatment of COVID-19 pneumonia or ARDS, including the following trials registered at clinicaltrials.gov: NCT04327401, NCT04344288, NCT04344730, NCT04348305, NCT04355637, NCT04359511, NCT04360876 (For registered clinical trials evaluating use of methylprednisolone, see Methylprednisolone in this Evidence Table.) Randomized controlled studies evaluating use of corticosteroids (e.g., hydrocortisone, dexamethasone, methylprednisolone, prednisolone) in septic shock suggest a small, but uncertain mortality reduction.</td>
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<td>NIH recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients unless they are in the intensive care unit.</td>
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**suggest that use of more potent immuno-suppression with corticosteroids may be beneficial in such patients.**

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. The decision to use corticosteroids in patients with early signs of cytokine storm should be balanced with the known adverse effects.

**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. 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. Clinicians considering corticosteroids for such patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding.

If corticosteroids are prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia.

**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. The guidelines

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<td>also recommend 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.</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 patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral corticosteroids may be necessary. 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. Additional study is needed to determine the optimum corticosteroid stress dosage regimens in patients with COVID-19. 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.</td>
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<td>COVID-19 Convalescent Plasma</td>
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<td>Theoretically, plasma obtained from pts who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2, including neutralizing antibody, may provide short-term passive immunity that could prevent infection or could be beneficial in the treatment of pts with COVID-19 in terms of decreasing viral load and improving outcomes. ¹⁻⁵</td>
<td>Uncontrolled pilot study of COVID-19 convalescent plasma in China: Ten 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; 9 pts also received umifenovir [Arbidol®], some pts also received ribavirin, oseltamivir, peramivir, and/or interferon α, and 6 pts also received methylprednisolone. Time from onset of symptoms to transfusion of convalescent plasma was 10-20 days (mean 16.5 days). COVID-19 symptoms (fever, cough, shortness of breath, chest pain) improved in all pts within 1-3 days after the transfusion and all pts showed improvement on chest CTs. Titers of neutralizing antibody increased in 5 pts after the transfusion, but did not increase in 4 pts. Prior to the transfusion, RT-PCR tests for SARS-CoV-2 RNA were positive in 7 pts and negative in 3 pts; after transfusion, SARS-CoV-2 RNA was undetectable in 3 pts</td>
<td>Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. ¹¹</td>
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<td>Most appropriate criteria for selection of pts 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</td>
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<td>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</td>
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<td>Logistics of obtaining, processing, storing, and distributing COVID-19</td>
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<td>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),(^4)</td>
<td>on day 2, 3 pts on day 3, and 1 pt on day 6.(^9)</td>
<td><strong>Uncontrolled case series in China:</strong> Five 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) in conjunction with continued methylprednisolone therapy and various antiviral treatments that included LPV/RTV, favipiravir, umifenovir (Arbidol(^b)), darunavir, and/or interferon α-1b. Pts received the convalescent plasma transfusions 10-22 days after hospital admission. Following the transfusions, body temperature normalized within 3 days in 4/5 pts, sequential organ failure assessment (SOFA) scores improved in all pts (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 pts, and viral loads decreased and became negative within 12 days.(^10)</td>
<td>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.(^1)(^1)(^4)(^5)(^14)(^15)</td>
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</table>

**Efficacy data not available from controlled clinical studies to date.**\(^1\)

**Multiple clinical trials initiated in the US and other countries to evaluate use of COVID-19 convalescent plasma, including the following trials registered at clinicaltrials.gov:**

- NCT04323800 (US)
- NCT04338360 (US)
- NCT04340050 (US)
- NCT04343261 (US)
- NCT04343755 (US)
- NCT04344015 (US)
- NCT04344535 (US)
- NCT04344977 (US)
- NCT04264858
- NCT04292340
- NCT04327349

**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 that may exacerbate clinical severity) and steps to mitigate such risks not determined.**\(^1\)\(^5\)

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<table>
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<tr>
<th>Drug(s)</th>
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<th>Trials or Clinical Experience</th>
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<td>NCT04332380</td>
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<td>unable to participate in randomized critical 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.</td>
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Information on a protocol that is in place is available at [https://www.uscovidplasma.org](https://www.uscovidplasma.org). |
| NCT04332835 | | | | | |
| NCT04333251 | | | | | |
| NCT04333355 | | | | | |
| NCT04342182 | | | | | |
| NCT04345523 | | | | | |
| NCT04345679 | | | | | |

3). Single Patient Emergency IND (eIND): Licensed physicians seeking to administer COVID-19 convalescent plasma to an individual pt may request an eIND from the FDA. Consult the FDA guidance document for specific information on applying for an eIND.

FDA guidance suggests that collection of donor plasma at least 28 days after complete resolution of symptoms or collection at least 14 days after resolution of symptoms and negative results for COVID-19 (based on one or more nasopharyngeal swabs or by a molecular diagnostic blood test) be considered.

FDA guidance suggests that a minimum neutralizing antibody titer of at least 1:160 in donor plasma should be considered.

FDA guidance suggests that the following pt eligibility criteria to receive COVID-19 convalescent plasma be considered: Laboratory-confirmed COVID-19 with **severe** disease (defined as one or more of the following: shortness of breath, respiratory frequency 30/minute or greater, blood oxygen saturation 93% or lower, \( \text{PaO}_2/\text{FiO}_2 \) ratio less than 300, lung infiltrates greater than 50% within 24-48 hours) or with **life-threatening disease** (defined as one or more of the following: respiratory failure, septic shock, multiple organ dysfunction or failure) and informed consent provided by the pt or healthcare proxy.
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| Epoprostenol (inhaled)  
*Added 4/3/20* | 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.  
*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.  
Various dosages of inhaled epoprostenol have been used in ARDS studies.  
Dosages up to 50 ng/kg per minute have been used (titrated to response).  
To provide a clinically important increase in PaO₂ 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.  
Additional studies are needed to evaluate the potential role of inhaled epoprostenol in the treatment of ARDS.  
The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against use of inhaled prostacyclins in COVID-19 patients with severe ARDS. |

| Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®)  
*Updated 5/1/20* | 68:04 Adrenal | 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.  
(See Corticosteroids in this Evidence Table.)  
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.  
Retrospective, observational, single-center study: In 46 patients with confirmed severe COVID-19 pneumonia that progressed to acute respiratory failure, use of methylprednisolone was associated with improved clinical symptoms (i.e., fever, hypoxia) and a shortened disease course in patients who received the drug compared with those who did not. Death occurred in 3 patients during hospitalization; 2 of these patients received methylprednisolone.  
Open-label, multicenter, randomized controlled study (NCT04244591) was recently completed in China that compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to  
Dosage used in the retrospective study (Wu et al) not provided.  
Dosage used in the retrospective study (Wang et al) was 1-2 mg/kg daily IV for 5-7 days.  
Dosage used in the randomized, controlled study (NCT04244591) was 40 mg IV every 12 hours for 5 days.  
Findings from observational studies suggest that for patients with COVID-19 pneumonia who progress to ARDS, 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. (See Corticosteroids in this Evidence Table.) |

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<th>Trials or Clinical Experience</th>
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| Nitric oxide (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 2, 3, 9.  
In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential effectiveness for COVID-19 1. | No studies evaluating use specifically in COVID-19 patients 10  
In a small pilot study (Chen et al.) conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide in ICU patients with SARS reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support 2, 3.  
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) 3, 5, 6. | In the Chen et al. study in severe SARS patients, 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) 2.  
Phase 2 clinical trial protocol (NCT04306393) for treatment of mechanically ventilated COVID-19 patients: 80 ppm for the first 48 hours, followed by 40 ppm and then subsequently wean 3. | 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 4, 5, 6, 9.  
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 10.  
Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway (NCT04338828, NCT04305457, NCT04306393, NCT04312243) 3, 7.

Updated 5-04-20. The current version of this document can be found on the ASHP COVID-19 Resource Center.  
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| Ruxolitinib (Jakafi®)  
*Updated 4/24/20* | 10:00 Antineoplastic Agents | Janus kinase (JAK) 1 and 2 inhibitor; ² ³ may potentially combat cytokine release syndrome (CRS) in severely ill patients ⁴ ⁵  
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 ⁴ ⁵  | Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19  
**Phase 3 clinical trial** evaluating ruxolitinib plus standard of care vs standard of care alone is being initiated pending FDA approval of the protocol in patients with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.) ¹  
**Expanded-access (managed-access, compassionate use) program** (NCT04337359) being initiated for eligible adults and children ≥6 years of age with severe or very severe COVID-19 illness; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) ¹ ²  
Other noncomparative, open-label clinical trials registered but not yet recruiting (NCT04331665, NCT04334044, NCT04338958); small parallel-group or uncontrolled studies also registered in Chinese Clinical Trial Registry (ChiCTR2000029580, ChiCTR2000030170) ³ ⁶  | Various dosages are being evaluated ² ³ ⁶  | 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; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit ⁸  |
| Sarilumab (Kefzara®)  
*Updated 5/1/20* | 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) and pulmonary symptoms in severely ill patients ¹ ² ⁵  | Currently no known published clinical trial evidence supporting efficacy or safety in treatment of patients with COVID-19  
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 ³ ⁴  | Not available (see Trials or Clinical Experience)  | 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 ⁷  |
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| **Sirolimus** (Rapamune®)  
*Updated 4/22/20* | 92:44 Immunosuppressiv e 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> | Clinicaltrials.gov link: [https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4](https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4)  
For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)<sup>6</sup> | Dosage being investigated in NCT04341675 trial: 6 mg orally on day 1 followed by 2 mg daily for a maximum treatment duration of 14 days or until hospital discharge<sup>4</sup> | Although possible clinical application, current data not specific to COVID-19; additional study needed<sup>5</sup> |
| **Tocilizumab** (Actemra®)  
*Updated 5/1/20* | 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, 3, 6, 10, 14</sup> | Case reports and observational studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world<sup>1, 3, 10, 12</sup>  
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)<sup>3</sup>  
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. | 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>  
**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<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>4</sup>  
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<sup>9</sup>  
The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study<sup>14</sup> |
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<td>About one-third of the patients received 2 or more doses of tocilizumab. Elevated C-reactive protein (CRP) levels rapidly decreased in most patients following treatment, and a gradual decrease in IL-6 levels was noted in patients who stabilized following tocilizumab administration. Clinical outcomes were equivocal. 10</td>
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<td>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. 12</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 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 under way globally 1, 5, 7, 8</td>
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<td><strong>US/Global randomized, placebo-controlled trial</strong>: 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</td>
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<td>ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)</td>
<td>24:32 Renin-Angiotensin-Aldosterone System Inhibitor</td>
<td><strong>Hypothetical harm:</strong> Human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2). Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs. Increased expression of ACE2 may potentially facilitate COVID-19 infections.</td>
<td>Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection. 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)</td>
<td>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 may lead to clinical instability and adverse health outcomes.</td>
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<td>Anticoagulants (low molecular weight heparin [LMWH], unfractionated heparin [UFH])</td>
<td>20:12.04.16 (Heparins)</td>
<td>A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which may contribute to their risk of poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), a high</td>
<td>Limited data from China suggest that patients with severe COVID-19 infection or markedly elevated levels of D-dimer (&gt;6 x ULN) have decreased mortality when given prophylactic doses of LMWH or UFH. A randomized open-label clinical trial (NCT04345848) is currently being conducted to evaluate prophylactic- and therapeutic-dose anticoagulation in hospitalized adults with severe COVID-19 infection.</td>
<td>Additional study is needed to understand the anticoagulant needs of COVID-19 patients. Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy. The International Society for Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) recommend that all hospitalized COVID-19 patients, including non-ICU patients, receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, platelet count &lt;25×10^9/L, fibrinogen</td>
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<td>less than 0.5 g/L. 4, 5 Abnormal PT or aPTT is not a contraindication for prophylaxis. 4, 5</td>
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<td>UFH also may be considered for thromboprophylaxis; practical concerns (e.g., convenience of administration and risk of medical staff exposure) may influence institutional choice of anticoagulant. 8, 9</td>
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<td>Because thrombotic complications have continued to occur in some COVID-19 patients despite thromboprophylaxis, some clinicians have suggested the use of high prophylactic doses. 11, 17</td>
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<td>The American Society of Hematology (ASH) states that therapeutic anticoagulation is not required in COVID-19 patients unless there is documented VTE or atrial fibrillation. 4 The efficacy of intermediate or full therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is being evaluated. 4 In patients already on anticoagulation for VTE or atrial fibrillation, therapeutic doses of anticoagulant therapy should continue but may need to be held if the platelet count is less than 30-50 x 10^9/L or if fibrinogen is less than 1 g/L. 4</td>
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<td>incidence of venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. 1-6, 8, 11, 16, 18</td>
<td>Early anticoagulation in patients with severe COVID-19 infection may prevent clot formation and reduce thrombotic complications. 2, 4, 5, 14 An additional benefit may be the anti-inflammatory effect of heparins. 5, 7, 8, 17</td>
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<td>However, some clinicians recommend that therapeutic anticoagulation (with a preference for UFH rather than LMWH) be considered in critically ill patients with COVID-19; since these patients have a severe hypercoagulable state associated with progressive end-organ dysfunction, more aggressive anticoagulation is recommended to prevent significant clinical deterioration. 14</td>
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<td>The risk of venous thromboembolism and anticoagulation requirements should be assessed in all patients on an individual basis. 4, 5, 10, 17, 18</td>
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<td><strong>HMG-CoA Reductase Inhibitors</strong> (statins)</td>
<td>24:06 Antilipemic Agents</td>
<td>In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects which may prevent acute lung injury. 1 Statins affect ACE2 as part of their function in reducing endothelial dysfunction. 2, 8</td>
<td>Data are lacking on the use of statins in patients with COVID-19. 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. 3, 6 Clinical trials are evaluating the effectiveness of statins (with and without other potential treatment agents) for the treatment of COVID-19. 9, 10 (NCT04348695, NCT04333407)</td>
<td>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; 2 recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. 2 Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections. 3 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. 3 Most statins are substrates for the CYP450 system; potential for drug interactions. 7 Clinicians should ensure that their high-risk primary prevention (for ASCVD) patients are on guideline-directed statin therapy. 3</td>
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<td><strong>Immune Globulin</strong> (IGIV, IVIG, γ-globulin)</td>
<td>80:04 Immune Globulin</td>
<td>Commercially available immune globulin (IGIV, IVIG, γ-globulin) is derived from pooled plasma; contains many antibodies normally present in adult human blood; used for replacement therapy in pts with primary humoral immunodeficiency unable to produce sufficient IgG antibodies and also used to provide passive immunity</td>
<td><strong>SARS Experience:</strong> IGIV has been used in some pts for the treatment of SARS. 4, 7, 15 Benefits in such pts were unclear because of comorbidities, differences in stage of illness, and effect of other treatments; 5 IGIV may have contributed to hypercoagulable state and thrombotic complications in some pts. 6, 7 <strong>COVID-19 case reports in China (Cao et al):</strong> Treatment with IGIV at the early stage of clinical deterioration was reported to provide some clinical benefit in 3 adults with IGIV dosage of 0.3-0.5 g/kg daily for 5 days has been used in some pts with COVID-19; 8 IGIV dosage of 0.5 g/kg daily for 5 days being investigated in a clinical trial in China. 12</td>
<td>Role of commercially available immune globulin (IGIV, IVIG, γ-globulin) in the treatment of COVID-19 unclear. 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,</td>
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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>to certain viral infections in other individuals. 1 May modulate immune responses to infections. 2 Commercially available preparations of immune globulin (IGIV, IVIG, γ-globulin) may contain antibodies against some previously circulating coronaviruses; 3 however, depending on time of donor plasma collection, such preparations may not contain antibodies against SARS-CoV-2. 3, 13</td>
<td>severe COVID-19; 2 pts also received antivirals and 1 pt also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration. 8 COVID-19 clinical experience in China: IGIV has been used as an adjunct in the treatment of COVID-19. 9-11 Efficacy data not available from controlled clinical studies to date. COVID-19 clinical trial in China (NCT04261426): Open-label randomized trial initiated to evaluate efficacy and safety of IGIV with standard care for treatment of severe COVID-19 12</td>
<td>aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury). 13 IGIV mentioned in Chinese guidelines as other therapeutic measure for treatment of severe and critical cases of COVID-19 in children. 14</td>
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<td>Ivermectin</td>
<td>8:08 Anthelmintic</td>
<td>In vitro activity against some human and animal viruses 1-6 In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug 1</td>
<td>Currently no known published data regarding efficacy or safety in the treatment of COVID-19</td>
<td>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 7 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 8</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. 1, 2</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. 3</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. 1</td>
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<td>Drug(s)</td>
<td>AHFS Class</td>
<td>Rationale</td>
<td>Trials or Clinical Experience</td>
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<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>In drug repurposing screens, was found to inhibit replication and antigen synthesis of SARS-CoV; did not interfere with virion’s attachment into cells&lt;sup&gt;1,2&lt;/sup&gt;</td>
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<td></td>
<td>Anthelmintic</td>
<td>In vitro evidence of activity against SARS-CoV and MERS-CoV&lt;sup&gt;1,2&lt;/sup&gt;</td>
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<td>Not commercially available in the US</td>
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<td></td>
<td>3/20/20</td>
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<td></td>
<td>No data to date support use in treatment of COVID-19</td>
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<td>Nitazoxanide</td>
<td>8:30.92</td>
<td>In vitro activity against various viruses, including coronaviruses&lt;sup&gt;4,5&lt;/sup&gt;</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&lt;sup&gt;6,7,8&lt;/sup&gt;</td>
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<td>Updated 5/1/20</td>
<td>Antiprotozoal</td>
<td>Structurally similar to niclosamide&lt;sup&gt;3,5&lt;/sup&gt;</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&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Protocol in one ongoing trial (NCT04348409) for treatment of moderate COVID-19 specifies a nitazoxanide dosage of 600 mg twice daily for 7 days&lt;sup&gt;8&lt;/sup&gt;</td>
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<td>In vitro evidence of activity against SARS-CoV-2&lt;sup&gt;1&lt;/sup&gt;</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).&lt;sup&gt;7&lt;/sup&gt; 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&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Protocol in two ongoing trials (NCT04343248, NCT04359680) evaluating pre- and/or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks&lt;sup&gt;8&lt;/sup&gt;</td>
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<td>In vitro activity against MERS-CoV&lt;sup&gt;4&lt;/sup&gt;</td>
<td>COVID-19: Randomized, double-blind, placebo-controlled proof-of-concept trial (NCT04348409) initiated to evaluate nitazoxanide for treatment of moderate COVID-19&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Current data not specific to COVID-19; additional study needed&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Drug(s)</td>
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<td>Nonsteroidal Anti-inflammatories (NSAIAs)</td>
<td>28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)</td>
<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</td>
<td>Two randomized, double-blind, placebo-controlled clinical trials have been initiated by the manufacturer (Romark) to evaluate efficacy and safety for pre- or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers (NCT04359680) and post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (NCT04343248).</td>
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<td><strong>Indomethacin:</strong> Possible antiviral activity against other coronaviruses SARS-CoV &amp; CanineCoV (interferes with viral RNA synthesis)</td>
<td>Multiple other clinical trials planned or initiated to evaluate nitazoxanide in combination with other drugs (chloroquine, hydroxychloroquine, or ivermectin) or alone for treatment of COVID-19.</td>
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<td><strong>Ibuprofen:</strong> None; anecdotal</td>
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<td><strong>Indomethacin:</strong> Speculative; one in vitro &amp; animal model study with other coronaviruses SARS-CoV &amp; CanineCoV</td>
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**Ibuprofen:** A letter published in The Lancet Respir Med stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2; however, this appears to be based on animal studies. A statement attributed to WHO spokesperson Christian Lindmeier recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position 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.”

In addition, there have been unsubstantiated reports of younger, healthy patients who took ibuprofen and suffered severe outcomes with COVID-19. Official case reports are lacking.
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On 3/19/20, FDA issued a statement that it is not aware of scientific evidence connecting the use of NSAIAIs, 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. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory drugs-nsaids-covid-19

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.

NIH COVID-19 Treatment Guidelines Panel states that patients who are receiving NSAIAIs for other conditions should continue receiving the drugs; states antipyretic strategy (e.g., use of acetaminophen or NSAIAIs) 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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<tr>
<td>Tissue Plasminogen Activator (t-PA; alteplase)</td>
<td>20:12.20</td>
<td>Thrombolytic agents</td>
<td>A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which may contribute to their risk of poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).</td>
<td>Results of a small phase 1 study conducted in 2001 suggest possible benefit of plasminogen activators for 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 with urokinase or streptokinase; such therapy improved PaO₂ and also appeared to improve survival. A registered open-label randomized trial (NCT04357730) will evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure. A registered open-label nonrandomized pilot study (NCT04356833) will 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. The open-label systemic fibrinolytic therapy trial (NCT04357730) will evaluate t-PA (alteplase) dosages of 50 mg (administered as a 10-mg IV bolus followed by IV administration 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 ARDS associated 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 (Beth Israel Deaconess et al study); however, the optimum dose, route of administration, and duration of treatment remain to be determined.</td>
<td>t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). However, there are currently no clinical trial data to inform this practice and a lack of clinical experience with the use of fibrinolytic agents in ARDS patients in general. Several institutions (Beth Israel Deaconess, University of Colorado Anschutz Medical Campus, Denver Health) are currently testing the use of t-PA as salvage therapy in patients with severe COVID-19 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 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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Updated 4/29/20

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**REFERENCES**

**ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)**

**Anakinra**

**Anticoagulants**

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Ascorbic acid:

Azithromycin:


Baloxavir:

Baricitinib:

Chloroquine and Hydroxychloroquine:


Colchicine:


Corticosteroids, including methylprednisolone:


COVID-19 Convalescent Plasma:


Epoprostenol:


Favipiravir:


5. McCray EK, Pogue M, on behalf of the Society of Infectious Diseases Pharmacists. COVID-19 Treatment: a review of early and emerging options. Open Forum Infectious Diseases, ofaa105. DOI: 10.1093/ofid/ofaa105

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HIV Protease Inhibitors:

**HMG-CoA Reductase Inhibitors (statins)**

**Immune Globulin (IGIV, IVIG, γ-globulin):**
Ivermectin:

Nebulized drugs:

Neuraminidase Inhibitors (e.g., oseltamivir):

Niclosamide:

Nitzoxanide:

Nitric Oxide (Inhaled):

NSAIDs, including ibuprofen:
Remdesivir:


Ruxolitinib

Sarilumab:

Sirolimus:

Tissue Plasminogen Activator (t-PA; alteplase):
1. Moore HB, Barrett CD, Moore EE et al. Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)?. J Trauma Acute Care Surg. DOI: 10.1097/TAC.0000000000002694

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Tocilizumab:

Umifenovir:
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.