

## Assessment of Evidence for COVID-19-Related Treatments: Updated 10/8/2020

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Selected entries were updated 10/8/20; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by \*\*.

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## ANTIVIRAL AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
Baloxavir  <i>Updated 9/10/20</i>	8:18.92 Antiviral	Antiviral active against influenza viruses  In vitro antiviral activity against SARS-CoV-2 demonstrated in one trial <sup>1</sup>	<b>Only very limited data available</b> regarding use of baloxavir for treatment of COVID-19  Exploratory, open-label, randomized controlled study at a single center in China (ChiCTR2000029544): 29 adults hospitalized with COVID-19 receiving antiviral treatment with lopinavir/ritonavir, darunavir/cobicistat, or umifenovir (Arbidol®), in combination with inhaled interferon-α, were randomized to treatment with baloxavir marboxil (80 mg orally on day 1 and on day 4, and 80 mg orally on day 7 as needed) (n=10), favipiravir (1600 or 2200 mg orally on day 1, followed by 600 mg three times daily for up to 14 days) (n=9), or control (standard antiviral treatment) (n=10). Percentage of pts with viral conversion (2 consecutive tests with undetectable viral RNA results) after 14 days of treatment was 70, 77, and 100% in the baloxavir, favipiravir, and control groups, respectively, with median time to clinical improvement of 14, 14, and 15 days, respectively. <sup>1</sup>  There are no clinical trials registered at clinicaltrials.gov to evaluate baloxavir for treatment of COVID-19.	A baloxavir marboxil dosage of 80 mg on day 1 and on day 4, and another dose of 80 mg on day 7 (as needed; not to exceed 3 total doses) was used in one open-label COVID-19 study in adults in China. <sup>1</sup>	No data support use of baloxavir in the treatment of COVID-19
Chloroquine Phosphate  <i>Updated 10/8/20</i>	8:30.08 Antimalarial (4-aminoquinoline derivative)	In vitro activity against various viruses, including coronaviruses <sup>1-3, 13, 14</sup>  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 <sup>1, 4, 12</sup>  Active in vitro against SARS-CoV-1 and MERS-CoV <sup>2, 3, 5, 9</sup>  Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections <sup>1-3, 13, 15-16</sup>	<b>Only limited clinical trial data available</b> to date to evaluate use of chloroquine for treatment or prevention of COVID-19  <b>Clinical experience</b> in treating pts with COVID-19: Majority of data to date involves use in pts with mild or moderate COVID-19; <sup>35</sup> only limited clinical data on use in pts with severe and critical disease. <sup>35</sup>  <b>Small, randomized study in hospitalized adults in China compared chloroquine with LPV/RTV (Huang et al):</b> 10 pts (7 with moderate and 3 with severe COVID-19) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate and 5 with severe COVID-19) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR	<b>Optimal dosage and duration of treatment not known</b> <sup>25</sup>  <b>Consider:</b> 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base <sup>17</sup>  <b>Oral chloroquine phosphate dosage suggested in the EUA (now revoked):</b> For treatment of hospitalized adults and adolescents weighing 50 kg or more, suggested dosage was 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation. <sup>25</sup> <b>FDA now states that this dosage regimen is unlikely to have an antiviral effect in pts with COVID-19 based on a reassessment of in vitro EC<sub>50</sub>/EC<sub>90</sub> data and calculated lung concentrations;</b> it is	Efficacy and safety of chloroquine for <i>treatment or prevention</i> of COVID-19 not established <sup>10, 24, 39</sup>  No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19  Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration

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		<p>Known pharmacokinetics and toxicity profile based on use for other indications<sup>13,17</sup></p>	<p>results for SARS-CoV-2 by day 13 and were discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from the hospital by day 14. <b>Note:</b> Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively).<sup>20</sup></p> <p><b>Double-blind, randomized, phase 2b study in Brazil (Borba et al; NCT04323527):</b> Efficacy and safety of two different chloroquine dosages were evaluated for adjunctive therapy in hospitalized adults with severe COVID-19. According to the initial study protocol, pts were randomized 1:1 to receive high-dose chloroquine (600 mg twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. Analysis of data available for the first 81 enrolled pts indicated that, by day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QTc &gt;500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). <b>Note:</b> The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data at the time of the interim analysis were insufficient to evaluate efficacy.<sup>37</sup></p> <p>See Hydroxychloroquine in this Evidence Table for additional information on clinical trials and experience with 4-aminoquinoline antimalarials in the</p>	<p>unclear whether this dosage regimen would provide any beneficial immunomodulatory effects.<sup>57</sup></p> <p><b>Oral chloroquine phosphate dosage in Chinese guidelines:</b> 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)<sup>11</sup></p>	<p>Additional data needed regarding toxicity profile when used in patients with COVID-19</p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of chloroquine for the <i>treatment</i> of COVID-19 in hospitalized pts and <b>recommends against</b> use of chloroquine for the <i>treatment</i> of COVID-19 in nonhospitalized patients, except in a clinical trial. The panel also <b>recommends against</b> use of high-dose chloroquine (i.e., 600 mg twice daily for 10 days) for the <i>treatment</i> of COVID-19 because such dosage has been associated with more severe toxicities compared with lower-dose chloroquine.<sup>35</sup></p> <p>IDSA <b>recommends against</b> use of chloroquine for the <i>treatment</i> of COVID-19 in hospitalized pts and also <b>recommends against</b> use of a combined regimen of chloroquine and azithromycin for the <i>treatment</i> of COVID-19 in hospitalized pts.<sup>38</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> the use of any agents, including chloroquine, for preexposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for <i>prevention</i> of SARS-CoV-2 infection, except in a clinical trial. The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure.<sup>35</sup></p> <p>Because 4-aminoquinolines (chloroquine, hydroxychloroquine) are associated with QT prolongation, caution is advised if considering use of the drugs in pts with COVID-19 at risk for QT prolongation or receiving other drugs associated with arrhythmias;<sup>13, 17, 36, 39</sup> diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects.<sup>35, 36, 39</sup> (See Hydroxychloroquine in this Evidence Table.)</p>

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			<p>management of COVID-19.</p> <p>Several clinical trials to evaluate chloroquine for <i>treatment</i> of COVID-19 are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>, including the following:<sup>10</sup></p> <p>NCT04328493 NCT04331600 NCT04344951 NCT04345419 NCT04353336 NCT04420247 NCT04428268</p> <p>Several clinical trials to evaluate chloroquine for <i>prevention</i> of COVID-19 in the healthcare setting are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>, including the following:<sup>10</sup></p> <p>NCT04303507 NCT04333732 NCT04349371</p>		<p>NIH panel states that 4-aminoquinolines (chloroquine, hydroxychloroquine) should be used concomitantly with drugs that pose a moderate to high risk for QT<sub>c</sub> prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, fluoroquinolones, macrolides [including azithromycin]) <i>only</i> if necessary. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving chloroquine (or hydroxychloroquine).<sup>35</sup></p> <p>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; <b>FDA cautions against</b> 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 <a href="https://www.fda.gov/medwatch">FDA MedWatch</a>.<sup>39</sup></p> <p><b>Emergency use authorization (EUA) for chloroquine (now revoked):</b> Effective June 15, 2020, FDA has revoked the EUA for chloroquine and hydroxychloroquine<sup>57</sup> previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible.<sup>24, 57</sup> <b>Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met.</b><sup>57</sup> Based on the totality of scientific evidence available, FDA concluded that it is unlikely that chloroquine and hydroxychloroquine may be effective in</p>

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<p>Favipiravir (Avigan<sup>®</sup>, Avifavir<sup>®</sup>, Favilavir)</p> <p><b>Updated 10/8/20</b></p>	<p>8:18.32 Antiviral</p>	<p>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses <sup>1-5</sup></p> <p>In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug <sup>1, 5, 16</sup></p> <p>Licensed in Japan and China for treatment of influenza <sup>2, 4, 6</sup></p>	<p><b>Limited clinical trial data available</b> to date to evaluate use of favipiravir in the treatment of COVID-19</p> <p><b>Open-label, prospective, randomized, multicenter study</b> 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<sup>®</sup>; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe to critical COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe to critical disease compared with the group receiving umifenovir. <sup>6</sup></p> <p><b>Open-label, prospective, randomized, multicenter study</b> in 60 hospitalized adults with moderate COVID-19 pneumonia in Russia (NCT04434248): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg twice daily on days 2–14 or 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–14) was associated with higher rate of viral clearance at 10 days (92.5 vs 80%) compared with the control group receiving the standard of care. Favipiravir also was associated with decreased median time to normalization of body temperature (2 vs 4 days) and higher improvement rate on chest CT imaging on day 15 (90 vs 80%)</p>	<p>A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days was used in several open-label COVID-19 studies in adults and adolescents <math>\geq 16</math> years of age in other countries <sup>6, 15, 24</sup></p> <p>Protocols in many registered trials generally specify a favipiravir dosage of 1600 or 1800 mg twice daily on day 1, then a total daily dosage of 1200–2000 mg in 2, 3, or 4 divided doses for 4–13 days for treatment of COVID-19 in adults <sup>7</sup></p> <p>Protocol in one trial (<a href="#">NCT04448119</a>) specifies a <i>prophylactic</i> favipiravir dosage of 1600 mg twice daily on day 1, then 800 mg twice daily on days 2–25 and a <i>treatment</i> favipiravir dosage of 2000 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 in older adults in long-term care homes experiencing COVID-19 outbreaks. The prophylactic regimen is considered pre-exposure prophylaxis, post-exposure prophylaxis, or pre-emptive therapy in this setting; those diagnosed with COVID-19 will be offered the treatment regimen <sup>7</sup></p> <p>Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2, <sup>1, 5, 13</sup> 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. <sup>11, 19, 20</sup> One such favipiravir regimen used in the treatment</p>	<p>treating COVID-19 and, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of chloroquine and hydroxychloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA. <sup>57</sup> (See Hydroxychloroquine in this Evidence Table.)</p> <p>Not commercially available in the US</p> <p>Efficacy and safety of favipiravir for treatment of COVID-19 not established</p> <p>Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dosage and treatment duration</p> <p>Given the lack of pharmacokinetic and safety data for the high favipiravir dosages proposed for treatment of COVID-19, the drug should be used with caution at such dosages. <sup>19, 20</sup> Favipiravir is associated with QT prolongation. <sup>21</sup> Some have suggested close cardiac and hepatic monitoring during treatment, as well as monitoring of plasma and tissue concentrations of the drug and, if possible, the active metabolite. <sup>19, 20, 21</sup> Some data suggest that favipiravir exposure may be greater in Asian populations. <sup>17, 19</sup></p> <p>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. <sup>14</sup></p> <p>If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g. <sup>17, 18</sup></p>

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			<p>compared with the control group. Data are based on interim results of the pilot stage of the study.<sup>24</sup></p> <p><b>Open-label, prospective, randomized, multicenter study</b> in patients hospitalized with asymptomatic or mild COVID-19 in Japan (JRCTs041190120): Early treatment (beginning on day of hospital admission) with favipiravir (two 1800-mg doses given orally at least 4 hours apart on day 1, then 800 mg orally twice daily for a total of up to 19 doses over 10 days) (n=36) was not associated with significant improvement in viral clearance compared with late treatment with favipiravir (same regimen beginning day 6 after admission) (n=33). Viral clearance occurred by day 6 in 66.7 and 56.1% of patients in the early and late treatment groups, respectively. Viral clearance was assessed by RT-PCR of nasopharyngeal specimens. Most common adverse effect was transient hyperuricemia (84.1% of patients).<sup>29</sup></p> <p><b>In a small, open-label, nonrandomized study</b> in patients with non-severe COVID-19 in China (ChiCTR2000029600), favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (n=35) was associated with decreased median time to viral clearance (4 vs 11 days) and higher improvement rate on chest CT imaging on day 14 (91 vs 62%) compared with the control group receiving lopinavir/ritonavir (n=45); both groups also received aerosolized interferon <math>\alpha</math>-1b.<sup>15</sup></p> <p><b>**In a prospective, observational, single-center study</b> in 174 adults in Turkey with probable or confirmed COVID-19 (20.1% with mild disease, 61.5% with moderate disease, 18.4% with severe pneumonia) admitted to the hospital within a median of 3 days after symptom onset, 32 pts received a regimen that included favipiravir. Most pts who received favipiravir (93.8%) received the drug either in combination with, or as sequential therapy to, hydroxychloroquine with or without azithromycin. In pts who received a favipiravir-containing regimen, the median time to</p>	<p>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.<sup>12,13</sup></p> <p>For the treatment of COVID-19, one pharmacokinetic simulation model suggested that a dosage of 2400 mg twice daily on day 1, followed by 1600 mg twice daily on days 2–10 should achieve adequate favipiravir trough plasma concentrations and may be more pharmacologically relevant than lower dosages<sup>19</sup></p> <p><b>Pharmacokinetic data are available from a study in critically ill pts with COVID-19 requiring mechanical ventilation who received a favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–5 (or longer if needed) via NG tube.</b> Trough serum concentrations of the drug in most samples were lower than the lower limit of quantification and lower than the in vitro EC<sub>50</sub> of the drug reported for SARS-CoV-2; trough concentrations in these critically ill pts also were much lower than those previously reported in healthy individuals who received the same dosage<sup>22</sup></p>	

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			<p>defervescence and to clinical improvement on therapy was 3 and 6 days, respectively. Critically ill pts with sepsis and/or ARDS at the time of admission were excluded.<sup>31</sup></p> <p><b>**In a prospective, single-center study</b> in 13 pts requiring mechanical ventilation for severe COVID-19 in Japan, pts received favipiravir (3600 mg orally on day 1, then 1600 mg orally on days 2–14), along with methylprednisolone, and low molecular weight heparin (LMWH) or unfractionated heparin. Improvements in PaO<sub>2</sub>/FiO<sub>2</sub> (P/F ratio), interleukin-6 concentration, and procalcitonin concentration suggested that favipiravir may have some effect on inflammatory mediators, but could not completely control inflammatory mediators or respiratory status.<sup>32</sup></p> <p><b>In a retrospective, observational, multi-center study</b> in 63 adults with COVID-19 in Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and median maintenance doses of 17.9 mg/kg per day for a median total duration of 12 days), clinical improvement at day 7 was reported in 66.7% of patients (92.5% in patients <i>not</i> requiring oxygen supplementation, 47.2% in patients requiring oxygen supplementation) and clinical improvement at day 14 was reported in 85.7% of patients (100% in patients <i>not</i> requiring oxygen supplementation, 75% in patients requiring oxygen supplementation). Overall mortality at day 28 was 4.8%. Nearly all patients also received a chloroquine-based therapy and an HIV protease inhibitor. Multivariate analysis revealed that older age, higher baseline disease severity, and loading doses &lt;45 mg/kg per day were negative predictors of early clinical improvement.<sup>23</sup></p> <p>In a <b>case series</b> of 11 adults admitted to the ICU with COVID-19 at a single center in Japan from 4/6/20 to 4/21/20 who received favipiravir (3600 mg on day 1, then 1600 mg daily thereafter for a median of 14 days) in combination with nafamostat mesylate (not commercially available in the US), 8 pts required mechanical ventilation at baseline and 7 of these were weaned</p>		

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			<p>from mechanical ventilation and 1 died.<sup>25</sup></p> <p>In <b>other small case series</b> and <b>case reports</b> of adults with critical or severe COVID-19 pneumonia in Japan (total of 15 pts) who received favipiravir (e.g., 1800 mg twice daily on day 1, then 800 mg twice daily for 9 or 13 days) in combination with other treatments (e.g., systemic corticosteroids), improvements in respiratory status and chest imaging studies were reported<sup>26, 27, 28</sup></p> <p>In a <b>case series</b> of 8 asymptomatic adults in rehabilitation with delayed SARS-CoV-2 clearance (median duration of positive SARS-CoV-2 detection of 61 days) who received favipiravir (1600 mg twice daily on day 1, then 600 mg twice daily on days 2–10 or until negative), 7 pts had rapid viral clearance within 6 days and were discharged after 2 consecutive negative tests performed ≥24 hours apart. One pt remained SARS-CoV-2 positive throughout the 14-day follow-up period.<sup>30</sup></p> <p>In a <b>meta-analysis</b> of 13 studies assessing the efficacy and safety of favipiravir in the treatment of COVID-19, clinical deterioration was less likely with favipiravir than with other antiviral agents, although the difference was not statistically significant, and those treated with favipiravir had substantial clinical and radiological improvements compared with those treated with standard of care. Viral clearance, requirement for oxygen or noninvasive ventilation, and adverse effects were similar between the favipiravir and standard of care treatment groups.<sup>33</sup></p> <p><b>US:</b> Randomized, controlled open-label proof-of-concept trial (<a href="#">NCT04358549</a>) of favipiravir for the treatment of COVID-19<sup>7, 10</sup></p> <p><b>US:</b> Randomized, double-blind, placebo-controlled trial (<a href="#">NCT04346628</a>) to evaluate efficacy of favipiravir in pts with mild or asymptomatic COVID-19<sup>7</sup></p> <p><b>Multiple clinical trials initiated</b> in pts with COVID-19 in China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents.</p>		

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<p>HIV Protease Inhibitors</p> <p><i>Updated 9/3/20</i></p>	<p>8:18.08.08 HIV Protease Inhibitors</p>	<p><b>Lopinavir (LPV):</b> Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells;<sup>19</sup> evidence of in vitro activity against SARS-CoV-1 and MERS-CoV;<sup>1, 2, 9</sup> and some evidence of benefit in animal studies for treatment of MERS-CoV.<sup>2, 7, 9, 11</sup></p> <p><b>Atazanavir (ATV):</b> Some evidence that ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells,<sup>17, 19</sup> human epithelial pulmonary cells (A549),<sup>17</sup> and human monocytes.<sup>17</sup></p> <p><b>Darunavir (DRV):</b> In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations in Caco-2 cells;<sup>18</sup> in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells.<sup>19</sup></p> <p><b>Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):</b> Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells.<sup>19</sup></p>	<p><b>Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (Cao et al)</b> 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, <b>time to clinical improvement was not shorter with LPV/RTV compared with standard care</b> (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. <b>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.</b> LPV/RTV stopped early in 13 pts because of adverse effects.<sup>3</sup></p> <p><b>LPV/RTV vs chloroquine in small, randomized study in hospitalized adults with COVID-19 in China (Huang et al):</b> 10 pts (7 with moderate and 3 with severe disease) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate and 5 with severe disease) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR results for SARS-CoV-2 by day 13 and were discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from the hospital by day 14. <b>Note:</b> Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and</p>	<p><b>LPV/RTV (COVID-19):</b> LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days.<sup>3, 16, 24</sup></p> <p><b>LPV/RTV (COVID-19):</b> LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours).<sup>6</sup></p> <p><b>LPV/RTV (COVID-19):</b> LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days<sup>13</sup> 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.<sup>5, 13</sup></p> <p><b>LPV/RTV (SARS):</b> 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).<sup>1</sup></p> <p><b>LPV/RTV (MERS):</b> LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α; LPV 400 mg/RTV 100 mg orally twice daily with interferon β-1b (0.25 mg/mL sub-Q on alternate days) for 14 days.<sup>1, 4, 8</sup></p>	<p><b>LPV/RTV:</b> Efficacy for the treatment of COVID-19, with or without other antivirals, not established.<sup>22, 23</sup></p> <p><b>Darunavir:</b> Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/c for treatment of COVID-19. Results of an open-label, controlled study in China indicated that a 5-day regimen of DRV/c was not effective for treatment of COVID-19<sup>21, 26</sup> and there are no published clinical studies that have evaluated efficacy and safety of DRV/RTV or the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide for treatment of COVID-19.<sup>21</sup></p> <p><b>Atazanavir, Nelfinavir, Saquinavir, Tipranavir:</b> No data to date to support use in the treatment of COVID-19.<sup>22</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial. The panel states that, based on the pharmacodynamics of HIV protease inhibitors, there are concerns whether drug concentrations achieved with oral doses of the drugs are adequate to inhibit SARS-CoV-2 protease. In addition, clinical trials to date using LPV/RTV have not demonstrated a clinical benefit in patients with COVID-19.<sup>22</sup></p> <p>IDSA recommends that LPV/RTV be used for the treatment of COVID-19 <i>only</i> in the context of a clinical trial.<sup>23</sup></p>

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			<p>the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively).<sup>24</sup></p> <p><b>LPV/RTV with ribavirin and interferon <math>\beta</math>-1b vs LPV/RTV alone in open-label, randomized trial in adults with mild to moderate COVID-19 in Hong Kong (Hung et al; NCT04276688):</b> 127 pts were randomized 2:1 to receive LPV/RTV (LPV 400 mg/RTV 100 mg) twice daily for 14 days) with ribavirin (400 mg twice daily) and interferon <math>\beta</math>-1b (8 million IU sub-Q on alternate days for up to 3 doses depending on how soon treatment initiated after symptom onset) or a 14-day regimen of LPV/RTV alone. Median time to negative RT-PCR results for SARS-CoV-2 in nasopharyngeal samples was 7 days in pts treated with the 3-drug regimen vs 12 days in those treated with LPV/RTV alone; median duration of hospitalization was 9 or 14.5 days, respectively. Adverse effects reported in 48% of those treated with the 3-drug regimen and in 49% of those treated with LPV/RTV alone. <b>Note:</b> Results indicate a 3-drug regimen that included LPV/RTV, ribavirin, and interferon <math>\beta</math>-1b was more effective than LPV/RTV alone in pts with mild to moderate COVID-19, especially when treatment was initiated within 7 days of symptom onset.<sup>25</sup></p> <p><b>LPV/RTV retrospective cohort study in China (Deng et al)</b> evaluated use of LPV/RTV with or without umifenovir (Arbidol<sup>®</sup>) in adults. Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 6/17 pts (35%) treated with LPV/RTV alone vs 12/16 (75%) treated with both drugs; chest CT scans were improving in 29% of pts treated with LPV/RTV alone vs 69% of pts treated with both drugs.<sup>6</sup> (See Umifenovir in this Evidence Table.)</p> <p><b>LPV/RTV Clinical Experience (COVID-19):</b> Only limited data on LPV/RTV used with or without interferon in pts with COVID-19 outside of clinical trials.<sup>5, 12, 14, 16</sup></p>		

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			<p><b>LPV/RTV Clinical Experience (SARS and MERS):</b> Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon.<sup>1, 8-11</sup></p> <p><b>Darunavir and cobicistat (DRV/c) randomized, open-label trial in China (Chen et al):</b> A total of 30 adults with mild, laboratory-confirmed COVID-19 were randomized 1:1 to receive DRV/c (fixed combination darunavir 800 mg/cobicistat 150 mg once daily for 5 days) or no DRV/c (control group); all pts received interferon alfa-2b and standard of care. The primary end point was viral clearance rate at day 7 (defined as RT-PCR negative for SARS-CoV-2 in at least 2 consecutive oropharyngeal swabs collected at least 1-2 days apart). At day 7, viral clearance rate in the intention-to-treat (ITT) population was 47% in those treated with DRV/c and 60% in the control group. In the per-protocol (PP) population, viral clearance rate at day 7 was 50% in those treated with DRV/c and 60% in the control group. The median time from randomization to negative RT-PCR result was 8 and 7 days, respectively. <b>This study indicated that a 5-day regimen of DRV/c in pts with mild COVID-19 did not provide clinical benefits compared with use of standard care alone.</b><sup>26</sup></p> <p><b>LPV/RTV COVID-19 Clinical Trials:</b> Some clinical trials registered at clinicaltrials.gov listed below:<sup>15</sup> NCT04330690 (LPV/RTV vs hydroxychloroquine vs remdesivir) NCT04372628 (LPV/RTV vs placebo) NCT04403100 (LPV/RTV vs hydroxychloroquine vs LPV/RTV plus hydroxychloroquine vs placebo in pts with mild disease) NCT04315948 (LPV/RTV plus interferon β-1a vs LPV/RTV vs remdesivir [each regimen given with standard care] vs standard care) NCT04425382 (LPV/RTV vs DRV/cobicistat) NCT04455958 (LPV/RTV vs placebo)</p> <p><b>Darunavir COVID-19 Clinical Trials:</b> A few trials registered at clinicaltrials.gov:<sup>15</sup> NCT04252274 (Open-label randomized trial to evaluate DRV/c)</p>		

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<p>Hydroxychloroquine (Plaquenil®)</p> <p><b>Updated 10/8/20</b></p>	<p>8:30.08 Antimalarial</p> <p>(4-aminoquinoline derivative)</p>	<p>In vitro activity against various viruses, including coronaviruses<sup>5, 8, 12-14</sup></p> <p>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<sup>8, 12</sup></p> <p>Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections<sup>3, 8, 13, 15, 16</sup></p> <p>Known pharmacokinetics and toxicity profile based on use for other indications<sup>13</sup></p> <p>Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects;<sup>13, 14</sup> may have more favorable dose-related toxicity profile than chloroquine,<sup>13-16</sup> but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs<sup>13, 35</sup></p>	<p>NTC04303299 (Open-label randomized trial includes treatment arms to evaluate DRV/RTV plus oseltamivir with or without hydroxychloroquine or DRV/RTV plus favipiravir followed by hydroxychloroquine) NCT04425382 (DRV/c vs LPV/RTV)</p> <p><b>Clinical experience</b> in treating pts with COVID-19: Majority of data to date involves use in pts with mild or moderate COVID-19;<sup>7, 18, 31, 35, 47, 49</sup> only limited clinical data on use in pts with severe and critical disease.<sup>35</sup></p> <p><b>Hydroxychloroquine small pilot study conducted in China:</b> 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone;<sup>18</sup> <b>both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV.</b><sup>30</sup> Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).<sup>18</sup></p> <p><b>Hydroxychloroquine randomized, parallel-group study in adults in China (ChiCTR2000029559):</b> 31 pts with COVID-19 and pneumonia received <b>hydroxychloroquine sulfate</b> (200 mg twice daily for 5 days) and <b>standard treatment (O<sub>2</sub>, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids)</b> and 31 other pts received <b>standard treatment alone</b> (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</p>	<p><b>Optimal dosage and duration of treatment not known</b><sup>26</sup></p> <p><b>Oral hydroxychloroquine sulfate dosage suggested in the EUA (now revoked):</b> For treatment of hospitalized adults and adolescents weighing 50 kg or more, suggested dosage was 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation.<sup>26</sup> <b>FDA now states that this dosage regimen is unlikely to have an antiviral effect in pts with COVID-19 based on a reassessment of in vitro EC<sub>50</sub>/EC<sub>90</sub> data and calculated lung concentrations;</b> it is unclear whether this dosage regimen would provide any beneficial immunomodulatory effects.<sup>57</sup></p> <p><b>Oral hydroxychloroquine sulfate dosage used or being investigated in clinical trials:</b> 400 mg once or twice daily for 5-10 days<sup>10, 18</sup></p> <p><b>Oral hydroxychloroquine sulfate with azithromycin (France):</b> 200 mg 3 times daily for 10 days with or without azithromycin (500 mg on day 1, then 250 mg once daily on days 2-5)<sup>7, 34, 47</sup></p>	<p>Efficacy and safety of hydroxychloroquine for <i>treatment</i> or <i>prevention</i> of COVID-19 not established<sup>10, 24, 39</sup></p> <p>No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19</p> <p>Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration</p> <p>Data from randomized, controlled clinical trials are insufficient to date to draw any conclusions regarding possible benefits and safety of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.)</p> <p>Additional data needed regarding toxicity profile when used in patients with COVID-19</p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of hydroxychloroquine for the <i>treatment</i> of COVID-19 in hospitalized pts and <b>recommends against</b> use of hydroxychloroquine for the <i>treatment</i> of COVID-19 in nonhospitalized pts, except in a clinical trial. The panel also <b>recommends against</b> use of hydroxychloroquine with azithromycin for the treatment of COVID-19, except in a clinical trial.<sup>35</sup></p> <p>IDSA <b>recommends against</b> use of hydroxychloroquine for the <i>treatment</i> of COVID-19 in hospitalized pts and also <b>recommends against</b> use of a combined regimen of hydroxychloroquine and</p>

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			<p>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).<sup>31</sup> <b>Note:</b> This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery,<sup>32</sup> data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported.<sup>31</sup></p> <p><b>Hydroxychloroquine randomized, parallel-group, open-label study in hospitalized adults with mild to moderate COVID-19 in China (ChiCTR2000029868):</b> 150 pts (148 with mild to moderate disease and 2 with severe disease) were randomized 1:1 to receive hydroxychloroquine (1200 mg daily for 3 days, then 800 mg daily for total treatment duration of 2-3 weeks) with standard of care or standard of care alone. Mean time from onset of symptoms to randomization was 16.6 days (range: 3-41 days). Standard of care included IV fluids, O<sub>2</sub>, various antivirals (e.g., umifenovir, LPV/RTV), antibiotics, and/or glucocorticoid therapy. By day 28, 73% of pts (53 treated with hydroxychloroquine with standard of care and 56 treated with standard of care alone) had converted to negative for SARS-CoV-2. The probability of negative conversion by day 28 in those treated with hydroxychloroquine was similar to that in those treated with standard of care alone; the median time to negative seroconversion (6 and 7</p>		<p>azithromycin for the <i>treatment</i> of COVID-19 in hospitalized pts.<sup>38</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for <i>prevention</i> of SARS-CoV-2 infection, except in a clinical trial.<sup>35</sup> The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure.<sup>35</sup></p> <p>Because 4-aminoquinolines (hydroxychloroquine, chloroquine) and azithromycin are independently associated with QT prolongation and because concomitant use of the drugs may further increase the risk of QT prolongation, caution is advised if considering use of hydroxychloroquine (with or without azithromycin) in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias.<sup>35, 36, 38, 39, 41-44</sup></p> <p>NIH panel states that 4-aminoquinolines (hydroxychloroquine, chloroquine) should be used concomitantly with drugs that pose a moderate to high risk for QT<sub>c</sub> prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, fluoroquinolones, macrolides [including azithromycin]) <i>only</i> if necessary. In addition, because of the long half-lives of both hydroxychloroquine (up to 40 days) and azithromycin (up to 72 hours), caution is warranted even when these drugs are used sequentially. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving hydroxychloroquine (or chloroquine).<sup>35</sup></p> <p>The benefits and risks of hydroxychloroquine (with or without azithromycin) should be carefully assessed; diagnostic</p>

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			<p>days) also was similar in both groups. Adverse effects reported in 30% of those treated with hydroxychloroquine and 9% of those treated with standard of care alone.</p> <p><b>Note: Results indicate that use of hydroxychloroquine in pts with mild to moderate COVID-19 did not provide additional benefits compared with use of standard of care alone.</b><sup>49</sup></p> <p><b>Hydroxychloroquine with azithromycin open-label, nonrandomized study in France (Gautret et al):</b> Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6.<sup>7</sup> <b>Note:</b> This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity were unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented.</p> <p><b>Hydroxychloroquine with azithromycin open-label, uncontrolled study in France (Molina et al):</b> 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities</p>		<p>testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects.<sup>35, 36, 38, 39, 41-44</sup></p> <p>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 <b>cautions against</b> use of chloroquine or hydroxychloroquine for treatment or prevention of COVID-19 outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to <a href="#">FDA MedWatch</a>.<sup>39</sup></p> <p><b>Emergency use authorization (EUA) for hydroxychloroquine (now revoked):</b> Effective June 15, 2020, FDA has revoked the EUA for hydroxychloroquine and chloroquine<sup>57</sup> previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible.<sup>24, 57</sup> <b>Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met.</b> Based on the totality of scientific evidence available, FDA concluded that it is unlikely that hydroxychloroquine and chloroquine may be effective in treating COVID-19 and, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of hydroxychloroquine and chloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA.<sup>57</sup></p>

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			<p>associated with poor outcomes and 10/11 had fever and received O<sub>2</sub>. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen was discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested.<sup>53</sup> <b>Note:</b> In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.</p> <p><b>Hydroxychloroquine with azithromycin uncontrolled, retrospective, observational study in France (Gautret et al):</b> 80 adults with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O<sub>2</sub> 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 O<sub>2</sub>; 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.<sup>34</sup> <b>Note:</b> Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a</p>		<p><b>The basis for the FDA decision to revoke the EUA for hydroxychloroquine and chloroquine is summarized below:</b></p> <p><b>1)</b> Suggested hydroxychloroquine and chloroquine dosage regimens as detailed in the EUA fact sheets for healthcare providers are unlikely to produce an antiviral effect.<sup>57</sup></p> <p><b>2)</b> Earlier observations of decreased viral shedding with hydroxychloroquine or chloroquine treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between hydroxychloroquine and standard of care alone.<sup>57</sup></p> <p><b>3)</b> Current US treatment guidelines do not recommend the use of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19 outside of a clinical trial and the NIH guidelines now recommend against such use outside of a clinical trial.<sup>57</sup></p> <p><b>4)</b> Recent data from a large, randomized, controlled trial showed no evidence of benefit in mortality or other outcomes such as hospital length of stay or need for mechanical ventilation for hydroxychloroquine treatment in hospitalized patients with COVID-19.<sup>57</sup></p> <p><b>Consult the FDA letter regarding the revocation of the EUA for hydroxychloroquine and chloroquine and the FDA memorandum explaining the basis for the revocation for additional information.</b><sup>57</sup></p>

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			<p>regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease.</p> <p><b>Hydroxychloroquine with azithromycin uncontrolled, observational, retrospective analysis in France (Million et al):</b> Data for 1061 pts with PCR-documented SARS-CoV-2 RNA who were treated with a regimen of hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) were analyzed for clinical outcomes and persistence of viral shedding. Pts were included in the analysis if they received the combined regimen for at least 3 days and were clinically assessable at day 9. There were 56 asymptomatic and 1005 symptomatic pts; the majority (95%) had relatively mild disease and were considered low risk for clinical deterioration; median age was 43.6 years (range: 14-95 years) and mean time between onset of symptoms and initiation of treatment was 6.4 days. Within 10 days of treatment, good clinical outcome reported in 973 pts (91.7%) and poor clinical outcome reported in 46 pts (4.3%). Persistent nasal carriage of SARS-CoV-2 reported at completion of treatment in 47 pts (4.4%); 8 pts died.<sup>47</sup></p> <p><b>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):</b> Data for 368 males (median age &gt;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</p>		

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			<p>compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation.<sup>40</sup> <b>Note:</b> The pt population included only elderly males 59-75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures.</p> <p><b>Two different retrospective studies analyzed outcome data for hospitalized pts with confirmed COVID-19 in New York to assess the effects of treatment with hydroxychloroquine with or without azithromycin (Rosenberg et al, Geleris et al):</b> Results of these studies suggest that use of hydroxychloroquine with or without azithromycin is <b>not</b> associated with decreased in-hospital mortality.<sup>45, 46</sup></p> <p><b>Rosenberg et al</b> analyzed data for 1438 hospitalized pts (735 received hydroxychloroquine with azithromycin, 271 received hydroxychloroquine alone, 211 received azithromycin alone, 221 received neither drug) and assessed in-hospital mortality (primary outcome). Overall, in-hospital mortality was 20.3%; in-hospital mortality was 25.7, 19.9, 10, or 12.7% in those treated with hydroxychloroquine with azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug, respectively.<sup>45</sup></p> <p><b>Geleris et al</b> analyzed data for 1376 hospitalized pts (811 received hydroxychloroquine [486 of these also received azithromycin] and 565 did not receive hydroxychloroquine [127 of these received azithromycin]) and assessed the primary end point of time from study baseline to intubation or death. Overall, 346 pts (25.1%) progressed to a primary end point of intubation and/or death and the composite end point of intubation or death was not affected by hydroxychloroquine treatment (intubation or death reported in 32.3% of pts treated with hydroxychloroquine and 14.9% of pts not treated with the drug).<sup>46</sup></p>		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p><b>Large, randomized, controlled, adaptive trial evaluating efficacy of 6 different treatments for prevention of death in hospitalized pts with COVID-19 compared with usual care alone (NCT04381936; RECOVERY):</b> Study protocol included a treatment arm to evaluate efficacy of hydroxychloroquine sulfate (two 800-mg doses given 6 hours apart followed by two 400-mg doses given 12 and 24 hours after the initial dose on day 1, then 400 mg every 12 hours thereafter for 9 days).<sup>53, 54</sup> <b>The investigators announced preliminary results</b> for the hydroxychloroquine treatment arm. A total of 1542 pts were randomized to receive hydroxychloroquine with usual care and 3132 pts were randomized to usual care alone. Data for these pts indicate that hydroxychloroquine did <b>not</b> provide a significant difference in the primary end point of 28-day mortality (25.7% in those treated with hydroxychloroquine with usual care compared with 23.5% in those treated with usual care alone). In addition, there was no evidence of beneficial effects on duration of hospitalization or other outcomes.<sup>53</sup> <b>Note:</b> Data regarding pt demographics and clinical characteristics (e.g., age, disease severity, comorbidities) and time from diagnosis to study enrollment have not been provided to date.</p> <p><b>Retrospective, comparative cohort study evaluating clinical outcomes in hospitalized COVID-19 pts treated with hydroxychloroquine vs hydroxychloroquine with azithromycin vs azithromycin alone (Arshad et al):</b> Data for 2541 consecutive pts with laboratory-confirmed COVID-19 who were admitted to hospitals within the Henry Ford Health System in Michigan and received hydroxychloroquine and/or azithromycin or did not receive these drugs were analyzed. Median age of patients was 64 years; the majority had BMI of 30 or greater and many had various other comorbidities; 68% received corticosteroid treatment and 4.5% received tocilizumab; mSOFA scores were not available for 25% of pts and data were not available regarding duration of symptoms prior to hospitalization; and the median length of</p>		



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			<p>hospitalization was 6 days. The primary end point was inpatient mortality; median follow-up was 28.5 days. Results indicated that crude mortality rates were 18.1% in the entire group, 13.5% in the hydroxychloroquine group, 20.1% in the hydroxychloroquine with azithromycin group, 22.4% in the azithromycin group, and 26.4% in those not treated with hydroxychloroquine and/or azithromycin. The primary causes of mortality were respiratory failure (88%), cardiac arrest (4%), and cardiopulmonary arrest and multi-organ failure (8%). <b>Note: Only selected pts with minimal cardiac risk factors received hydroxychloroquine with azithromycin and all pts treated with hydroxychloroquine were monitored closely with telemetry and serial QTc evaluations.</b><sup>58</sup></p> <p><b>Open-label, randomized study in hospitalized pts with mild to moderate COVID-19 (Cavalcanti et al; Brazil; NCT04322123):</b> Adults hospitalized with COVID-19 were randomized 1:1:1 to receive standard care (control group), hydroxychloroquine (400 mg twice daily for 7 days) with standard care, or hydroxychloroquine (same dosage) plus azithromycin (500 mg once daily for 7 days) with standard care. Pts <i>not</i> requiring supplemental oxygen or only requiring supplemental oxygen at a rate of 4 L/min or less at baseline were enrolled; pts with a history of severe ventricular tachycardia or with QT<sub>c</sub> of 480 msec or greater at baseline were excluded. The median time from onset of symptoms to randomization was 7 days. The primary outcome was clinical status at day 15 evaluated using a 7-point ordinal scale. Data for the 504 pts in the modified intention-to-treat population with laboratory-confirmed COVID-19 (173 pts in the control group, 159 pts in the hydroxychloroquine group, 172 pts in the hydroxychloroquine and azithromycin group) indicated there was no significant difference in clinical status at day 15 in those treated with hydroxychloroquine with or without azithromycin compared with the control group. There also were no significant differences in secondary outcomes (e.g., need for mechanical ventilation, duration of hospitalization, in-hospital death) among the groups.<sup>61</sup></p>		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p><b>Open-label, randomized study in outpatients with mild COVID-19 (Mitja et al; Spain):</b> Total of 293 adults with laboratory-confirmed COVID-19 who did not require hospitalization and had mild symptoms (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, influenza-like illness) for less than 5 days before study enrollment were randomized 1:1 to receive hydroxychloroquine (800 mg on day 1, then 400 mg once daily for 6 days) or usual care only. The primary outcome was reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment initiation. Median age of pts was 41.6 years, 53% reported chronic health conditions, and 87% were healthcare workers. The median time from symptom onset to randomization was 3 days, and the mean viral load at baseline was 7.9 log<sub>10</sub> copies/mL. <b>Results indicated that a 7-day hydroxychloroquine regimen did not provide any clinical benefits compared with usual care alone in these outpatients with mild COVID-19.</b> There was no significant reduction in viral load at day 3 or 7 in those treated with hydroxychloroquine vs those treated with usual care only and there was no decrease in median time to resolution of COVID-19 symptoms (10 and 12 days, respectively) and no decrease in risk of hospitalization (7 and 6%, respectively).<sup>59</sup></p> <p><b>Double-blind, randomized, placebo-controlled study in outpatients with confirmed or probable early COVID-19 (Skipper et al; US and Canada; NCT04308668):</b> A total of 423 symptomatic adults with laboratory-confirmed COVID-19 or with symptoms compatible with COVID-19 and a high-risk exposure to a contact with laboratory-confirmed COVID-19 were randomized 1:1 to receive hydroxychloroquine (initial dose of 800 mg, 600 mg given 6-8 hours later, then 600 mg once daily for the next 4 days) or placebo. Enrolled pts had been symptomatic for no more than 4 days and did not require hospitalization at the time of enrollment. The primary efficacy end point specified in the initial study protocol was subsequently changed to overall symptom severity over</p>		

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			<p>14 days; symptoms and severity were self-reported by the pts at days 3, 5, 10, and 14 using a survey with a 10-point visual analog scale. Median age of pts was 40 years, 68% reported no chronic medical conditions, 57% were healthcare workers, 25% had been exposed to COVID-19 through household contacts, and 56% of pts had enrolled within 1 day of symptom onset. <b>Results indicated that a 5-day hydroxychloroquine regimen did not provide any substantial improvement in symptom severity in these outpatients with confirmed or probable COVID-19.</b> At day 5, 54% of pts in the hydroxychloroquine group and 56% in the placebo group reported symptoms. At day 14, 24% of those treated with hydroxychloroquine had ongoing symptoms compared with 30% of those treated with placebo. Overall, the decrease in prevalence of symptoms and the reduction in symptom severity score over 14 days were not significantly different between the two groups (symptom severity in the 10-point scale decreased 2.6 points in those treated with hydroxychloroquine and 2.3 points in those treated with placebo). In addition, there was no difference between the groups in the incidence of hospitalization or death.<sup>60</sup></p> <p><b>Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to assess the effects of hydroxychloroquine or chloroquine used with or without a macrolide (Mehra et al; now retracted):</b> Original publication included data obtained worldwide for 96,032 pts hospitalized with COVID-19 between Dec 20, 2019 and Apr 14, 2020, including 14,888 pts who received chloroquine or hydroxychloroquine with or without a macrolide (azithromycin or clarithromycin) initiated within 48 hours of diagnosis (treatment group) and 81,144 pts who did not receive these drugs (control group). Based on those data, in-hospital mortality rate in the control group was 9.3% compared with 18% in those treated with hydroxychloroquine alone (n=3016), 23.8% in those treated with hydroxychloroquine and a macrolide (n=6221), 16.4% in those treated with</p>		



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			<p>chloroquine alone (n=1868), and 22.2% in those treated with chloroquine and a macrolide (n=3783).<sup>50</sup> <b>Note: This published study has now been retracted by the publisher at the request of 3 of the original authors.</b><sup>52</sup> Concerns were raised with respect to the veracity of the data and analyses conducted by a global healthcare data collaborative.<sup>51, 52</sup></p> <p><b>Hydroxychloroquine for postexposure prophylaxis of COVID-19 randomized, placebo-controlled trial in the US and Canada (NCT04308668):</b> Asymptomatic adults with occupational or household exposure to an individual with COVID-19 were randomly assigned 1:1 to receive postexposure prophylaxis with a 5-day regimen of hydroxychloroquine sulfate (initial 800-mg dose followed by a 600-mg dose given 6-8 hours after first dose on day 1, then 600 mg once daily for 4 additional days) or placebo (folate tablets). A total of 821 asymptomatic adults were enrolled within 4 days after COVID-19 exposure (414 randomized to hydroxychloroquine and 407 randomized to placebo); 66% were healthcare workers. Overall, 88% of participants reported high-risk exposures (occurred at a distance of &lt;6 feet for &gt;10 minutes while not wearing a face mask or eye shield) and the others reported moderate-risk exposures (occurred at a distance of &lt;6 feet for &gt;10 minutes while wearing a face mask but no eye shield). <b>Note: Participants were recruited primarily through social media outreach and traditional media platforms and were enrolled using an internet-based survey. The exposure event and subsequent onset of new symptoms and illness compatible with COVID-19 after enrollment were self-reported using email surveys on days 1, 5, 10, and 14 and at 4-6 weeks.</b> Results of these surveys and information obtained using additional forms of follow-up indicated that confirmed or probable COVID-19 (based on self-reported symptoms or PCR testing) developed in 13% of participants overall (107/821) and did not differ significantly between those who received hydroxychloroquine prophylaxis (11.8%) and those who received</p>		

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			<p>placebo (14.3%).<sup>55</sup> <b>Note: The various limitations of the trial design should be considered when interpreting the results.</b> Exposure to someone with confirmed COVID-19, time from the exposure event to initiation of prophylaxis, and all outcome data (including possible COVID-19 symptoms and PCR test results) were self-reported by study participants. COVID-19 was confirmed with PCR testing in only a small percentage (&lt;3%) of participants who self-reported COVID-19 symptoms. Survey results indicated that full adherence to the 5-day prophylaxis regimen was reported by only 75% of patients randomized to hydroxychloroquine and 83% of those randomized to placebo. In addition, a total of 52 participants did not complete any surveys after study enrollment.<sup>55, 56</sup></p> <p><b>**Double-blind, placebo-controlled, randomized trial in the US to evaluate hydroxychloroquine for preexposure prophylaxis of COVID-19 (Abella et al; NCT04329923):</b> Healthcare personnel working ≥20 hours per week in hospital-based units (nurses, physicians, certified nursing assistants, emergency technicians, respiratory therapists) who had no known history of SARS-CoV-2 infection and no symptoms suggestive of COVID-19 within 2 weeks prior to trial enrollment were randomized 1:1 to receive hydroxychloroquine (600 mg daily) or placebo for preexposure prophylaxis of COVID-19. Nasopharyngeal swab tests for SARS-CoV-2 and serologic tests for anti-nucleocapsid IgG, anti-spike protein receptor-binding domain (RBD) IgM, and anti-RBD IgG were performed at the time of randomization (baseline) and at 4 and 8 weeks; participants also were surveyed weekly for adherence and adverse events. The primary outcome was rate of conversion to SARS-CoV-2-positive status based on nasopharyngeal swab testing at 8 weeks. A total of 125 participants were evaluable for the primary outcome (64 in the hydroxychloroquine arm and 61 in the placebo arm); 22 of the evaluable participants (17.6%) discontinued study treatment early. Results indicate that <b>preexposure prophylaxis with hydroxychloroquine</b></p>		



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			<p><b>did not provide clinical benefits in hospital-based healthcare personnel.</b> The rate of COVID-19 positivity was similar in the hydroxychloroquine group (6.3%) and placebo group (6.6%); cases of infection occurred throughout the 8-week study period. All 8 individuals who became infected (4 in each group) were either asymptomatic or had mild disease with full recovery; none required hospitalization. After reviewing data at the time of a second planned interim analysis, the data safety and monitoring board recommended that the trial be terminated early. Grade 3 or 4 adverse events were not reported in any participants; the incidence of adverse events was significantly higher in the hydroxychloroquine group than the placebo group (45 vs 26%). <b>Note:</b> Limitations of this trial include the possibility that it was insufficiently powered because of low enrollment, data are not available to quantify the frequency of participant exposures to the virus or specific timing of such exposures, and most participants were young and healthy.<sup>62</sup></p> <p><b>**Retrospective cohort study in the US to evaluate possible SARS-CoV-2 preventive benefits of hydroxychloroquine therapy used in pts with rheumatic conditions (Gentry et al):</b> Possible benefit of long-term hydroxychloroquine therapy used for management of rheumatic conditions for prevention of SARS-CoV-2 infection in such pts was investigated retrospectively using data obtained from the US Veterans Affairs Medical Centers (VAMCs) database. Adults in the database with ICD-10 diagnostic code entries for rheumatoid arthritis, systemic lupus erythematosus, and associated rheumatologic conditions were identified and each such pt receiving hydroxychloroquine was matched to 2 such pts not receiving hydroxychloroquine (controls). The primary end point was the proportion of pts with PCR-confirmed SARS-CoV-2 infection between March 1 and June 30, 2020 among those receiving long-term hydroxychloroquine therapy versus the propensity-matched patients not receiving hydroxychloroquine. Data analyses indicated that <b>long-term hydroxychloroquine</b></p>		

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			<p>therapy in patients receiving the drug for rheumatic conditions was not associated with a preventive effect against SARS-CoV-2 infection. The incidence of SARS-CoV-2 infection was similar in pts receiving hydroxychloroquine (0.3%; 31 of 10,703 pts) and those not receiving the drug (0.4%; 78 of 21,406 pts). In those who developed active SARS-CoV-2 infection, there were no significant differences in secondary outcomes between the hydroxychloroquine group and control group.<sup>63</sup></p> <p>Multiple clinical trials to evaluate hydroxychloroquine for <i>treatment</i> of COVID-19 are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>, including the following:<sup>10</sup></p> <p>NCT04342169 NCT04344457 NCT04345692 NCT04353336</p> <p>Multiple clinical trials to evaluate hydroxychloroquine for <i>prevention</i> of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>, including the following:<sup>10</sup></p> <p>NCT04303507 NCT04318015 NCT04318444 NCT04334148 NCT04335084 NCT04341441 NCT04363450 NCT04353037</p>		
<p>Neuraminidase inhibitors (e.g., oseltamivir)</p> <p><i>Updated 8/20/20</i></p>	8:18.28	<p>Antivirals active against influenza viruses</p> <p>Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture<sup>4</sup></p> <p>Oseltamivir did not inhibit the replication of SARS-CoV-2 in infected Vero E6 cells in vitro<sup>6</sup></p>	<p>In a <b>retrospective case series</b> of 99 adults with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of pts received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died.<sup>1</sup></p> <p>In a <b>retrospective case series</b> of 79 adults with COVID-19 who were negative for influenza A and B, early use of oseltamivir had no effect on COVID-19 and did not effectively slow the progression of the disease<sup>6</sup></p>	<p>Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours.<sup>1</sup></p> <p>Dosages of oseltamivir from registered trials (either recruiting, or not yet recruiting) vary, but include 300 mg orally daily, 75 mg orally once or twice daily, and 4–6 mg/kg orally (frequency not specified).<sup>5</sup></p>	No data to date support use in the treatment of COVID-19

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			<p>In a <b>retrospective cohort study</b> of 1190 adults with COVID-19 at a single center in Wuhan from 12/29/19 to 2/28/20, 61.6% of pts received antiviral therapy (e.g., oseltamivir, ganciclovir, lopinavir/ritonavir, interferon, umifenovir). A survival analysis indicated that administration of oseltamivir appeared to have reduced the risk of death in pts with severe disease and seemed to have been associated with less deterioration (i.e., progression from nonsevere to severe disease or severe disease to death).<sup>7</sup></p> <p>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.<sup>2</sup></p> <p>Some clinical trials for COVID-19 that include oseltamivir are listed below<sup>5</sup>:</p> <p><a href="#">NCT04303299</a>  <a href="#">NCT04261270</a>  <a href="#">NCT04255017</a>  <a href="#">NCT04338698</a>  <a href="#">NCT04516915</a></p>		
<p>Remdesivir (Veklury®)</p> <p><i>Updated 10/8/20</i></p>	<p>8:18.32 Antiviral</p>	<p>Broad-spectrum antiviral (nucleotide analog pro-drug) with activity against various viruses, including coronaviruses<sup>24</sup></p> <p>In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells<sup>1,18</sup></p> <p>In Rhesus macaques infected with SARS-CoV-2, treatment with a 6-day regimen of IV remdesivir initiated 12 hours after virus inoculation was associated with some benefits (lower disease severity scores, fewer pulmonary infiltrates, lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce</p>	<p><b>Randomized, double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al):</b> 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. <b>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%).</b> When remdesivir was initiated within 10 days of symptom onset, median time to clinical improvement was numerically shorter (but not statistically</p>	<p><b>Optimal dosage and duration of remdesivir treatment not known</b><sup>20, 25, 26</sup></p> <p><b>Emergency use authorization (EUA) remdesivir dosage and duration of treatment recommended for hospitalized adults and children weighing 40 kg or more:</b> Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts <b>not</b> requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.<sup>26</sup></p>	<p>An investigational direct-acting antiviral (DAA) not currently approved by FDA for any indication.</p> <p><b>Emergency use authorization (EUA) for remdesivir:</b> FDA issued an EUA on May 1, 2020 that permitted use of the drug for the treatment of COVID-19 <i>only</i> in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 and severe disease (defined as oxygen saturation [SpO<sub>2</sub>] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO).<sup>25</sup> On August 28, 2020, FDA broadened the EUA for remdesivir to include treatment of all hospitalized adults and pediatric patients with suspected or laboratory-confirmed COVID-19, irrespective of disease severity.<sup>38</sup> Distribution of remdesivir under the EUA was previously directed by the HHS Office of the Assistant Secretary for</p>

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		<p>viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control<sup>19</sup></p> <p>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<sup>1-8</sup></p> <p>Pharmacokinetic data available from evaluations for Ebola</p>	<p>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. <b>Note:</b> Enrollment was terminated before the pre-specified number of pts was attained (lack of available pts); <b>trial was insufficiently powered to detect assumed differences in clinical outcome.</b><sup>21</sup></p> <p><b>Phase 3 randomized, open-label trial in hospitalized pts with severe COVID-19 (NCT04292899; GS-US-540-5773; SIMPLE-Severe)</b> sponsored by the manufacturer (Gilead): Initial study protocol was designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care in adults with <b>severe COVID-19</b> not receiving mechanical ventilation at study entry;<sup>10</sup> protocol was subsequently modified to include pts 12 years of age or older, add an extension phase, and include a cohort of pts receiving mechanical ventilation.<sup>10,23</sup> Data for the initial 397 pts <b>not requiring mechanical ventilation</b> at study entry (200 received a 5-day regimen and 197 received a 10-day regimen) indicate similar clinical improvement with both treatment durations after adjusting for baseline clinical status. Pt demographics and clinical characteristics at baseline generally were similar in both groups, although the 10-day group included a higher percentage of pts in the most severe disease categories and a higher proportion of men (who are known to have worse COVID-19 outcomes than women); median duration of symptoms before first dose of remdesivir was similar in both groups (8 or 9 days). <b>At day 14, 129/200 pts (65%) in the 5-day group and 106/197 pts (54%) in the 10-day group achieved clinical</b></p>	<p><b>Emergency use authorization (EUA) remdesivir dosage and duration of treatment recommended for hospitalized children weighing 3.5 to less than 40 kg (using the lyophilized powder formulation only):</b> Loading dose of 5 mg/kg by IV infusion on day 1, followed by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2. For pts <b>not</b> requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.<sup>26</sup></p> <p><b>NIH COVID-19 Treatment Guidelines Panel-recommended duration of remdesivir treatment when supplies are limited:</b> The NIH panel recommends that hospitalized pts who require supplemental oxygen, but are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, receive remdesivir for a duration of 5 days or until hospital discharge, whichever comes first. If such pts progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO during such treatment, the panel recommends that the remdesivir course be completed. The panel states that there are insufficient data on the optimal duration of remdesivir treatment for pts who have not shown clinical improvement after a 5-day regimen; some experts would extend the total duration of remdesivir treatment to up to 10 days in these patients.<sup>20</sup></p> <p><b>Phase 3 trial in adults and children ≥12 years of age with severe COVID-19 (NCT04292899; SIMPLE-Severe):</b> 200 mg IV on day 1, then 100 mg IV</p>	<p>Preparedness and Response (ASPR) in collaboration with state health departments.<sup>25, 38</sup> **On October 1, 2020, FDA revised the EUA to designate the manufacturer (Gilead) and its authorized distributor(s) as the parties responsible for distribution of the drug.<sup>39</sup> Healthcare providers should contact Gilead's sole US distributor (AmerisourceBergen at 800-746-6273) to purchase remdesivir for use under the EUA.<sup>40</sup> The EUA requires that the drug be administered by a healthcare provider in an inpatient hospital setting via IV infusion at dosages recommended in the EUA.<sup>26,39</sup> The EUA also requires that healthcare facilities and healthcare providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to <a href="#">FDA MedWatch</a>).<sup>26,39</sup> Consult the EUA,<sup>39</sup> EUA fact sheet for healthcare providers,<sup>26</sup> and EUA fact sheet for patients and parents/caregivers<sup>27</sup> for additional information.</p> <p><b>The NIH COVID-19 Treatment Guidelines Panel issued guidelines regarding prioritizing use of remdesivir when supplies are limited:</b> The panel recommends the drug be prioritized for use in hospitalized pts with COVID-19 who require supplemental oxygen, but are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, because efficacy in this pt population has been demonstrated. (For recommendations on treatment duration in such pts, see Dosage.) The NIH panel states that they cannot make a recommendation either for or against initiating remdesivir in pts who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO because of uncertainty regarding whether initiating remdesivir in such pts confers clinical benefit. The panel states that these recommendations for prioritizing use of remdesivir are largely based on data from the phase 3 adaptive trial (NCT04280705; ACTT-1) in</p>

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			<p><b>improvement (defined as an improvement of at least 2 points from baseline on a 7-point ordinal scale).</b> After adjusting for baseline imbalances in disease severity, data indicate that clinical status at day 14, time to clinical improvement, recovery, and death (from any cause) were similar in both groups. Although eligibility criteria according to the initial study protocol excluded pts receiving invasive mechanical ventilation, 4 pts in the 5-day group and 9 pts in the 10-day group were receiving invasive mechanical ventilation or ECMO (need identified after initial screening and before treatment initiation or pts were accepted as protocol deviations). There also were more pts in the 10-day group (30%) who required high-flow oxygen support at baseline compared with the 5-day group (24%). Post-hoc analysis among pts receiving mechanical ventilation or ECMO at day 5 indicate that, by day 14, 40% of such individuals who had received the 5-day regimen had died compared with 17% of those who had received the 10-day regimen. Treatment with remdesivir beyond 5 days did not appear to improve outcomes among pts who were receiving <i>noninvasive</i> positive-pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air. <b>Note:</b> Results for the initial 397 study pts with severe COVID-19 not requiring mechanical ventilation at study entry cannot be extrapolated to critically ill pts receiving mechanical ventilation.<sup>23</sup></p> <p><b>Comparative analysis of data from phase 3 SIMPLE-Severe trial and real-world retrospective cohort of patients:</b> The manufacturer announced results of an analysis that compared data for 312 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial with a retrospective cohort of 818 pts with similar baseline characteristics and disease severity who received standard of care treatment (without remdesivir) during the same time period. More than 90% of pts in both groups were enrolled at North American trial sites and the rest were enrolled at European or Asian trial sites. Clinical recovery (improvement in clinical status</p>	<p>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);<sup>10</sup> 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)<sup>10</sup></p> <p><b>Phase 3 trial in adults and children ≥12 years of age with moderate COVID-19 (NCT04292730; SIMPLE-Moderate):</b> 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)<sup>11</sup></p>	<p>hospitalized adults with COVID-19 indicating that the benefit of remdesivir treatment was most apparent in pts who required supplemental oxygen, but did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline. (See Trials or Clinical Experience.)<sup>20</sup></p> <p>NIH panel states that data are insufficient to recommend either for or against use of remdesivir for the treatment of <b>mild or moderate COVID-19</b>.<sup>20</sup></p> <p>Concomitant use of remdesivir and chloroquine or hydroxychloroquine is <b>not recommended</b>,<sup>20,26,33</sup> FDA warns that there is in vitro evidence that chloroquine antagonizes intracellular metabolic activation and antiviral activity of remdesivir.<sup>26</sup></p> <p>Concomitant use of remdesivir and drugs that are strong inducers of cytochrome P-450 (CYP) isoenzymes (e.g., rifampin) is <b>not recommended</b>; remdesivir plasma concentration may be modestly reduced and the clinical relevance of such decreased concentrations is unknown. Although drug interaction studies have not been performed to date, remdesivir plasma concentrations are unlikely to be substantially altered by concomitant use with drugs that are weak to moderate inducers or strong inhibitors of CYP isoenzymes, P-glycoprotein (P-gp), or organic anion transport polypeptide (OATP).<sup>20</sup></p> <p>Concomitant use of remdesivir and dexamethasone is expected to result in minimal or no reduction in remdesivir exposure.<sup>20</sup></p>

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			<p>based on a 7-point ordinal scale) and mortality rate for these 2 groups were compared. By day 14, recovery was reported in 74.4% of pts treated with remdesivir and 59% of pts in the retrospective cohort treated with standard of care and the mortality rate was 7.6 and 12.5%, respectively.<sup>34</sup></p> <p><b>Subgroup analyses of data from Phase 3 SIMPLE-Severe trial:</b> The manufacturer announced results of subgroup analyses of 229 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial and were enrolled at US trial sites. Clinical improvement was defined as a 2-point or greater improvement on a 7-point ordinal scale. At day 14, the rate of clinical improvement was 84% in black pts (n=43), 76% in Hispanic white pts (n=17), 67% in Asian pts (n=18), 67% in non-Hispanic white pts (n=119), and 63% in pts who did not identify with any of these groups (n=32). An analysis of 397 pts who were enrolled globally indicated that black race, age less than 65 years, treatment outside of Italy, and requirement of only low-flow oxygen support or room air at baseline were factors significantly associated with clinical improvement of at least 2 points on day 14. Another subgroup analysis was performed to evaluate outcomes in pts who received concomitant therapy with remdesivir and hydroxychloroquine vs those who received only remdesivir. At a median follow-up of 14 days, the rates and likelihood of recovery were lower in those treated with both drugs (57%) compared with those treated with remdesivir alone (69%). Although concomitant hydroxychloroquine was not associated with increased mortality at 14 days, the overall rate of adverse effects was higher and, after adjusting for baseline variables, the incidence of grade 3-4 adverse events was significantly higher in those treated with both drugs.<sup>34</sup></p> <p><b>Phase 3 randomized, open-label trial in hospitalized pts with moderate COVID-19 (NCT04292730; GS-US-540-5774; SIMPLE-Moderate)</b> sponsored by the manufacturer (Gilead): Initial study protocol was designed to evaluate safety and antiviral</p>		



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			<p>activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care compared with standard care alone in adults with <b>moderate COVID-19</b> (i.e., hospitalized with evidence of pulmonary infiltrates and SpO<sub>2</sub> &gt;94% on room air); protocol was subsequently modified to change the primary end point to clinical status on day 11 based on a 7-point ordinal scale, include pts 12 years of age or older, and add an extension phase to include additional pts.<sup>11, 30</sup> Data for the initial group of adults who received a 5-day regimen of remdesivir with standard care (n=191), 10-day regimen of the drug with standard care (n=193), or standard care alone (n=200) have been published. At day 11, 70, 65, or 61% of pts in the 5-day, 10-day, or standard of care alone group, respectively, had clinical improvement based on at least a 2-point improvement from baseline on a 7-point ordinal scale. Pts in the 5-day remdesivir group had statistically significant higher odds of a better clinical status distribution on the 7-point scale on day 11 than those receiving standard care (odds ratio: 1.65) but the difference was of uncertain clinical importance; the difference in clinical status distribution between pts in the 10-day remdesivir group and the standard care group was not statistically significant. At day 11, 4 deaths were reported in the standard care alone group compared with none in the 5-day group and 2 in the 10-day group. There were no significant differences between the 5- or 10-day remdesivir groups and standard care group for any of the exploratory end points at day 11 (time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, time to discontinuation of oxygen support). At day 14, the clinical status of pts in the 5-day and 10-day remdesivir groups was significantly different than that of the standard care group. <b>Note:</b> Effect of remdesivir on SARS-CoV-2 viral load was not assessed. Limitations of this study include the open-label design and use of an ordinal scale to</p>		

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			<p>evaluate outcomes that was not ideal for detecting differences in pts with moderate COVID-19.<sup>30</sup></p> <p><b>Phase 3 adaptive, randomized, double-blind, placebo-controlled trial (NCT04280705; NIAID Adaptive COVID-19 Treatment Trial 1 [ACTT-1]) in hospitalized adults with COVID-19:</b> 1063 pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10 or until hospital discharge or death) or placebo.<sup>13,22</sup> All pts received supportive care according to the standard of care for the trial site hospital. Baseline demographics and clinical characteristics (e.g., age, disease severity, comorbidities at study enrollment, time to initiation of treatment after symptom onset) were similar in both groups. Overall, 88.7% of pts had severe disease at study enrollment and the median time from symptom onset to randomization was 9 days (range: 6-13 days). Preliminary data analysis that included 1059 pts (538 randomized to remdesivir and 521 randomized to placebo) indicated <b>shorter median time to recovery in the remdesivir group (11 days) vs the placebo group (15 days)</b> and suggested that remdesivir treatment may have provided a survival benefit (Kaplan-Meier estimates of mortality by day 14 were 7.1% in the remdesivir group vs 11.9% in the placebo group). Based on preliminary subgroup analyses, the benefit of remdesivir was most apparent in the 421 pts who required supplemental oxygen but were not on mechanical ventilation or ECMO at baseline (recovery rate ratio 1.47). The recovery rate ratio in the subgroup of 272 pts on mechanical ventilation or ECMO at enrollment was 0.95. However, additional data analyses are needed and are ongoing regarding outcomes in these subgroups.<sup>22</sup></p> <p><b>Data from the manufacturer's compassionate use program (adults):</b> 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</p>		

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			<p>full 10-day regimen (200 mg IV on day 1, then 100 mg IV on days 2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects.<sup>16</sup> <b>Note:</b> Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load.</p> <p><b>Data from the manufacturer's compassionate use program (pediatric pts):</b> The manufacturer announced that preliminary data are available for 77 pediatric pts treated with remdesivir in the compassionate use program. Analysis of day-28 data indicated that 73% of these pediatric pts were discharged from the hospital, 12% remained hospitalized but on ambient air, and 4% had died. There were 39 critically ill pediatric pts who required invasive mechanical ventilation at baseline and 80% of these pts recovered; there were 38 pediatric pts who did not require invasive ventilation and 87% of these pts recovered. No new safety signals were identified for remdesivir in this population.<sup>34</sup></p>		

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			<p><b>Data from the manufacturer's compassionate use program (pregnant and postpartum women):</b> The manufacturer announced that preliminary data are available for 86 pregnant and postpartum women treated with remdesivir in the compassionate use program. Analysis of data for these pts (median age 33 years) indicated that 96% of the pregnant women and 89% of the postpartum women achieved improvement in oxygen support levels. Those with more severe illness at baseline achieved similarly high rates of clinical recovery (93 or 89% in those who were pregnant or postpartum, respectively). Pregnant women not on invasive oxygen support at baseline had the shortest median time to recovery (5 days), and both pregnant and postpartum women on invasive ventilation at baseline had similar median times to recovery (13 days). No new safety signals were identified for remdesivir in this population; the most common adverse events were due to underlying disease and most laboratory abnormalities were grades 1–2.<sup>34</sup></p> <p><b>Phase 2/3 single-arm, open-label trial in pediatric patients (NCT04431453; CARAVAN):</b> The manufacturer (Gilead) initiated a trial to evaluate safety, tolerability, pharmacokinetics, and efficacy of remdesivir in pediatric pts (birth to &lt;18 years of age) with laboratory-confirmed COVID-19.<sup>35</sup></p> <p><b>Expanded access IND protocol (NCT04323761):</b> The manufacturer (Gilead) established a protocol for emergency access to remdesivir for the treatment of acute COVID-19 in hospitalized adults and children 12 years of age or older.<sup>17</sup></p> <p><b>Compassionate use access for pregnant women and children &lt;18 years of age:</b> The manufacturer (Gilead) is accepting individual remdesivir compassionate use requests <i>only</i> for pregnant women and children &lt;18 years of age with confirmed COVID-19 and severe manifestations of the disease.<sup>15</sup>  <a href="https://rdvcu.gilead.com/">(https://rdvcu.gilead.com/)</a></p>		

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			<p><b>Compassionate use access (NCT04302766):</b> May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command.<sup>12</sup></p> <p><b>Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib (NCT04401579; ACTT2):</b> This iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) is evaluating possible benefits of using baricitinib (a Janus kinase [JAK] inhibitor) in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and evidence of lung involvement (abnormal chest x-rays, SpO<sub>2</sub> of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO). Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization up to 10 days total) with either oral baricitinib (4 mg once daily for the duration of hospitalization up to 14 days total) or placebo.<sup>29, 31</sup></p> <p><b>Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with interferon beta-1a (NCT04492475; ACTT3):</b> This iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) will evaluate possible benefits of using interferon beta-1a in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection.<sup>36, 37</sup> Inclusion criteria include evidence of lung involvement (radiographic infiltrates, SpO<sub>2</sub> of 94% or lower on room air, or requiring supplemental oxygen or mechanical ventilation); exclusion criteria include need for ECMO, prior treatment with ≥3 doses of remdesivir, treatment with any interferon preparation within the previous 2 weeks, prior treatment with convalescent plasma or IGIV or various other drugs used for management of COVID-19. Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration</p>		

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			<p>of hospitalization up to 10 days total) with either sub-Q interferon beta-1a (44 mcg once daily on days 1, 3, 5, and 7 during hospitalization for a total of 4 doses) or placebo.<sup>36,37</sup></p> <p><b>Randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with tocilizumab (NCT04409262; REMDACTA):</b> This trial is evaluating possible benefits of using tocilizumab (an interleukin-6 [IL-6] inhibitor) in conjunction with remdesivir in hospitalized patients 12 years of age or older with severe COVID-19 pneumonia. Pts will be randomized to receive remdesivir (IV loading dose on day 1, then once-daily IV maintenance doses on days 2-10) with either tocilizumab (single IV infusion on day 1) or placebo.<sup>32</sup></p> <p><b>**Phase 3 randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of remdesivir for treatment of COVID-19 in outpatients (NCT 04501952):</b> Manufacturer (Gilead) initiated a study to evaluate a 3-day regimen of IV remdesivir in adults and pediatric pts ≥12 years of age with early-stage COVID-19 to determine efficacy in an outpatient setting for reducing the rate of hospitalization or death.<sup>41</sup></p>		
<p>SARS-CoV-2-Specific Monoclonal Antibodies</p> <p><b>**Added 10/8/20</b></p>	<p>8:18.24 Monoclonal Antibodies</p>	<p>Monoclonal antibodies (mAbs) used in the treatment or prevention of infectious diseases are engineered versions of antibodies naturally produced by the immune system in response to invading viruses or other pathogens.<sup>1, 6, 21, 30, 31</sup></p> <p>mAbs that are specific for certain infectious agents or their toxins (e.g., respiratory syncytial virus, <i>Bacillus anthracis</i>, <i>Clostridioides difficile</i>) have been used for the treatment or prevention of infections caused by these agents.<sup>1</sup></p>	<p>Clinical trials have been initiated to evaluate several different SARS-CoV-2-specific mAbs, including the following:</p> <p><b>REGN-COV2:</b></p> <p>Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of REGN-COV2 for <i>treatment of COVID-19 in hospitalized adults</i> (NCT04426695).<sup>22</sup></p> <p>Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of REGN-COV2 for <i>treatment of COVID-19 in ambulatory adults</i></p>	<p>Because mAbs generally have long half-lives, it is likely that only a single dose of the SARS-CoV-2-specific mAbs may be required.<sup>1</sup></p>	<p>SARS-CoV-2-specific mAbs are not commercially available.</p> <p>Safety and efficacy of investigational SARS-CoV-2-specific mAbs for the <i>treatment or prevention</i> of COVID-19 have not been established.</p> <p>Although results of controlled clinical trials are needed to provide information on safety and efficacy of mAbs that specifically target SARS-CoV-2, it has been suggested that such mAbs may offer some advantages over other immunotherapies used for the treatment of COVID-19 (e.g., COVID-19 convalescent plasma, IGIV) in terms of specificity and safety.<sup>2, 3, 30, 31</sup></p>

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		<p>Animal studies evaluating neutralizing mAbs specific for other coronaviruses (SARS-CoV-1, MERS-CoV) have demonstrated benefits in such models. <sup>1, 2, 4, 5, 6, 30</sup></p> <p>SARS-CoV-2-specific mAbs are designed to directly target the virus and may act as neutralizing antibodies (nAbs). Most SARS-CoV-2-specific mAbs being investigated target epitopes on the spike protein (S protein) of the virus and block the receptor-binding domain (RBD) of the S protein from interacting with human angiotensin-converting enzyme 2 (ACE2), thereby preventing the virus from entering cells and inhibiting viral replication. <sup>1-6, 25, 27, 30</sup></p> <p>SARS-CoV-2-specific mAbs potentially could limit or modify SARS-CoV-2 infection and may be effective for both treatment and prevention since such mAbs could provide immediate and longer-term (weeks or months) protection against the virus. <sup>1-3, 30</sup></p> <p>Various mAbs specific for SARS-CoV-2 are being investigated for the treatment and prevention of COVID-19, including the following:</p> <p><b>REGN-COV2:</b> Contains two different SARS-CoV-2-specific mAbs (REGN10933 and REGN10987) that target non-overlapping epitopes on the S protein of SARS-CoV-2 to block the</p>	<p>(NCT04425629). <sup>23</sup> Enrolled pts were randomized 1:1:1 to receive a single IV infusion of 8 g of REGN-COV2 (high dose), 2.4 g of REGN-COV2 (low dose), or placebo. The manufacturer announced results for the first 275 pts enrolled in this trial and stated that data analysis showed that REGN-COV2 reduced viral load and time to alleviation of symptoms in these outpatients and there was a positive trend in reduction of medical visits; the greatest treatment benefit appeared to be in pts who had not mounted their own effective immune response. <sup>25</sup></p> <p>Randomized, controlled, open-label, adaptive, phase 3 trial with a REGN-COV2 arm is evaluating REGN-COV2 with standard of care vs standard of care alone in hospitalized pts with COVID-19 (RECOVERY). <sup>26</sup></p> <p>Randomized, double-blind, placebo-controlled, phase 3 trial sponsored by the manufacturer (Regeneron) is evaluating safety, tolerability, and efficacy of a single sub-Q dose of REGN-COV2 for <i>prevention</i> of SARS-CoV-2 infection in healthy, asymptomatic, adult household contacts of individuals infected with SARS-CoV-2 (NCT04452318). <sup>24</sup></p> <p><b>LY-CoV555 (LY3819253):</b></p> <p>Randomized, placebo-controlled, double-blind, sponsor-unblinded, single ascending dose, phase 1 study sponsored by the manufacturer (Eli Lilly) evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of an IV dose of LY-CoV555 in hospitalized adults with COVID-19. Study completed; results not yet published (NCT04411628). <sup>9</sup></p> <p>Randomized, double-blind, placebo-controlled phase 2 study is evaluating efficacy and safety of LY-CoV555 used alone or in conjunction with a second mAb (LY-CoV016 [LY3832479]) for early <i>treatment</i> of COVID-19 in adults who are outpatients with mild to moderate disease (NCT04427501; BLAZE-1). <sup>10</sup> Manufacturer announced in a press release that proof-of-concept data from an interim analysis of</p>		

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		<p>virus from entering cells; <sup>21, 25, 27, 29</sup> preclinical studies demonstrated neutralizing activity in vitro and protective effects against SARS-CoV-2 infection and viral replication in animal models. <sup>27, 28</sup></p> <p><b>LY-CoV555:</b> Neutralizing IgG<sub>1</sub> mAb that specifically binds to an epitope on the S protein of SARS-CoV-2 overlapping the ACE2 binding site; <sup>12, 13</sup> preclinical studies demonstrated neutralizing activity against SARS-CoV-2 in Vero E6 cells and protective effects against SARS-CoV-2 infection and viral replication in an animal model. <sup>13</sup></p> <p><b>VIR-7831 (GSK4182136):</b> mAb that specifically targets the S protein of SARS-CoV-2; preclinical studies demonstrated affinity for and highly potent neutralizing activity against the virus. <sup>15</sup></p> <p><b>STI-1499 (COVI-GUARD) and STI-2020 (COVI-AMG)</b> Both of these mAbs specifically target the S protein of SARS-CoV-2; preclinical studies demonstrated that both have neutralizing activity against SARS-CoV-2 in Vero E6 cells and protective effects against the virus in an animal model; STI-2020 is an affinity-matured version of STI-1499 and has greater in vitro potency than STI-1499. <sup>17, 18</sup></p> <p><b>AZD7442:</b> Contains two mAbs (AZD8895 and AZD1062) that specifically</p>	<p>this ongoing study suggests that a single dose of LY-CoV555 in the outpatient setting reduces the rate of hospitalization. The LY-CoV555 arm of the study is evaluating dosages of 700 mg, 2.8 g, and 7 g and, at the time of the interim analysis, the 2.8-g dose met the prespecified end point of change from baseline in viral load at day 11. <sup>12</sup></p> <p>Randomized, double-blind, placebo-controlled phase 3 trial initiated by the manufacturer (Eli Lilly) in collaboration with NIAID is evaluating efficacy and safety of a single dose of LY-CoV555 for <i>prevention</i> of SARS-CoV-2 infection in residents and staff of skilled nursing or assisted living facilities (NCT04497987; BLAZE-2). <sup>11</sup></p> <p><b>VIR-7831 (GSK4182136):</b></p> <p>Manufacturer (Vir Biotechnology) in collaboration with GlaxoSmithKline initiated a randomized, double-blind, placebo-controlled, phase 1/phase 2 trial to assess safety, tolerability, efficacy, and pharmacokinetics of a single IV dose of VIR-7831 for early <i>treatment</i> of COVID-19 in outpatients (NCT04545060; COMET-ICE). <sup>14, 15</sup></p> <p><b>STI-1499 (COVI-GUARD):</b></p> <p>Manufacturer (Sorrento Therapeutics) initiated a randomized, placebo-controlled, dose-ranging, phase 1 study to evaluate safety, efficacy, and pharmacokinetics of single 10-, 30-, 100-, and 200-mg IV injections of STI-1499 for <i>treatment</i> of COVID-19 in hospitalized adults with moderate disease (NCT04454398). <sup>16</sup></p> <p><b>AZD7442:</b></p> <p>Double-blind, placebo-controlled, phase 1 trial initiated by the manufacturer (AstraZeneca) to evaluate safety, tolerability, and pharmacokinetics of IV and IM doses of AZD-7742 in <i>healthy</i> adults (NCT04507256). <sup>19</sup></p>		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
		<p>target SARS-CoV-2 at two non-overlapping sites;<sup>20, 30</sup> has an extended half-life and reduced Fc receptor binding.<sup>20</sup></p> <p>Note that various recombinant humanized monoclonal antibodies that target key immunologic and inflammatory mediators (e.g., complement, granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-6 [IL-6]) but do <b>not</b> target the SARS-CoV-2 virus are being investigated for the treatment of COVID-19.<sup>7, 8</sup> (See Sarilumab, Situximab, and Tocilizumab in this Evidence Table.)</p>			
<p>Umifenovir (Arbidol®)</p> <p><i>Updated 8/20/20</i></p>	<p>8:18.92 Antiviral</p>	<p>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses<sup>4</sup></p> <p>Although data limited, in vitro activity against SARS-CoV-1<sup>4</sup> and SARS-CoV-2<sup>5</sup> reported</p> <p>Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza<sup>4</sup></p>	<p><b>Retrospective cohort study</b> in 50 adults with COVID-19 in China suggests better viral suppression with umifenovir vs LPV/RTV. All pts received conventional therapy, including interferon <math>\alpha</math>-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<sup>8</sup></p> <p><b>Retrospective cohort study</b> 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<sup>1</sup></p>	<p><b>Dosage recommended for treatment of COVID-19 in China:</b> Adults, 200 mg orally 3 times daily for no more than 10 days<sup>5, 7</sup></p> <p><b>Dosage used or being investigated in COVID-19 clinical trials:</b> 200 mg orally 3 times daily for duration of 7-10 days or longer<sup>2, 3, 6, 8</sup></p>	<p>Not commercially available in the US</p> <p>Included in some guidelines for treatment of COVID-19<sup>7</sup></p> <p>Efficacy for the treatment of COVID-19 not established</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p><b>Retrospective cohort study</b> in 81 hospitalized, non-ICU adults with COVID-19 in China found <i>no difference</i> in clearance of SARS-CoV-2 virus between pts receiving umifenovir vs those who did not. At 7 days, SARS-CoV-2 undetectable in pharyngeal specimens in 33/45 pts (73.3%) treated with umifenovir vs 28/36 pts (77.8%) who did not receive umifenovir. No difference in median time from onset of symptoms to negative SARS-CoV-2 test (18 vs 16 days)<sup>9</sup></p> <p><b>Open-label, prospective, randomized, multicenter study</b> in 236 adults with COVID-19 in China (<a href="#">ChiCTR200030254</a>): When favipiravir was compared with umifenovir, clinical recovery rate was greater in those treated with favipiravir than in those treated with umifenovir.<sup>6</sup> (See Favipiravir in this Evidence Table.)</p> <p><b>Randomized, single-center, partially blinded trial in China (NCT0425885)</b> evaluated efficacy of umifenovir in conjunction with standard care vs LPV/RTV in conjunction with standard care vs standard care without an antiviral in hospitalized adults with mild/moderate COVID-19.<sup>2,10</sup> Data for the 86 enrolled pts suggest no difference in mean time for positive-to-negative conversion of SARS-CoV-2 nucleic acid in respiratory specimens and no difference in clinical outcomes between pts treated with umifenovir or LPV/RTV compared with no antiviral therapy<sup>10</sup></p>		

## SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
Anakinra (Kineret®)  Updated 10/1/20	92:36 Disease-modifying Anti-rheumatic Drug	<p>Recombinant human interleukin-1 (IL-1) receptor antagonist<sup>1</sup></p> <p>IL-1 levels are elevated in patients with COVID-19; anakinra may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients<sup>2,3,4,7</sup></p> <p>Anakinra has been used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis. IL-1 levels are elevated in patients with these conditions. Case reports and series describe a favorable response to anakinra in these syndromes, including survival benefit in sepsis and reversing cytokine storm in adults with MAS after tocilizumab failure.<sup>7</sup></p>	<p>There are case study data but no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19<sup>7</sup></p> <p><b>France:</b> A cohort study (Ana-COVID) included a prospective cohort of 52 adults with severe COVID-19 treated with anakinra plus standard of care and a historical comparison group of 44 patients who received standard and supportive care at Groupe Hospitalier Paris Saint-Joseph. Inclusion criteria included severe COVID-19-associated bilateral pneumonia on chest x-ray or lung CT scan, laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and an oxygen saturation of <math>\leq 93\%</math> under oxygen <math>\geq 6</math> L/min or deterioration (saturation <math>\leq 93\%</math> under oxygen 3 L/min with loss of 3% oxygen saturation in ambient air over previous 24 hours). Anakinra was given subcutaneously in a dosage of 100 mg twice daily on days 1–3, then 100 mg once daily from day 4–10. The primary outcome measure was a composite of either ICU admission for invasive mechanical ventilation or death. Admission to the ICU or death occurred in 13 (25%) of anakinra-treated patients and in 32 (73%) of patients in the historical comparison group.<sup>9</sup></p> <p><b>France:</b> A small case series (9 patients) of open-label anakinra treatment in hospitalized (non-ICU) adults with moderate to severe COVID-19 pneumonia has been published with encouraging results<sup>8</sup></p> <p><b>Italy:</b> Retrospective cohort study (part of NCT04318366) with high- or low-dose anakinra in adults with COVID-19, moderate to severe acute respiratory distress syndrome (ARDS), and hyperinflammation (defined as elevated serum C-reactive protein [CRP] and/or ferritin levels) managed with non-invasive ventilation outside of the ICU at a Milan hospital. Patients received standard therapy (hydroxychloroquine and lopinavir/ritonavir) and either high-dose anakinra (5 mg/kg twice daily by IV infusion for</p>	<p>Various dosage regimens are being studied<sup>3,8</sup></p> <p>Trial protocol in Italy (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days<sup>3</sup></p> <p>Some studies under way in Europe are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge<sup>3</sup></p> <p>In a French case series and a French cohort study, anakinra was given subcutaneously in a dosage of 100 mg twice daily (i.e., every 12 hours) on days 1–3, then 100 mg once daily from day 4–10<sup>8,9</sup></p> <p>A retrospective cohort study in Italy compared high-dose anakinra by IV infusion (5 mg/kg twice daily) and low-dose anakinra (100 mg twice daily) given subcutaneously<sup>10</sup></p> <p>(Note: Anakinra is approved only for subcutaneous administration in the U.S.)<sup>1,7</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of anakinra in the treatment of COVID-19<sup>7</sup></p> <p><b>Safety profile:</b> Well established in adults with sepsis and has been studied extensively in severely ill pediatric patients with complications of rheumatologic conditions; pediatric data on use in acute respiratory distress syndrome/sepsis are limited<sup>7</sup></p> <p><b>Pregnancy:</b> Limited evidence to date: unintentional first trimester exposure considered unlikely to be harmful<sup>7</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>a median of 9 days followed by daily low-dose subcutaneous administration [100 mg twice daily] for 3 additional days to prevent relapse) or low-dose anakinra (100 mg twice daily subcutaneously) and were compared with a historical cohort of patients who did not receive anakinra. At 21 days, high-dose anakinra was associated with reduced CRP levels and progressive improvement in respiratory function in 21 of 29 (72%) of patients; 5 patients (17%) were placed on mechanical ventilation and 3 patients (10%) died. High-dose IV anakinra appeared to be relatively well tolerated. Anakinra was discontinued in the low-dose subcutaneous anakinra group after 7 days because of a lack of improvement in CRP levels and clinical status. In the standard treatment alone group (retrospective cohort), 8 out of 16 patients (50%) showed respiratory improvement at 21 days; 1 patient (6%) was placed on mechanical ventilation and 7 patients (44%) died.<sup>10</sup></p> <p><b>Italy:</b> Phase 3 randomized, open-label, multicenter trial (NCT04324021) initiated by the manufacturer (Swedish Orphan Biovitrum) to evaluate efficacy and safety of anakinra or emapalumab with standard of care in reducing hyperinflammation and respiratory distress in patients with COVID-19 is recruiting<sup>3</sup></p> <p>Numerous other clinical trials evaluating anakinra in the treatment of COVID-19 are planned or under way, mainly in Europe<sup>3</sup></p>		
<p>Ascorbic acid</p> <p><b>Updated 10/8/20</b></p>	<p>88:12 Vitamin C</p>	<p>Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress.<sup>3-5, 7</sup></p> <p>Presence of infection may decrease vitamin C concentrations.<sup>2-5</sup></p>	<p><b>IV ascorbic acid:</b> Phase 3 randomized, blinded, placebo-controlled trial (NCT03680274; LOVIT) evaluating effect of high-dose IV ascorbic acid on mortality and persistent organ dysfunction in septic ICU patients (including COVID-19 patients); other clinical trials of high-dose IV ascorbic acid for treatment of COVID-19 registered, including:<sup>1</sup> NCT04264533 NCT04323514 NCT04401150 (LOVIT-COVID) NCT04395768</p>	<p><b>IV ascorbic acid:</b> Various dosages of IV ascorbic acid used in COVID-19 studies; 50 mg/kg IV every 6 hours for 4 days used in NCT03680274 and NCT04401150<sup>1</sup></p> <p>Various dosages of IV ascorbic acid used in sepsis studies; 50 mg/kg every 6 hours for 4 days used in CITRIS-ALI study; 1.5 g every 6 hours used in VITAMINS, HYVCTTSSS, and ORANGES studies, but treatment duration varied by study<sup>4, 8-10, 13, 14</sup></p>	<p>Current clinical trial data not specific to COVID-19; additional study needed.<sup>6</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of ascorbic acid for the treatment of COVID-19 in <b>critically ill patients</b>. The panel states that there are no completed controlled trials of ascorbic acid in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of ascorbic acid in patients with sepsis or ARDS have shown variable efficacy and limited safety concerns.<sup>12</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p><b>Oral ascorbic acid:</b> Randomized, open-label study (NCT04342728; COVIDatoZ) initiated to evaluate oral ascorbic acid (8 g daily), zinc, or both in combination in symptomatic outpatients receiving a positive COVID-19 test result; other clinical trials of outpatient oral ascorbic acid treatment registered, including NCT04395768.<sup>1</sup></p> <p>Included at lower dosages as an active or placebo-equivalent comparator (control) in other COVID-19 prevention or treatment studies.<sup>1</sup></p> <p>Included as a component of some combination regimens being studied for prevention or treatment of COVID-19.<sup>1</sup></p> <p><b>Other infections:</b> Sepsis: Meta-analysis of several small studies suggested beneficial effects from IV ascorbic acid.<sup>8</sup> However, primary end points not improved in CITRIS-ALI study (NCT02106975) in patients with sepsis and ARDS, VITAMINS study (NCT0333278) in patients with septic shock, or HYVCTSSS study (NCT03258684) in patients with sepsis or septic shock; one primary end point (resolution of shock [i.e., discontinuance of vasopressor support]) was improved but other primary end point (change in SOFA score) was not improved in ORANGES study (NCT03422159) in patients with sepsis or septic shock; variable findings reported with respect to certain primary or secondary outcomes.<sup>9, 10, 13, 14</sup> Additional studies under way.<sup>4, 6</sup></p> <p>Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia.<sup>2, 3</sup></p> <p>Common cold: Effect of oral supplementation studied extensively; decreases duration of symptoms, may decrease incidence of common cold in individuals under heavy physical stress but not in overall population.<sup>2, 3</sup></p>	<p><b>Oral ascorbic acid:</b> NCT04342728: Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses.<sup>1</sup></p> <p>NCT04395768 (outpatients): Ascorbic acid 1 g orally 3 times daily for 7 days following initial 200-mg/kg IV dose.</p> <p><b>Laboratory test interference:</b> May interfere with laboratory tests based on oxidation-reduction reactions (e.g., blood and urine glucose testing, nitrite and bilirubin concentrations, leukocyte counts).<sup>11</sup> High circulating vitamin C concentrations may affect accuracy of point-of-care glucometers.<sup>12</sup> Manufacturer states to delay oxidation-reduction reaction-based tests until 24 hours after infusion, if possible.<sup>11</sup></p> <p><b>Sodium content:</b> May be substantial with high-dose IV therapy (e.g., each mL of ascorbic acid 500-mg/mL injection provides 65 mg of sodium).<sup>11</sup></p> <p><b>Oxalate nephrolithiasis:</b> Potential for prolonged, high-dose IV therapy to increase risk of oxalate nephrolithiasis or nephropathy.<sup>11, 14</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel also states that there are insufficient data to recommend either for or against use of ascorbic acid for the treatment of COVID-19 in <b>noncritically ill patients</b>. The panel states that there is no compelling reason to use ascorbic acid in this setting since patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation.<sup>12</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
Azithromycin  <i>Updated 10/8/20</i>	8:12.12 Macrolides	<p>Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika)<sup>1, 3-5, 35</sup></p> <p>No data to date on in vitro activity against coronaviruses, including SARS-CoV-2</p> <p>Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated<sup>2, 6, 8, 9, 11-14, 17, 35</sup></p> <p>Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza)<sup>10, 13</sup></p> <p>Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the management of certain respiratory conditions (e.g., bronchiectasis, bronchiolitis, cystic fibrosis, COPD exacerbations, ARDS)<sup>6, 8, 17</sup></p>	<p><b>Adjunctive therapy in certain respiratory viral infections:</b> Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza).<sup>10, 12, 13</sup> 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.<sup>12</sup></p> <p><b>Adjunctive therapy in certain respiratory conditions:</b> Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS).<sup>8</sup> In a retrospective cohort study in pts with moderate or severe ARDS, a statistically significant improvement in 90-day survival was reported in those who received adjunctive azithromycin.<sup>8</sup></p> <p><b>Clinical experience in pts with COVID-19:</b> Has been used for antibacterial coverage in hospitalized pts with COVID-19<sup>15</sup></p> <p><b>Use in conjunction with hydroxychloroquine in pts with COVID-19:</b> Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts),<sup>7</sup> open-label uncontrolled study in France (11 pts),<sup>18</sup> uncontrolled observational study in France (80 pts),<sup>19</sup> and larger uncontrolled observational study in France (1061 pts).<sup>23</sup> Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.)</p> <p><b>Use in conjunction with hydroxychloroquine in hospitalized pts with COVID-19:</b> Data from 2 retrospective studies that analyzed outcome data for hospitalized pts in New York treated with hydroxychloroquine with or without azithromycin indicate that use of the 4-aminoquinoline antimalarial</p>	<p><b>Adjunctive treatment in certain viral infections:</b> 500 mg once daily has been used<sup>13</sup></p> <p><b>COVID-19:</b> 500 mg on day 1, then 250 mg once daily on days 2-5 in conjunction with a 5-, 7-, or 10-day regimen of hydroxychloroquine has been used or is being investigated<sup>7, 18, 19, 23, 24, 29</sup></p>	<p>Current data are insufficient to establish pros and cons of adjunctive use of azithromycin in the management of COVID-19, including use for empiric antibacterial coverage for suspected secondary bacterial pneumonia.<sup>22</sup></p> <p>Empiric coverage for bacterial pathogens is not required and is not recommended in all pts with confirmed COVID-19-related pneumonia. If bacterial pneumonia or sepsis is strongly suspected or confirmed, empiric antibacterial treatment should be administered.<sup>21, 32</sup> Although data are limited, bacterial pathogens in COVID-19 pts with community-acquired pneumonia (CAP) are likely the same as those seen in other pts with CAP. Therefore, if antibacterial coverage for CAP is indicated in COVID-19 pts, the usually recommended regimens for empiric treatment of CAP should be used.<sup>32</sup> Antimicrobial stewardship policies should be used to guide appropriate use of antibacterials in COVID-19 pts.<sup>21</sup></p> <p>Data from randomized, controlled clinical trials are insufficient to date to draw conclusions regarding possible benefits of using a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19; there are data indicating that combined use of azithromycin and chloroquine or hydroxychloroquine may be associated with an increased risk of adverse cardiac effects.<sup>21, 22, 33</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial, because of the potential for toxicities.<sup>21</sup> (See Hydroxychloroquine in this Evidence Table.)</p> <p>IDSA <b>recommends against</b> use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in hospitalized pts.<sup>22</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>with or without azithromycin is <b>not</b> associated with decreased in-hospital mortality.<sup>30, 31</sup> (See Hydroxychloroquine in this Evidence Table.)</p> <p><b>**Open-label, randomized, multicenter trial in adults hospitalized with severe COVID-19 in Brazil (NCT04321278; COALITION II):</b> Patients were randomized 1:1 to receive oral azithromycin (500 mg once daily for 10 days) plus standard of care (n=214) or standard of care (control group; n=183). All pts received oral hydroxychloroquine (400 mg twice daily for 10 days) as part of standard of care; concomitant use of corticosteroids, other immunomodulators, antibiotics (no macrolides), and antivirals was allowed. Inclusion criteria required at least one severity criterion (use of oxygen supplementation at more than 4 L/minute, high-flow nasal cannula, noninvasive positive-pressure ventilation, or mechanical ventilation). Exclusion criteria included history of severe ventricular cardiac arrhythmia or QT<sub>c</sub> ≥480 msec in any ECG performed before randomization. The primary outcome was clinical status at day 15 based on a 6-level ordinal scale that ranged from not hospitalized (1) to death (6); the key secondary outcome was mortality at day 29. Results for the modified intention-to-treat (mITT) population (i.e., those with confirmed COVID-19) indicated that <b>addition of azithromycin to standard of care was not superior to standard of care alone</b>. At day 15, there was no difference in the proportional odds of being in higher categories on the 6-point ordinal scale between the azithromycin group and control group. At day 29, 42% of pts in the azithromycin group and 40% of those in the control group had died. There also was no difference between the groups in the proportion of pts with QT<sub>c</sub> interval prolongation (20% in azithromycin group and 21% in control group).<sup>34</sup></p> <p><b>Various clinical trials to evaluate azithromycin alone or in conjunction with other drugs for treatment of COVID-19</b> are registered at clinicaltrials.gov, including the following:<sup>29</sup></p>		<p>Because azithromycin and 4- amino-quinolines (hydroxychloroquine, chloroquine) are independently associated with QT prolongation, caution is advised if considering use of azithromycin with one of these drugs in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias.<sup>20-22, 25-28, 33</sup></p> <p>NIH panel states that macrolides (including azithromycin) should be used concomitantly with hydroxychloroquine (or chloroquine) <i>only</i> if necessary. In addition, because of the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the drugs are used sequentially. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving hydroxychloroquine (or chloroquine).<sup>21</sup></p> <p>The benefits and risks of a combined regimen of azithromycin and hydroxychloroquine (or chloroquine) should be carefully assessed; if the regimen is used, diagnostic testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects.<sup>20-22, 25-28, 33</sup> (See Hydroxychloroquine in this Evidence Table.)</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			NCT04332107 (azithromycin vs placebo) NCT04344457 (hydroxychloroquine with azithromycin and indomethacin) NCT04349592 (hydroxychloroquine with or without azithromycin) NCT04381962 (azithromycin plus standard care vs standard care)		
Baricitinib (Olumiant <sup>®</sup> )  <i>Updated 10/1/20</i>	92:36 Disease-modifying Anti-rheumatic Drug	Janus kinase (JAK) 1 and 2 inhibitor; disrupts regulators of endocytosis (AP2-associated protein kinase 1 [AAK1] and cyclin G-associated kinase [GAK]), which may help reduce viral entry and inflammation; also may interfere with intracellular virus particle assembly <sup>1,2</sup>  Inhibits JAK1 and JAK2-mediated cytokine release; may combat cytokine release syndrome (CRS) in severely ill patients <sup>1,2,4,5</sup>  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 <sup>5</sup>	Currently no known published controlled clinical trial evidence supporting efficacy or safety in patients with COVID-19 <sup>11</sup>  In a small (12 patients) open-label study in Italy (NCT04358614), use of baricitinib (4 mg orally once daily for 2 weeks) in combination with lopinavir/ritonavir was evaluated in patients with moderate COVID-19 pneumonia. <sup>13,14</sup> Baricitinib was well tolerated with no serious adverse events reported. <sup>13</sup> At week 1 and week 2, patients who received baricitinib had significant improvement in respiratory function parameters and none of the patients required ICU support. <sup>13</sup>  Baricitinib is included in the second phase of <b>NIAID's Adaptive COVID-19 Treatment Trial (ACTT 2; NCT04401579)</b> . <sup>3,12,15,17</sup> Inclusion criteria: Laboratory-confirmed COVID-19 infection and evidence of lung involvement (abnormal chest X-rays, SpO <sub>2</sub> of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO). <sup>12,17</sup> Patients randomized to receive treatment with remdesivir with or without baricitinib. <sup>12</sup> Remdesivir administered as one 200-mg IV dose on day 1 followed by 100 mg IV daily for the duration of hospitalization (up to 10-day treatment course). Baricitinib administered as a 4-mg oral dose administered once daily for the duration of hospitalization (up to 14-day treatment course). <sup>12</sup>  <b>Adaptive phase 2/3 clinical trial:</b> Open-label study planned to evaluate safety and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232) <sup>6</sup>  <b>A randomized, double-blind, placebo-controlled, phase 3 trial (COV-BARRIER; NCT04421027) sponsored by the manufacturer (Lilly) is currently under way to</b>	Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1 <sup>1,2,5</sup>  Dosage information not yet available (see Trials or Clinical Experience)  NIH COVID-19 Treatment Guidelines Panel recommends dosage adjustment if baricitinib is administered concurrently with a strong OAT3 inhibitor <sup>11</sup>	Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and many other drugs; <sup>4,14</sup> however, dosage adjustment recommended when used with strong OAT3 inhibitors <sup>11</sup>  Not recommended in patients with severe hepatic or renal impairment <sup>11</sup>  NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial <sup>11</sup>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>evaluate the efficacy and safety of baricitinib in hospitalized adults with COVID-19 who have at least one elevated marker of inflammation but do not require mechanical ventilation upon study entry. Targeted enrollment is 400 patients; study will be conducted in the U.S., Europe, and Latin America. Patients in the baricitinib treatment arm will receive an oral dosage of 4 mg daily for up to 14 days or until hospital discharge in addition to their background therapy.<sup>15, 16</sup></p> <p>Other planned clinical trials will evaluate baricitinib in combination with or without an antiviral agent for the treatment of COVID-19 (NCT04346147, NCT04320277, NCT04345289, NCT04321993)<sup>7-10</sup></p>		
<p>Colchicine</p> <p><i>Updated 8/20/20</i></p>	<p>92:16 Antitubercular Agents</p>	<p>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></p> <p>May combat the hyper-inflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines<sup>2</sup></p> <p>NLRP3 inflammasome activation results in release of interleukins, including IL-1<math>\beta</math><sup>3,5,6,8,11</sup></p> <p>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>3,11</sup></p>	<p>Limited anecdotal experience and clinical trial data reported to date in COVID-19<sup>4, 16, 17</sup></p> <p><b>Retrospective review</b> of computerized healthcare database found no difference in baseline use of colchicine (0.53 vs 0.48%) between patients with a positive RT-PCR result for SARS-CoV-2 (n = 1317) and those with a negative result (n = 13,203), suggesting a lack of protective effect for colchicine against SARS-CoV-2 infection; indication for and duration of colchicine use were unknown<sup>15</sup></p> <p><b>Uncontrolled case series:</b> 9 patients in community setting with COVID-19 received colchicine (1 mg orally every 12 hours on day 1, then 1 mg daily until third day of temperature &lt;37.5°C); colchicine was initiated at a median of 8 days (range: 6-13 days) after symptom onset and after 3-5 days of spiking fever despite acetaminophen or antibiotic treatment. Defervescence occurred within 72 hours in all patients. One patient was hospitalized because of persistent dyspnea and discharged after 4 days of oxygen therapy. Basis for diagnosis of COVID-19 not stated.<sup>16</sup></p> <p><b>Open-label, randomized, 16-hospital clinical trial (NCT04326790, GRECCO-19) in hospitalized adults with RT-PCR-confirmed COVID-19:</b> 55 patients received colchicine plus standard treatment and 50 received</p>	<p>Dosage in NCT04326790 (GRECCO-19): Colchicine loading dosage: 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin); maintenance dosage: 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing &lt;60 kg) until hospital discharge or maximum of 21 days<sup>17</sup></p> <p>Dosage in another ongoing trial: Colchicine 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose is 1 mg if body weight <math>\geq</math>80 kg); dosage is reduced for renal impairment.<sup>18</sup></p> <p>Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days<sup>1</sup></p> <p>Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19<sup>2</sup></p> <p>Consider possible need for colchicine dosage adjustment;<sup>2</sup> 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>	<p>Safety and efficacy for treatment of COVID-19 not established</p> <p>The potential for toxic doses of colchicine to affect alveolar type II pneumocytes (which may inhibit surfactant release and contribute to ARDS) and increase the risk of multiple-organ failure and disseminated intravascular coagulation (DIC) has been raised as a possible concern with the use of colchicine in COVID-19 patients<sup>14</sup></p>

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		<p>Potential to limit COVID-19 -related myocardial damage also has been hypothesized<sup>2,3</sup> based on the drug's mechanisms of action and promising results of ongoing research on colchicine in various cardiac conditions<sup>3,6-10</sup></p> <p>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-1<math>\beta</math> production<sup>2,12,13</sup></p>	<p>standard treatment alone; colchicine was administered orally as a loading dose of 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin) followed by a maintenance dosage of 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing &lt;60 kg) until hospital discharge or for a maximum of 21 days. Most patients also received chloroquine or hydroxychloroquine (98%) and azithromycin (92%). <b>Clinical deterioration (2-grade increase on a 7-grade ordinal scale) was observed in a greater proportion of control patients than colchicine-treated patients</b> (7 patients [14%] vs 1 patient [1.8%]); cumulative 10-day event-free survival was higher with colchicine than with control (97 vs 83%). Baseline score on the 7-grade scale was 3 or 4 in 97% of study patients. No difference observed between the groups in baseline or peak high-sensitivity cardiac troponin or peak C-reactive protein concentration. Small number of clinical events limited the statistical robustness of the results.<sup>17</sup></p> <p><b>Interim analysis (not peer reviewed) of a single-center, randomized, double-blind, placebo-controlled trial in hospitalized adults with moderate to severe, RT-PCR-confirmed COVID-19 with pneumonia (not requiring ICU admission):</b> Analysis of first 38 patients randomized 1:1 to colchicine or placebo indicated <b>shorter duration of oxygen supplementation (3 vs 7 days) and shorter hospital stay (6 vs 8.5 days)</b> in colchicine group vs placebo group. One patient in each group required ICU admission. Median duration of symptoms prior to treatment was 9 days (colchicine group) or 7 days (placebo group). Colchicine dosage was 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose was 1 mg if body weight <math>\geq</math>80 kg); dosage was reduced for renal impairment. Standard concomitant treatment included 7-day azithromycin regimen, up to 10-day hydroxychloroquine regimen, and heparin with or without methylprednisolone (depending on oxygenation status).<sup>18</sup></p>	<p>P-glycoprotein (P-gp) inhibitors<sup>5</sup></p> <p>Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated<sup>5</sup></p>	

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			<p><b>Phase 3, randomized, double-blind, placebo-controlled study</b> (NCT04322682; COL-CORONA) initiated in adults ≥40 years of age with COVID-19 and at least one high-risk criterion to evaluate effect of colchicine on mortality, hospitalization rate, and need for mechanical ventilation; study excludes enrollment of currently hospitalized patients; enrollment target is approximately 6000 pts<sup>1</sup></p> <p>Other registered randomized, parallel-group studies are evaluating the effects of colchicine on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in patients with COVID-19: NCT04322565, NCT04328480, NCT04350320, NCT04355143, NCT04392141, NCT04375202, NCT04360980, NCT04367168, NCT04403243, NCT04363437, NCT04416334, NCT04324463<sup>2,3</sup></p>		
<p>Corticosteroids (systemic)</p> <p><i>Updated 9/24/20</i></p>	<p>68:04 Adrenals</p>	<p>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<sup>3,9</sup></p> <p>Evidence suggests that cytokine storm, a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), is a contributing factor in COVID-19-associated mortality.<sup>8,18</sup> Immunosuppression from corticosteroids has been proposed as a treatment option for such hyperinflammation.<sup>18</sup></p> <p>May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low<sup>4,11</sup></p>	<p><b>Observational studies in other respiratory infections (e.g., SARS, MERS, influenza):</b> In these studies, corticosteroid use was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes).<sup>1,24,25</sup></p> <p><b>Randomized controlled studies in acute respiratory distress syndrome (ARDS):</b> Systemic corticosteroid therapy has been studied in several randomized controlled studies for the treatment of ARDS; overall evidence is low to moderate in quality and most studies were performed prior to widespread implementation of lung protection strategies.<sup>5,8,9,14,17</sup></p> <p><b>Randomized, controlled, open-label, adaptive trial with a Dexamethasone arm (NCT04381936; RECOVERY):</b> This trial was conducted to evaluate the effect of potential treatments (including low-dose dexamethasone) on all-cause mortality in hospitalized patients with COVID-19. The study enrolled patients with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the dexamethasone treatment arm, 2104 patients were randomized to receive</p>	<p>The NIH COVID-19 Treatment Guidelines Panel recommends an <b>IV or oral Dexamethasone dosage of 6 mg daily for up to 10 days or until hospital discharge, whichever comes first</b>, in COVID-19 patients requiring mechanical ventilation and in patients who require supplemental oxygen but who are not mechanically ventilated. Although the clinical benefits of other corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone) are not clear, the panel recommends using total daily dosages of these drugs equivalent to dexamethasone 6 mg (IV or oral) as follows:</p> <p><b>Hydrocortisone 160 mg, Methylprednisolone 32 mg, or Prednisone 40 mg.</b> Based on half-life and duration of action, frequency of administration varies among these corticosteroids. <b>Dexamethasone</b> is long-acting and administered once daily. <b>Methylprednisolone</b> and <b>Prednisone</b> are intermediate-acting and administered once daily or in 2 divided doses daily. <b>Hydrocortisone</b> is</p>	<p>Data on the use of corticosteroids in COVID-19 are limited.<sup>3,5,7,24,25</sup> The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19.<sup>1,7</sup></p> <p>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.<sup>1,2,8,12,24,25,43</sup></p> <p><b>Non-critical patients:</b> Corticosteroids generally should not be used in the treatment of early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding.<sup>3,8,24</sup></p> <p>The WHO Guideline Development Group suggests not using systemic corticosteroids in the treatment of patients with <b>non-severe</b> COVID-19, regardless of hospitalization status. However, if the</p>

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			<p>dexamethasone (6 mg once daily orally or IV for up to 10 days) plus standard care and 4321 patients were randomized to receive standard care alone. Preliminary data analysis indicates that overall 28-day mortality was reduced in patients receiving dexamethasone compared with those receiving standard care alone with the greatest benefit observed in patients requiring mechanical ventilation at enrollment. Overall, 22.9% of patients receiving dexamethasone and 25.7% of those receiving standard care died within 28 days of study enrollment. In patients receiving dexamethasone, the incidence of death was lower than that in the standard care group among those receiving invasive mechanical ventilation (29.3 vs 41.4%) and among those receiving supplemental oxygen without invasive mechanical ventilation (23.3 vs 26.2%). However, no survival benefit was observed with dexamethasone and there was a possibility of harm in patients who did not require respiratory support at enrollment; the incidence of death in such patients receiving dexamethasone compared with standard care was 17.8 vs 14%, respectively. Dexamethasone was associated with a reduction in 28-day mortality among patients with symptoms for &gt;7 days compared with those having more recent symptom onset. Dexamethasone treatment also was associated with a shorter duration of hospitalization and a greater probability of discharge within 28 days with the greatest effect observed among patients receiving invasive mechanical ventilation at baseline.<sup>24, 32, 33</sup> <b>Note:</b> Data regarding potential adverse effects, efficacy in combination with other treatments (e.g., remdesivir), and efficacy in other patient populations (e.g., pediatric patients and pregnant women) not available to date.<sup>24</sup></p> <p><b>Dexamethasone randomized, controlled, open-label, multicenter study (NCT04327401; CoDEX):</b> This trial was conducted to determine whether IV dexamethasone increases the number of ventilator-free days among patients with COVID-19-associated ARDS. The study enrolled adults with COVID-19 and moderate or severe</p>	<p>short-acting and administered in 2-4 divided doses daily.<sup>24</sup></p> <p>Regimens used in early cases of COVID-19 in China were typically <b>methylprednisolone 40-80 mg IV daily for a course of 3-6 days</b>. Some experts suggest that equivalent dosages of <b>dexamethasone (i.e., 7-15 mg daily, typically 10 mg daily)</b> may have an advantage of producing less fluid retention, since dexamethasone has less mineralocorticoid activity.<sup>8</sup> This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial.<sup>8, 17</sup> However, lower dosages of dexamethasone (i.e., 6 mg once daily for 10 days) were used in the RECOVERY trial.<sup>32, 33</sup></p> <p>Higher dosages of IV <b>Dexamethasone</b> (i.e., 20 mg once daily for 5 days followed by 10 mg once daily for an additional 5 days or until ICU discharge, whichever came first) were used in the CoDEX trial in patients with COVID-19 and moderate or severe ARDS.<sup>39</sup></p> <p>Continuous IV infusion of <b>Hydrocortisone</b> 200 mg/day for 7 days, followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days) was used in the CAPE COVID study. If a patient's respiratory and general status sufficiently improved by day 4, a shorter treatment regimen of <b>Hydrocortisone</b> was used at a dosage of 200 mg/day for 4 days followed by 100 mg/day for 2 days and then 50 mg/day for 2 days (total of 8 days).<sup>40</sup></p> <p>A fixed dosage of IV <b>Hydrocortisone</b> (50 or 100 mg every 6 hours for 7 days) or a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours for up to 28 days in the presence of clinically evident shock) was used in the REMAP-CAP study.<sup>41</sup></p>	<p>clinical condition of such non-severe patients worsens (e.g., increased respiratory rate, signs of respiratory distress, or hypoxemia), systemic corticosteroids are recommended for treatment. The WHO Guideline Development Group recommends against discontinuing systemic corticosteroids in patients with non-severe COVID-19 who are receiving systemic corticosteroids for chronic conditions (e.g., COPD, autoimmune diseases).<sup>43</sup></p> <p><b>Critically ill patients:</b> The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the <a href="#">Society of Critical Care Medicine</a> and the <a href="#">European Society of Intensive Care Medicine</a>) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS).<sup>12</sup> However, these experts generally support a <b>weak</b> recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS.<sup>12</sup></p> <p>Based on preliminary findings from the RECOVERY trial, the NIH COVID-19 Treatment Guidelines Panel recommends the use of <b>dexamethasone</b> (6 mg daily for up to 10 days or until hospital discharge, whichever comes first) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. The panel <b>recommends against</b> the use of dexamethasone in COVID-19 patients who do not require supplemental oxygen.<sup>24</sup></p> <p>The NIH guidelines panel also states that prolonged use of systemic corticosteroids in patients with COVID-19 may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus, strongyloidiasis, tuberculosis). The risk of reactivation of latent infections following a 10-day course of dexamethasone (6 mg once daily) is not</p>

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			<p>ARDS who were receiving mechanical ventilation from 41 ICUs in Brazil. In the dexamethasone treatment arm, 151 patients were randomized to receive dexamethasone (20 mg IV once daily for 5 days followed by 10 mg IV once daily for another 5 days or until ICU discharge) plus standard care; 148 patients were randomized to receive standard care alone. The primary study end point was ventilator-free days (defined as number of days alive and free from mechanical ventilation) during the first 28 days. Preliminary data analysis indicates that use of IV dexamethasone plus standard care was associated with a higher mean number of ventilator-free days (6.6 days) compared with those receiving standard care alone (4 days). Although there was no significant difference in all-cause mortality at 28 days between the treatment groups, the trial was terminated early after results of the RECOVERY trial became available and, therefore, likely underpowered to determine secondary outcomes such as mortality. Dexamethasone was not associated with an increased risk of adverse effects in this study population of critically ill COVID-19 patients.<sup>39</sup></p> <p><b>Hydrocortisone randomized, double-blind sequential trial (NCT02517489; CAPE COVID):</b> This trial was conducted to evaluate the effect of low-dose hydrocortisone compared with placebo on treatment failure in critically ill patients with COVID-19-related acute respiratory failure. The study enrolled adults with COVID-19-associated acute respiratory failure from 9 ICUs in France. In the hydrocortisone treatment arm, 76 patients received a continuous IV infusion of hydrocortisone at an initial dosage of 200 mg/day for 7 days followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days; some patients received a shorter regimen); 73 patients received placebo. The primary study end point was treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy) on day 21. Treatment failure on day 21 occurred in 42.1% of patients in the hydrocortisone group compared with</p>		<p>well established. When initiating dexamethasone in patients with COVID-19, appropriate screening and treatment to reduce the risk of <i>Strongyloides</i> hyperinfection in those at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) or fulminant reactivations of HBV should be considered.<sup>24, 37, 38</sup></p> <p>The NIH guidelines panel also states that it is not known at this time whether other corticosteroids will have a similar benefit as dexamethasone. However, if dexamethasone is not available, the panel recommends using <b>alternative corticosteroids</b> (e.g., hydrocortisone, methylprednisolone, prednisone).<sup>24</sup></p> <p>IDSA suggests the use of corticosteroids over no corticosteroid therapy in hospitalized patients with severe COVID-19 (i.e., defined as patients with SpO<sub>2</sub> ≤94% on room air and those who require supplemental oxygen, mechanical ventilation, or ECMO). These experts suggest the use of <b>dexamethasone</b> 6 mg orally or IV daily for 10 days or until hospital discharge, whichever comes first, or substitution of equivalent daily dosages of <b>other corticosteroids</b> (e.g., methylprednisolone 32 mg, prednisone 40 mg) if dexamethasone is unavailable. However, IDSA suggests against using corticosteroids in hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen.<sup>25</sup></p> <p>The WHO Guideline Development Group strongly recommends the use of systemic corticosteroids (e.g., dexamethasone 6 mg orally or IV daily or hydrocortisone 50 mg IV every 8 hours for 7-10 days) over no systemic corticosteroid therapy for the treatment of patients with <b>severe and/or critical</b> COVID-19, regardless of hospitalization status. This treatment recommendation includes critically ill patients with COVID-19 who could not be hospitalized or receive oxygen supplementation because of</p>

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			<p>50.7% of patients in the placebo group. The difference between the treatment groups was not statistically significant; however, the study was discontinued early after results of the RECOVERY trial were announced and, therefore, likely underpowered to determine a statistically and clinically important difference in the primary outcome.<sup>40</sup></p> <p><b>Hydrocortisone multicenter, ongoing, international open-label trial using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):</b> This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 corticosteroid domain, adults from 8 countries with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive a fixed 7-day regimen of IV hydrocortisone (50 or 100 mg every 6 hours), a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours when shock was clinically evident), or no hydrocortisone or other corticosteroid. The primary study end point was organ support-free days (defined as days alive and free of ICU-based respiratory or cardiovascular support) within 21 days. The 7-day fixed regimen and the shock-dependent regimen of hydrocortisone were associated with a 93 and 80% probability of benefit in terms of organ support-free days compared with no hydrocortisone. However, the trial was discontinued early after results of the RECOVERY trial were announced and no treatment strategy met the prespecified criteria for statistical superiority, precluding definitive conclusions. In addition, serious adverse effects were reported in 2.6% of patients in the study (4 patients receiving the fixed-dosage regimen and 5 patients receiving the shock-dependent regimen compared with 1 patient receiving no hydrocortisone).<sup>41</sup></p> <p><b>Prospective meta-analysis of studies using systemic corticosteroids (i.e., dexamethasone, hydrocortisone, or methylprednisolone) from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT)</b></p>		<p>resource limitations. This treatment recommendation is less clear for populations under-represented in recent clinical trials (e.g., children, patients with tuberculosis, immunocompromised individuals); however, the risk of not using systemic corticosteroids and depriving such patients of potentially life-saving therapy should be considered. The WHO treatment recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term dosage regimens, or prophylaxis.<sup>43</sup></p> <p><b>Cytokine storm:</b> There is no well-established or evidence-based treatment for cytokine storm in patients with COVID-19.<sup>8</sup> However, some experts suggest that use of more potent immunosuppression with corticosteroids may be beneficial in such patients.<sup>8</sup> 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.<sup>8</sup></p> <p><b>Septic shock:</b> The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different than the effects seen in those with ARDS.<sup>12</sup> 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.<sup>12, 24</sup></p> <p>Randomized controlled studies evaluating use of corticosteroids (e.g., hydrocortisone, dexamethasone, methylprednisolone, prednisolone) in septic shock suggest a small, but uncertain mortality reduction.<sup>3, 4</sup> Clinicians considering corticosteroids for such patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding.<sup>1</sup> If corticosteroids are</p>

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			<p><b>Working Group:</b> This meta-analysis pooled data from 7 randomized clinical trials in 12 countries that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The primary outcome was all-cause mortality up to 30 days after randomization to treatment. Administration of systemic corticosteroids was associated with lower all-cause mortality at 28 days compared with usual care or placebo (222 deaths among 678 patients who received corticosteroids and 425 deaths among 1025 patients who received usual care or placebo). The effect of corticosteroids on reduced mortality was observed in critically ill patients who were and were not receiving mechanical ventilation at randomization and also in patients from the RECOVERY trial who required supplemental oxygen with or without noninvasive ventilation but who were not receiving invasive mechanical ventilation at the time of randomization. The odds ratios for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone. The optimal dosage and duration of corticosteroid treatment could not be determined from this analysis; however, there was no evidence suggesting that a higher dosage of corticosteroids was associated with greater benefit than a lower dosage. The authors also concluded that there was no suggestion of an increased risk of serious adverse effects associated with corticosteroid use.<sup>42</sup></p> <p><b>Methylprednisolone open-label, multicenter, randomized, controlled study (NCT04244591):</b> This recently completed trial compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to acute respiratory failure; results have not yet been posted.<sup>23</sup></p> <p><b>Retrospective, observational study of systemic corticosteroid use in patients with COVID-19 from a New York hospital (Keller et al):</b> Data are available for 1806 patients hospitalized with COVID-19 between Mar 11 and Apr 13, 2020. Patients included in the analysis were those treated with</p>		<p>prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia.<sup>1,4</sup></p> <p><b>Patients receiving corticosteroid therapy for chronic conditions:</b> 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.<sup>24</sup> (See Corticosteroids [inhaled] in this Evidence Table for recommendations for use of inhaled corticosteroids in COVID-19 patients with asthma or COPD.)</p> <p>Rheumatology experts, including members of the American College of Rheumatology COVID-19 Clinical Guidance Task Force, state that abrupt discontinuance of corticosteroid therapy in patients with rheumatologic diseases should be avoided regardless of COVID-19 exposure or infection status. These experts also state that if indicated, corticosteroids should be used at the lowest effective dosage to control manifestations, but also acknowledge that higher dosages may be necessary in the context of severe, vital organ-threatening rheumatologic disease even following COVID-19 exposure.<sup>28-30</sup></p> <p>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.<sup>19,26</sup> 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.<sup>19</sup> These guidelines also apply to patients who are receiving</p>

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			<p>systemic corticosteroids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone) within the first 48 hours of hospital admission (140 patients) and those not treated with corticosteroids (1666 patients) as the control group. Treatment and control groups were similar except that corticosteroid-treated patients were more likely to have a history of COPD, asthma, rheumatoid arthritis, or lupus, or to have received corticosteroids in the year prior to admission. Primary goal of the study was to determine whether early systemic corticosteroid treatment was associated with reduced mortality or need for mechanical ventilation. Overall, early use of systemic corticosteroids was not associated with in-hospital mortality or mechanical ventilation. However, there was a significant treatment effect based on C-reactive protein (CRP) levels. Early use of corticosteroids in patients with initial CRP levels of <math>\geq 20</math> mg/dL was associated with a significantly <i>reduced</i> risk of mortality or need for mechanical ventilation (odds ratio: 0.23). Conversely, such treatment in patients with initial CRP levels of <math>&lt; 10</math> mg/dL was associated with a significantly <i>increased</i> risk of mortality or need for mechanical ventilation (odds ratio: 2.64). The authors state that these findings suggest that appropriate selection of COVID-19 patients for systemic corticosteroid treatment is critical to maximize the likelihood of benefit and minimize the risk of harm. <b>Note:</b> The limitations of the observational study design should be considered when interpreting these results. Corticosteroid dosages used in patients included in this study not provided. Further study is needed to determine the role of CRP levels in guiding the use of corticosteroid treatment in patients with COVID-19.<sup>36</sup></p> <p><b>Dexamethasone, hydrocortisone, or prednisone for treatment of COVID-19 pneumonia:</b> Registered clinical trials that have been initiated or underway include:<sup>22</sup>  NCT04344288  NCT04344730  NCT04348305  NCT04359511</p>		<p>prolonged therapy (&gt; 3 months) with corticosteroids for underlying inflammatory conditions, including asthma, allergy, and rheumatoid arthritis.<sup>19</sup> In such patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral corticosteroids may be necessary.<sup>19,26</sup> 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.<sup>19,20</sup> Additional study is needed to determine the optimum corticosteroid stress dosage regimens in patients with COVID-19.<sup>26,27</sup> 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.<sup>26,27</sup></p> <p><b>Pregnancy considerations:</b> For pregnant women with COVID-19, the NIH COVID-19 Treatment Guidelines Panel states that a short course of corticosteroids that cross the placenta (i.e., beta-methasone, dexamethasone) is routinely used for fetal benefit (e.g., to hasten fetal lung maturity). Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for this short course of corticosteroid therapy, the panel recommends the use of dexamethasone in pregnant women with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation.<sup>24</sup></p> <p>The WHO Guideline Development Group recommends antenatal corticosteroid therapy for <b>pregnant</b> women at risk of preterm birth from 24-34 weeks' gestation when there is no clinical evidence of maternal infection and adequate maternal and newborn care are</p>

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			<p>NCT04360876 NCT04395105</p> <p><b>Methylprednisolone studies for treatment of COVID-19 pneumonia or ARDS:</b> Registered clinical trials that have been initiated or underway include:<sup>22</sup> NCT03852537 NCT04263402 NCT04273321 NCT04323592 NCT04329650 NCT04343729 NCT04374071</p> <p><b>Methylprednisolone non-randomized pilot study (NCT04355247):</b> Trial has been initiated to evaluate use of the drug for the <i>prevention</i> of COVID-19 cytokine storm and progression to respiratory failure.<sup>22</sup></p>		<p>available. In cases where a pregnant woman presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroids may outweigh the risk of potential harm to the woman. The balance of benefits and risks for the woman and preterm infant should be considered during the informed decision-making process.<sup>43</sup></p> <p><b>Pediatric considerations:</b> The safety and efficacy of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality rates are significantly lower for pediatric patients with COVID-19 than for adult patients with the disease. Therefore, results of this trial should be interpreted with caution for patients &lt;18 years of age. The NIH COVID-19 Treatment Guidelines Panel states that use of dexamethasone may be beneficial in pediatric patients with respiratory disease due to COVID-19 who are receiving mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on an individual basis, and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of corticosteroids for the treatment of COVID-19 in pediatric patients, including in those with multisystem inflammatory syndrome in children (MIS-C).<sup>24</sup></p>
<p>Corticosteroids (inhaled)</p> <p><b>Updated 10/8/20</b></p>	<p>68:04 Adrenals</p>	<p>Inhaled corticosteroids may mitigate local inflammation and inhibit virus proliferation.<sup>35, 44</sup></p>	<p>There are currently no results from randomized controlled studies specifically evaluating use of inhaled corticosteroids in patients with COVID-19.<sup>34, 44, 45</sup></p> <p><b>**Early reports of an unexpectedly low prevalence of chronic respiratory conditions among outpatient and hospitalized COVID-19 patients resulted in speculation that respiratory treatments, specifically inhaled corticosteroids, may have a</b></p>	<p>Initial dosage of orally inhaled ciclesonide used in the published case series from Japan of 3 patients with COVID-19 pneumonia was 200 mcg 2 times daily. If necessary, the dosage was increased to 400 mcg 3 times daily. The authors suggested continued use of ciclesonide oral inhalation for about 14 days or longer.<sup>35</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel recommends that inhaled corticosteroids used daily for the management of asthma and COPD to control airway inflammation should not be discontinued in patients with COVID-19. The panel also states that no studies to date have investigated the relationship between inhaled corticosteroids in these clinical settings and virus acquisition, severity of illness, or viral transmission.<sup>24</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>protective effect against SARS-CoV-2.<sup>45, 46</sup></p> <p><b>**Retrospective, observational study of inhaled corticosteroid use in patients with COPD or asthma and associated risk of COVID-19-related death in the UK (Schultze et al):</b> This study was designed to assess the role of routine use of inhaled corticosteroids on COVID-19-related mortality. Data were extracted from primary care electronic health records and linked with mortality data for a cohort of patients with COPD (n = 148,557) and another cohort with asthma (n = 818,490) who were prescribed standard respiratory treatments within the 4 months prior to the index date. In patients with COPD, an increased risk of COVID-19-related death (hazard ratio: 1.39) was reported after adjusting for age and comorbidities among those who were prescribed inhaled corticosteroids combined with a long-acting <math>\beta</math>-agonist and/or long-acting antimuscarinic compared with those prescribed a long-acting <math>\beta</math>-agonist and long-acting antimuscarinic. In patients with asthma, an increased risk of COVID-19-related death (hazard ratio: 1.55) was reported in patients who were prescribed high-dose inhaled corticosteroids compared with those prescribed a short-acting <math>\beta</math>-agonist only; however, there was no increased risk of death (hazard ratio: 1.14) in asthma patients receiving low- or medium-dose inhaled corticosteroids compared with nonusers of inhaled corticosteroids. Sensitivity analyses suggest there may be other factors driving the increased risk of death observed with use of inhaled corticosteroids, including underlying disease differences between individuals that are not captured in the health records. The results of this study do not support evidence of benefit or harm with routine use of inhaled corticosteroids on COVID-19-related mortality among individuals with COPD or asthma.<sup>44, 45</sup></p> <p>A small case series from Japan observed possible clinical benefit in 3 patients with mild to moderate COVID-19 pneumonia following oral inhalation of ciclesonide; however, without a control group, it is not</p>		<p>Currently, there is no clinical evidence supporting adverse or beneficial effects of pre-morbid use or continued administration of inhaled corticosteroids in patients with acute respiratory infections due to coronaviruses. Randomized controlled clinical studies are needed to assess the benefits of inhaled corticosteroids for treatment of COVID-19 in patients with and without chronic respiratory conditions.<sup>34, 44</sup></p>

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			<p>known whether the patients would have improved spontaneously.<sup>35</sup></p> <p>Clinical trials evaluating the use of inhaled corticosteroids (e.g., budesonide, ciclesonide) in patients with COVID-19 are being planned or underway, including the following trials registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>:<sup>22</sup></p> <p>NCT04330586 NCT04331054 NCT04355637 NCT04377711 NCT04381364 NCT04416399 NCT04435795</p>		
<p>Inhaled prostacyclins (e.g., epoprostenol, iloprost)</p> <p><i>Updated 10/1/20</i></p>	<p>48:48 Vasodilating Agents</p>	<p>Selective pulmonary vasodilators; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19<sup>1-9</sup></p> <p>Inhaled prostacyclins are used to improve oxygenation in patients with ARDS who develop refractory hypoxemia<sup>1-3, 6, 8, 9</sup></p> <p><b>Inhaled</b> 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<sup>1, 2, 9</sup></p> <p>Experience with inhaled iloprost is more limited, but the drug is thought to have a similar theoretical benefit as epoprostenol in patients with ARDS<sup>1, 2, 9</sup></p>	<p>There are currently no published studies specifically evaluating use of inhaled prostacyclins in COVID-19 patients<sup>10</sup></p> <p>In patients with ARDS, inhaled prostacyclins have been shown to substantially reduce mean pulmonary artery pressure and improve oxygenation; however, data demonstrating clinical benefit (e.g., mortality reduction) are lacking<sup>3, 6-9</sup></p> <p>A phase 2, open-label study (ILOCOVID; NCT04445246) evaluating use of inhaled iloprost in adults with suspected or confirmed COVID-19 has been initiated<sup>13</sup></p> <p>A phase 2, open-label study (VPCOVID; NCT04452669) evaluating inhaled epoprostenol delivered via a dedicated delivery system (VentaProst) in patients with COVID-19 requiring mechanical ventilation has been initiated<sup>13</sup></p>	<p>Various dosages of inhaled epoprostenol have been used in patients with ARDS: Dosages up to 50 ng/kg per minute (titrated to response) have been used in clinical studies.<sup>1-4, 6, 9</sup> To provide a clinically important increase in PaO<sub>2</sub> 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<sup>9</sup></p> <p>Dosage of inhaled iloprost that will be evaluated in the phase 2, open-label study (NCT04445246) is 20 mcg every 8 hours for 5 days (delivered by nebulization)<sup>13</sup></p>	<p>The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against the use of inhaled prostacyclins in COVID-19 patients with severe ARDS<sup>10</sup></p> <p>The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment<sup>10, 12</sup></p>
<p>Interferons</p> <p><i>Updated 9/17/20</i></p>	<p>8:18.20 Interferons</p> <p>10:00 Antineoplastic Agents</p> <p>92:20 Immunomodulatory Agents</p>	<p>Interferons (IFNs) modulate immune responses to some viral infections;<sup>2, 7, 19</sup> in vitro studies indicate only weak induction of IFN following SARS-CoV-2 infection, and a possible role for IFNs in prophylaxis or</p>	<p><b>Only limited clinical trial data available</b> to date specifically evaluating efficacy of IFNs for treatment of COVID-19;<sup>10, 15, 20, 21</sup> for information on additional studies including IFN alfa or IFN beta as a component of combination therapy (e.g., background regimen), see antiviral entries in this Evidence Table.</p>	<p><b>IFN beta:</b> Various sub-Q dosages of IFN beta-1a and IFN beta-1b are being evaluated for treatment of COVID-19.<sup>10, 16</sup></p> <p>Open-label, randomized study in hospitalized adults with COVID-19, mainly mild disease (NCT04276688):</p>	<p>Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established.</p> <p>Relative effectiveness of different IFNs against SARS-CoV-2 not established.<sup>12</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
		<p>early treatment of COVID-19 has been suggested to compensate for possibly insufficient endogenous IFN production<sup>1,3,4,7,18</sup></p> <p><b>Type 1 IFNs (IFN alfa and IFN beta)</b> are active in vitro against MERS-CoV in Vero and LLCMK2 cells and in rhesus macaque model of MERS-CoV infection; type I IFNs also active in vitro against SARS-CoV-1 in Vero, fRhK-4, and human cell lines;<sup>8</sup> IFN beta is more active than IFN alfa in vitro against SARS-CoV-1 and MERS-CoV<sup>2,8,12</sup></p> <p>IFN alfa and IFN beta are active in vitro against SARS-CoV-2 in Vero cells at clinically relevant concentrations;<sup>1</sup> in vitro study suggests SARS-CoV-2 is more sensitive than SARS-CoV-1 to IFN alfa<sup>1,3</sup></p> <p>However, lack of clinical benefit observed with use of type 1 IFNs, generally in combination with ribavirin, for treatment of SARS and MERS<sup>2,8,9,11,12</sup></p> <p>IV IFN beta-1a did not reduce ventilator dependence or mortality in a placebo-controlled trial in patients with acute respiratory distress syndrome (ARDS)<sup>11,17</sup></p> <p><b>Type 3 IFNs (IFN lambda)</b> are thought to provide important immunologic defense against respiratory viral infections<sup>3,4,6,7,19</sup> and may have less potential than type 1 IFNs to produce systemic</p>	<p>Clinical trials are currently evaluating <b>IFN beta-1a</b> or <b>IFN beta-1b</b>, generally added to other antivirals, for treatment of COVID-19, including:<sup>16</sup></p> <p>NCT04492475 (IFN beta-1a)  NCT04465695 (IFN beta-1b)  NCT04494399 (IFN beta-1b)  NCT04324463 (IFN beta)  NCT04343768 (IFN beta-1a, IFN beta-1b)  NCT04385095 (SNG001 [inhaled IFN beta-1a]) (manufacturer announced very preliminary “positive” findings for a hospitalized subset of patients in a press release, but rigorous reporting of complete findings still pending<sup>22</sup>).</p> <p>Open-label, randomized study in Hong Kong in hospitalized adults with COVID-19, mainly mild disease (NCT04276688): Combination regimen of <b>LPV/RTV, ribavirin, and sub-Q IFN beta-1b</b> (IFN beta-1b was omitted to avoid proinflammatory effects when treatment was initiated 7-14 days after symptom onset) was associated with shorter median time from treatment initiation to negative RT-PCR result in nasopharyngeal swab (7 vs 12 days), earlier resolution of symptoms (4 vs 8 days), and shorter hospital stay (9 vs 14.5 days) compared with control (LPV/RTV). In the subset of patients initiating treatment 7 or more days after symptom onset (i.e., those not treated with IFN beta-1b), there was no significant difference in time to negative RT-PCR result, time to resolution of symptoms, or duration of hospital stay between the combination regimen (LPV/RTV and ribavirin) and control (LPV/RTV). IFN beta-1b (8 million units on alternate days) was administered for 1, 2, or 3 doses when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset (median of 2 IFN beta-1b doses given); 52 of 86 patients (60%) randomized to combination regimen received all 3 drugs, and 41 patients received control LPV/RTV.<sup>10</sup></p> <p>Open-label, randomized study in Iran in hospitalized adults with severe suspected or RT-PCR-confirmed COVID-19: <b>IFN beta-1a</b> (12 million units sub-Q 3 times weekly for 2 weeks) plus standard care (7- to</p>	<p><b>IFN beta-1b</b> 8 million units was given sub-Q on alternate days for 1, 2, or 3 doses (when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset) in conjunction with 14-day regimen of LPV/RTV and ribavirin.<sup>10,16</sup></p> <p>In an open-label, randomized study in hospitalized adults with severe COVID-19, <b>IFN beta-1a</b> 12 million units was given sub-Q 3 times weekly for 2 weeks.<sup>20</sup></p> <p><b>IFN alfa:</b> Chinese guidelines suggest IFN alfa dosage of 5 million units (or equivalent) twice daily via atomization inhalation for treatment of COVID-19.<sup>13</sup></p> <p><b>Peginterferon lambda-1a:</b>  For <i>treatment</i> of COVID-19 in adults (NCT04354259, NCT04388709): Peginterferon lambda-1a 180 mcg sub-Q; number of doses (1 dose or 2 doses given 1 week apart) depends on the protocol.<sup>5</sup></p> <p>For <i>postexposure prophylaxis</i> of CoV-2 infection in adults (NCT04344600): Two 180-mcg sub-Q doses of peginterferon lambda-1a given 1 week apart.<sup>5</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of IFNs for treatment of severe or critical COVID-19, except in the context of a clinical trial. The panel also states there are insufficient data to recommend either for or against use of IFN beta for the treatment of early (i.e., &lt;7 days from symptom onset) mild or moderate COVID-19. No benefit was observed with use of IFNs for treatment of other severe or critical coronavirus infections (SARS, MERS), and toxicity of IFNs outweighs the potential for benefit. IFNs may have antiviral activity early in the course of SARS-CoV-2 infection; however, there are insufficient data to assess the potential benefit of IFN use during early disease versus the risk of toxicity.<sup>11</sup></p> <p>Surviving Sepsis Campaign COVID-19 subcommittee states that there is insufficient evidence to issue a recommendation on use of interferons, alone or in combination with antivirals, in critically ill adults with COVID-19.<sup>12</sup></p> <p>Interferon alfa via atomization inhalation is included in Chinese guidelines as a possible option for treatment of COVID-19.<sup>13</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
		<p>inflammatory response, including inflammatory effects on respiratory tract;<sup>4, 7, 19</sup> IFN lambda receptor is expressed mainly on epithelial (including respiratory epithelial) cells and neutrophils, and is distinct from the ubiquitous type 1 IFN receptor;<sup>2, 4, 7, 19</sup> despite different receptors and expression patterns, type 1 and type 3 IFNs activate similar signaling cascades;<sup>4, 7, 19</sup> unknown whether limited receptor distribution might also affect efficacy<sup>4</sup></p>	<p>10-day regimen of hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir (n = 42) was compared with standard care (control; n = 39). Time to clinical response (primary outcome; defined as hospital discharge or 2-score improvement in a 6-category ordinal scale) did not differ significantly between the IFN beta-1a group and the control group (9.7 vs 8.3 days); durations of hospital stay, ICU stay, and mechanical ventilation also did not differ between the groups. Discharge rate on day 14 (67% vs 44%) was higher and 28-day overall mortality rate (19 vs 44%) was significantly lower with IFN beta-1a compared with control; early initiation of IFN beta-1a (&lt;10 days after symptom onset), but not late initiation of the drug (≥10 days after symptom onset), was associated with reduced mortality. <b>NOTE:</b> Total of 92 patients were randomized; results are based on the 42 IFN beta-1a-treated patients and 39 control patients who completed the study. Diagnosis of COVID-19 was based on RT-PCR testing (64%) or clinical manifestations/imaging findings (36%). Other concomitant therapies included corticosteroids and immune globulin (IFN beta-1a group: 62 and 36%, respectively; control group: 44 and 26%, respectively). Patients were recruited from general, intermediate, and ICU wards; 45% of the IFN beta-1a-treated patients and 59% of the control patients were admitted to ICU; 36 and 44%, respectively, required invasive mechanical ventilation. Mean time from symptom onset to treatment initiation was 11.7 days for the IFN beta-1a group and 9.3 days for the control group.<sup>20</sup></p> <p><b>Aerosolized IFN alfa</b> (not commercially available in U.S.) has been used in China in children and adults for treatment of COVID-19,<sup>13, 14, 15</sup> but limited clinical data presented to date.<sup>11</sup> In a retrospective study of 77 hospitalized adults with moderate COVID-19 disease who received aerosolized IFN alfa-2b (5 million units twice daily) (n = 7), umifenovir (Arbidol®) (n = 24), or both drugs (n = 46), time from symptom onset to negative RT-PCR result in throat swab appeared to be shorter in those receiving IFN</p>		

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			<p>alfa-2b alone or in combination with umifenovir compared with those receiving umifenovir alone; this exploratory study was small and nonrandomized, and treatment groups were of unequal size and demographically unbalanced in age, comorbidities, and time from symptom onset to treatment.<sup>15</sup></p> <p><b>Sub-Q peginterferon lambda-1a</b> (not commercially available in U.S.) is being evaluated for <i>treatment</i> (e.g., NCT04354259, NCT04388709) and <i>postexposure prophylaxis</i> (e.g., NCT04344600) of SARS-CoV-2 infection.<sup>5</sup></p>		
<p>Nitric oxide (inhaled)</p> <p><i>Updated 10/1/20</i></p>	<p>48:48 Vaso-dilating Agent</p>	<p>Selective pulmonary vasodilator with bronchodilatory and vasodilatory effects in addition to other systemic effects mediated through cGMP-dependent or independent mechanisms; may be useful for supportive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19<sup>2, 3, 9, 11, 14</sup></p> <p>Also has been shown to have antiviral effects.<sup>1, 14</sup> In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV-1)<sup>1, 14</sup></p> <p>In a small pilot study (Chen et al.) conducted during the SARS outbreak, treatment with inhaled nitric oxide was found to reverse pulmonary hypertension, improve severe hypoxia, and shorten the duration of ventilatory support in critically ill SARS patients.<sup>2, 3</sup></p> <p>Genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential benefit in patients with COVID-19<sup>1, 14</sup></p>	<p>Randomized controlled studies of inhaled nitric oxide in ARDS patients have generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment).<sup>4, 5, 6, 9</sup> Experience with inhaled nitric oxide specifically in COVID-19 patients is limited.<sup>15, 16</sup></p> <p>In a published case report, improvement in PaO<sub>2</sub> and oxygen saturations was observed after administration of inhaled nitric oxide in a 12-year-old patient with COVID-19 and severe thrombocytopenia who required mechanical ventilation; the dose of nitric oxide was not reported and the patient was treated with various other therapies.<sup>17</sup> Another case report described use of inhaled nitric oxide (obtained through an emergency investigational new drug application) in an outpatient setting to treat exacerbations of pulmonary arterial hypertension in a 34-year-old patient with concomitant COVID-19; however, the generalizability of this case study finding is limited.<sup>13</sup></p> <p>In a small case series, administration of inhaled nitric oxide (20 ppm for 30 minutes initially, with option to extend duration if response observed) to 10 mechanically ventilated patients with severe COVID-19 had a negligible effect on oxygenation (i.e., PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> did not change substantially).<sup>15</sup> Another report described the use of inhaled nitric oxide (25 ppm) in 16 mechanically ventilated COVID-19 patients with refractory hypoxemia and/or right ventricular dysfunction. Overall, nitric oxide</p>	<p>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)<sup>2</sup></p> <p>Various dosing protocols using different methods of delivery are being evaluated in ongoing studies in COVID-19 patients<sup>3</sup></p>	<p>The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign recommend against the routine use of inhaled nitric oxide in mechanically ventilated adults with COVID-19 and ARDS.<sup>10, 12</sup></p> <p>These experts state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; however, if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment.<sup>10, 12</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>did not improve oxygenation in these patients, but there was a trend towards response in patients with right ventricular dysfunction.<sup>16</sup></p> <p>Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway, including the following trials: NCT04388683 (NO-COVID-19), NCT04383002, NCT04421508 (COViNOX), NCT04397692, NCT04338828 (NO COV-ED), NCT04305457 (NoCovid), NCT04306393 (NOSARSCOVID), NCT04312243 (NOpreventCOVID)<sup>3</sup></p>		
<p>Ruxolitinib (Jakafi<sup>®</sup>)</p> <p><b>Updated 10/8/20</b></p>	<p>10:00 Antineoplastic Agents</p>	<p>Janus kinase (JAK) 1 and 2 inhibitor;<sup>7</sup> may potentially combat cytokine release syndrome (CRS) in severely ill patients<sup>4,5</sup></p> <p>May reduce inflammation via JAK inhibition, but study based on artificial intelligence (AI)-derived methodology suggests that clinically tolerated concentrations of ruxolitinib may be unlikely to reduce viral infectivity by disrupting regulators of endocytosis (e.g., AP2-associated protein kinase 1 [AAK1]).<sup>16</sup> (See Baricitinib entry in this table.)</p> <p>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<sup>5,7</sup></p>	<p>Limited published clinical trial evidence regarding efficacy and safety in patients with COVID-19</p> <p><b>Single-hospital retrospective chart review:</b> Based on the hospital's COVID-19 treatment algorithm, patients with severe COVID-19 were prospectively stratified using a newly developed clinical inflammation score (CIS; maximum score = 16); those identified as being at high risk for systemic inflammation (CIS <math>\geq</math>10, without sepsis) were evaluated for ruxolitinib treatment; 14 patients received ruxolitinib (median cumulative dose: 135 mg [52.5-285 mg], median treatment duration: 9 days [5-17 days]) initiated at a median of 15.5 days (5-24 days) after symptom onset. A decrease in CIS of <math>\geq</math>25% from baseline to day 7 was observed in 12 of 14 patients. At baseline, 10 required noninvasive ventilation, 3 required supplemental oxygen, and 1 required invasive ventilation.<sup>14</sup></p> <p><b>Prospective, randomized, single-blind, placebo-controlled study in adults with severe COVID-19:</b> Patients received ruxolitinib (5 mg orally twice daily) plus standard care (n = 20) or placebo (ascorbic acid 100 mg orally twice daily) plus standard care (n = 21); <b>no significant difference observed between ruxolitinib and placebo in time to clinical improvement</b> (defined as hospital discharge or a 2-point improvement on a 7-category ordinal scale) <b>although median time to improvement was numerically shorter with ruxolitinib (12 vs 15 days).</b> Chest CT improvement observed</p>	<p>Various dosages are being evaluated<sup>3, 6, 10</sup></p> <p><b>Phase 3 study (NCT04362137):</b> Ruxolitinib 5 mg orally twice daily for 14 days with possible extension to 28 days<sup>10</sup></p> <p><b>Phase 3 study (NCT04377620):</b> Ruxolitinib 5 or 15 mg orally twice daily (approximately every 12 hours)<sup>12</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial.<sup>8</sup></p> <p><b>Severe reactions</b> requiring drug discontinuance observed in 2 COVID-19 patients following initiation of ruxolitinib: purpuric lesions with thrombocytopenia and deep-tissue infection in one patient, and progressive decrease in hemoglobin and erythrodermic rash over the whole body surface area in the second patient; these cases differed in the timing of ruxolitinib initiation and the severity of COVID-19 illness<sup>11</sup></p>

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			<p>at day 14 in greater proportion of ruxolitinib-treated vs placebo-treated patients (90 vs 62%). By day 28, 3 patients had died (all 3 in placebo group). <b>Note:</b> Median time from symptom onset to randomization was 20 days; most patients in both treatment groups received systemic corticosteroids (71%) and antivirals (90%). Study excluded critically ill and ventilator-dependent patients. Interpretation is limited by small sample size.<sup>13</sup></p> <p><b>**Compassionate use of ruxolitinib in mainly older adults with RT-PCR-confirmed COVID-19 with severe respiratory manifestations but not requiring invasive mechanical ventilation in Italy:</b> Patients (n = 34) received ruxolitinib (5 mg twice daily, increased to 10 mg twice daily or 25 mg daily if respiratory function not improved); ruxolitinib was initiated at a median of 8 days after symptom onset; median dose was 20 mg daily and median treatment duration was 13 days. Median patient age was 80.5 years (53% were ≥80 years of age and 35% were 60-79 years of age); 85% of patients had ≥2 comorbidities. Concomitant therapies included hydroxychloroquine (91%), antimicrobials (77%), antivirals (62%), and corticosteroids (29%). Cumulative incidence of clinical improvement (decrease of ≥2 categories on a 7-category ordinal scale within 28 days) was 82%; overall survival at day 28 was 94%. Clinical improvement was not affected by low-flow versus high-flow oxygen support but was less frequent in patients with PaO<sub>2</sub>/FiO<sub>2</sub> ratio &lt;200.<sup>17</sup></p> <p><b>Compassionate use of ruxolitinib in combination with eculizumab</b> (a terminal complement inhibitor) in adults with RT-PCR-confirmed COVID-19 and associated pneumonia or acute respiratory distress syndrome (ARDS) in Italy: Consecutive patients received ruxolitinib (10 mg twice daily for 14 days) and eculizumab (900 mg IV once weekly for 2 or 3 doses) (n = 7) or best available therapy (n = 10; control). Greater improvement in median PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio and greater increase in platelet count observed on day 7 in</p>		

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			<p>patients receiving ruxolitinib and eculizumab compared with control patients. All patients received antibiotic prophylaxis (azithromycin) and all patients except 2 in control group received hydroxychloroquine; greater proportion of patients in the ruxolitinib and eculizumab group compared with the control group received low-dose corticosteroids (5/7 vs 3/10) and sub-Q heparin (7/7 vs 5/10). Randomized, controlled trials needed to confirm these preliminary data.<sup>15</sup></p> <p><b>**Small retrospective cohort study of adults with RT-PCR-confirmed COVID-19 and associated ARDS:</b> Total of 18 patients with PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 100 to &lt;200 and rapid clinical worsening of respiratory function received ruxolitinib (20 mg twice daily for initial 48 hours, with subsequent step-wise dosage reductions based on response, for a maximum of 14 days of treatment); ruxolitinib was initiated at a median of 9 days after symptom onset. Other therapies were used according to local practice. Clinical improvements in respiratory function within 48 hours and avoidance of mechanical ventilation reported in 16 patients; spontaneous breathing with pO<sub>2</sub> &gt;98% reported on day 7 in 11 patients; no response reported in 2 patients. No patients died.<sup>18</sup></p> <p><b>Phase 3 randomized, double-blind, placebo-controlled clinical trial</b> (NCT04362137; RUXCOVID) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Novartis)<sup>1,10</sup></p> <p><b>Phase 3, randomized, double-blind, placebo-controlled clinical trial</b> (NCT04377620; RUXCOVID-DEVENT) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in patients ≥12 years of age with COVID-19-associated acute respiratory distress syndrome (ARDS) who require mechanical ventilation (sponsored by Incyte)<sup>12</sup></p>		

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			<p><b>Expanded-access (managed-access, compassionate use) program</b> (NCT04337359) available for eligible adults and children ≥6 years of age with <b>severe or very severe COVID-19</b> illness; address inquiries to Incyte (855-463-3463 or <a href="mailto:medinfo@incyte.com">medinfo@incyte.com</a>)<sup>1, 2</sup></p> <p><b>Expanded-access program</b> (NCT04355793) available for emergency treatment of <b>cytokine storm</b> from COVID-19 infection in adults and pediatric patients ≥12 years of age; address inquiries to Incyte (855-463-3463 or <a href="mailto:medinfo@incyte.com">medinfo@incyte.com</a>)<sup>9</sup></p> <p>Other clinical trials also registered, including:<sup>3</sup>  NCT04338958  NCT04348695  NCT04403243  NCT04477993</p>		
Sarilumab (Kevzara®) <i>Updated 9/10/20</i>	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Sarilumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients <sup>1, 2, 5, 7</sup>	<p>Preliminary unpublished data from randomized clinical trials have not demonstrated efficacy in treatment of patients with COVID-19<sup>7, 11, 12</sup></p> <p>However, based on encouraging results in China with a similar drug, tocilizumab, a <b>large, U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled, adaptively designed study</b> (NCT04315298) evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 was performed.<sup>3, 4, 7, 9, 10, 12</sup> Patients in this study were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Randomization was stratified by severity of illness (e.g., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids.<sup>7, 12</sup> In the phase 2 part of the study, sarilumab at both dosages reduced C-reactive protein (CRP) levels.<sup>7</sup> The primary efficacy outcome measure in phase 3 was the change on a 7-point scale; this phase was modified to focus on the 400-mg dose of sarilumab in the critically ill patient group.<sup>7</sup> During the course of the trial, there were many amendments that increased the sample size and modified the dosing strategies, and multiple interim analyses were performed.<sup>7, 9</sup> The results did not demonstrate a clinical benefit of</p>	<p><b>Large US-based controlled study (NCT04315298):</b> Dosage of 400 mg IV as a single dose or multiple doses (based on protocol criteria); the lower-dose (200-mg) treatment arm was discontinued following a preliminary analysis of study results<sup>9, 10</sup> (see Trials or Clinical Experience)</p> <p>Note: IV formulation not commercially available in the U.S., but was studied in the above-mentioned clinical trial. The sub-Q formulation is not FDA-labeled to treat cytokine release syndrome (CRS) in the U.S.<sup>7</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of sarilumab in the treatment of COVID-19, except in a clinical trial<sup>7</sup></p> <p>No new safety findings observed with use in COVID-19 patients<sup>9</sup></p>

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			<p>sarilumab for any of the disease severity subgroups or dosing strategies studied.<sup>7,9,12</sup></p> <p><b>A second manufacturer-sponsored phase 3 clinical trial was conducted in countries outside the U.S.</b> (Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Spain) in 420 severely or critically ill patients hospitalized with COVID-19 did not meet its primary endpoint and key secondary endpoint when sarilumab was compared with placebo in addition to usual hospital care. Although not statistically significant, trends were observed toward a decrease in duration of hospital stay, an acceleration in time to improved clinical outcomes, reduced mortality in the critically ill patient group not seen in the severely ill group, and a shortened time to discharge.<sup>9,11</sup></p> <p><b>Italian case series (Benucci et al.)</b> describes 8 patients hospitalized with COVID-19 pneumonia at one hospital in Florence treated with sarilumab (initial 400-mg IV dose followed by 200-mg IV doses after 48 and 96 hours) in addition to standard therapy (hydroxychloroquine, azithromycin, darunavir, cobicistat, enoxaparin). Treatment was started within 24 hours of hospitalization. Sarilumab was used in these patients because of a lack of tocilizumab at this institution. Seven of the patients demonstrated an improvement in oxygenation and lung echo score and were discharged within 14 days; the remaining patient died in 13 days.<sup>8</sup></p> <p><b>Multiple clinical trials to evaluate sarilumab for treatment of COVID-19</b> are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a><sup>10</sup></p> <p><b>For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)</b><sup>6</sup></p>		
<p>Siltuximab (Sylvant®)</p> <p><i>Updated 9/10/20</i></p>	<p>10:00 Antineoplastic agents</p>	<p>Recombinant chimeric monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients<sup>1-5</sup></p>	<p>Only limited, unpublished data available describing efficacy in patients with COVID-19</p> <p><b>Italy:</b> Non-peer-reviewed findings from an observational cohort study of 30 patients with COVID-19 and pneumonia/acute respiratory distress syndrome (ARDS) who</p>	<p>In the SISCO study in Italy, patients received an initial dose of siltuximab 11 mg/kg by IV infusion over 1 hour; a second dose could be administered at the physician's discretion<sup>4</sup></p> <p>Other clinical studies under way are evaluating a single siltuximab dose of 11 mg/kg by IV infusion<sup>7,8</sup></p>	<p>Efficacy and safety of siltuximab in the treatment of COVID-19 not established</p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of siltuximab in the treatment of COVID-19, except in a clinical trial<sup>9</sup></p>

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			<p>participated in a compassionate use program in one hospital in Italy (SISCO study; NCT04322188) and were followed for at least 30 days showed reduced C-reactive protein (CRP) levels by day 14. The siltuximab-treated patients were compared with 30 propensity score-matched patients receiving best supportive care. The 30-day mortality rate was substantially lower in the siltuximab group compared with the matched-control cohort. Out of the 30 patients treated with siltuximab, 16 (53%) were discharged from the hospital, 4 (13%) remained hospitalized on mechanical ventilation, and 10 patients died.<sup>4,6</sup></p> <p>Other clinical trials evaluating siltuximab in the treatment of COVID-19 currently are recruiting in <b>Belgium</b> (NCT04330638),<sup>7</sup> <b>Spain</b> (NCT04329650),<sup>8</sup> and <b>Saudi Arabia</b> (NCT04486521)<sup>10</sup></p>		
<p>Sirolimus (Rapamune®)</p> <p><i>Updated 8/6/20</i></p>	<p>92:44 Immunosuppressive agent; mammalian target of rapamycin (mTOR) inhibitor</p>	<p>mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus<sup>1,2,5</sup></p> <p>In vitro studies demonstrated inhibitory activity against MERS-CoV infection<sup>2</sup></p> <p>Limited experience in patients with H1N1 pneumonia suggests possible benefit; in one study, treatment with sirolimus 2 mg daily in conjunction with corticosteroids for 14 days was associated with improved patient outcomes (e.g., shortened duration of mechanical ventilation, improved hypoxia and multiorgan function)<sup>3</sup></p> <p>T cell dysregulation has been observed in patients with severe COVID-19 and is thought to be a possible cause of cytokine storm; when given early prior to</p>	<p>Clinical trials evaluating sirolimus for the treatment of COVID-19 are planned or underway including the following trials:<sup>4</sup></p> <p>NCT04341675 (SCOPE)</p> <p>NCT04374903 (COVID19-HOPE)</p> <p>NCT04371640</p> <p>NCT04461340</p> <p>NCT04482712 (RAPA-CARDS)</p>	<p>Various dosing regimens are being evaluated in registered trials<sup>4</sup></p>	<p>Although possible clinical application, current data not specific to COVID-19; additional study needed<sup>5</sup></p>

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<p>Tocilizumab (Actemra®)</p> <p><i>Updated 9/10/20</i></p>	<p>92:36 Disease-modifying Anti-rheumatic Drug</p>	<p>the cytokine storm phase, sirolimus may prevent progression to severe COVID-19 by restoring T-cell functionality<sup>7</sup></p> <p>Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients<sup>1-3, 6, 9,10, 14</sup></p>	<p>Preliminary unpublished data from randomized clinical trials have not demonstrated efficacy in treatment of patients with COVID-19<sup>9</sup></p> <p>Case reports and observational and open studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world<sup>1, 3, 5, 10, 12, 15, 17</sup></p> <p>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></p> <p>In a retrospective, observational study in China (Luo et al.) involving 15 patients moderately to critically ill with COVID-19, tocilizumab (80-600 mg per dose) was given, and was used in conjunction with methylprednisolone in 8 of the patients. About one-third of the patients received 2 or more doses of tocilizumab. Elevated C-reactive protein (CRP) levels rapidly decreased in most patients following treatment, and a gradual decrease in IL-6 levels was noted in patients who stabilized following tocilizumab administration. Clinical outcomes were equivocal.<sup>10</sup></p> <p>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.<sup>12</sup></p>	<p>Tocilizumab is typically given IV to treat cytokine release syndrome (CRS) and in patients with COVID-19; however, the drug has been given subcutaneously in some patients<sup>9, 17</sup></p> <p>The subcutaneous formulation of tocilizumab is <i>not</i> intended for IV use<sup>9</sup></p> <p>IV infusion: <b>China</b> 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></p> <p><b>US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA):</b> 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></p>	<p><b>In China</b>, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels<sup>2</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of tocilizumab in the treatment of COVID-19, except in a clinical trial<sup>9</sup></p> <p>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></p>

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			<p><b>Italy:</b> A prospective, open, single-arm, multicenter study evaluated use of tocilizumab in 63 hospitalized adults with severe COVID-19. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg) based on drug availability; a second dose given within 24 hours was administered to 52 of the 63 patients. Following tocilizumab administration, fevers resolved in all but one patient within 24 hours and C-reactive protein (CRP), ferritin, and D-dimer levels declined from baseline to day 14. The PaO<sub>2</sub>/FiO<sub>2</sub> ratio improved between admission and Day 7. Overall mortality was 11%. Tocilizumab appeared to be well tolerated.<sup>17</sup></p> <p>Zhang et al. from China reported on a patient with COVID-19 and multiple myeloma who appeared to be successfully treated with tocilizumab.<sup>13</sup></p> <p>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.<sup>1, 5, 7, 8</sup></p> <p><b>France:</b> An open-label, phase 2, randomized clinical trial (CORIMUNO-TOCI, NCT04331808) is under way at Assistance Publique – Hôpitaux de Paris hospitals in Paris. Interim results from this study have been released in a press release (non-peer-reviewed). Sixty-five out of 129 adults with moderate to severe COVID-19 pneumonia not requiring intensive care upon admission were randomized to receive tocilizumab 8 mg/kg (1–2 doses) along with standard of care, and 64 patients were randomized to receive standard of care alone. A significantly lower proportion of the patients in the tocilizumab arm attained the primary outcome of need for ventilation or death at day 14. Results of this study will be submitted for publication in a peer-reviewed journal.<sup>15, 16</sup></p> <p><b>China:</b> Randomized, multicenter, controlled clinical trial evaluating efficacy &amp; safety in 188 patients with COVID-19 under way through 5/10/20. <b>Results not yet available.</b> Chinese Clinical Trial Registry link:</p>		

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			<p><a href="http://www.chictr.org.cn/showprojen.aspx?proj=49409">http://www.chictr.org.cn/showprojen.aspx?proj=49409</a></p> <p><b>US/Global randomized, placebo-controlled trial:</b> Manufacturer (Roche) conducted a randomized, double-blind, placebo-controlled phase 3 trial (COVACTA; NCT04320615) in collaboration with the US Health and Human Services' Biomedical Advanced Research Development Authority (BARDA). The study evaluated safety and efficacy of tocilizumab in combination with standard of care compared with placebo in adults hospitalized with severe COVID-19 pneumonia. The trial failed to meet its primary endpoint of improved clinical status at week 4 (determined using a 7-point scale to assess clinical status based on need for intensive care and/or ventilator use and requirement for supplemental oxygen) and several key secondary endpoints, including the key secondary endpoint of reduced patient mortality.<sup>18</sup></p>		
<p>Vitamin D</p> <p><i>Updated 9/17/20</i></p>	<p>88:16 Vitamin D</p>	<p>Vitamin D receptor is expressed on immune cells (e.g., B cells, T cells, antigen-presenting cells); these cells can synthesize and respond to active vitamin D.<sup>10,13</sup></p> <p>Vitamin D modulates innate and adaptive immune responses; may downregulate proinflammatory cytokines and upregulate anti-inflammatory cytokines, increase T regulatory cell activity, and reduce cytokine storm induced by innate immune system.<sup>10,12,13</sup></p> <p>Vitamin D deficiency is associated with increased autoimmunity and increased susceptibility to infection.<sup>10,13</sup> In observational studies, low vitamin D concentrations have been associated with increased risk of community-</p>	<p>No known published controlled clinical trial evidence supporting efficacy of vitamin D supplementation for treatment or prevention of COVID-19.</p> <p><b>Prevention of respiratory infections:</b> Efficacy of vitamin D supplementation for prevention of influenza or other respiratory infections is unclear.<sup>10</sup></p> <p>Meta-analysis of 25 randomized, double-blind, placebo-controlled trials including a total of 11,321 participants, either healthy or with comorbidities, indicated a protective effect for oral vitamin D supplementation against acute respiratory infection.<sup>5</sup></p> <p>A second systematic review and meta-analysis of 15 randomized controlled trials involving approximately 7000 healthy individuals found that vitamin D supplementation did not reduce the risk of respiratory infections compared with placebo or no treatment.<sup>11</sup></p> <p><b>Outcomes in critically ill patients:</b> Results of 2 randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with</p>	<p>Various dosages of vitamin D are being evaluated for prevention or treatment of COVID-19.<sup>4</sup></p> <p>High concentrations of vitamin D may cause hypercalcemia and nephrocalcinosis;<sup>1</sup> currently no convincing scientific evidence that very high intake of vitamin D will be beneficial in preventing or treating COVID-19.<sup>14</sup></p> <p>National Academy of Sciences (NAS) guidelines for <b>adequate dietary intake of vitamin D for bone health in US population:</b> Estimated Average Requirement (EAR) in children and adults 1-70 years of age is 400 units (10 mcg) daily; Recommended Dietary Allowance (RDA) in these age groups is 600 units (15 mcg) daily. In adults &gt;70 years of age, EAR is 400 units (10 mcg) daily and RDA is 800 units (20 mcg). These reference values assume minimal sun exposure.<sup>26</sup></p> <p>NAS states that data indicate that a serum 25-hydroxyvitamin D concentration of 50 nmol/L is sufficient to</p>	<p>Efficacy of vitamin D supplementation in the prevention or treatment of COVID-19 has not been established.<sup>1,2,3</sup> Some experts recommend maintaining recommended levels of vitamin D intake during the COVID-19 pandemic to maintain bone and muscle health and avoid deficiency.<sup>2,3,14</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of vitamin D for prevention or treatment of COVID-19.<sup>1</sup></p> <p>Joint guidance from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AAACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF), and International Osteoporosis Foundation (IOF) emphasizes importance of obtaining the recommended daily dosage of vitamin D; for those unable to obtain recommended durations of direct sun exposure during the pandemic, recommended intake of vitamin D can be obtained through</p>

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		<p>acquired pneumonia in older adults and upper respiratory viral infections in children.<sup>1, 8, 9</sup></p> <p>Vitamin D deficiency is common in the U.S., particularly in Hispanic and Black populations (groups overrepresented among U.S. COVID-19 cases).<sup>1, 14, 20</sup></p> <p>Vitamin D deficiency also is more common in older patients and patients with obesity and hypertension (factors potentially associated with worse COVID-19 outcomes).<sup>1, 20, 21, 23-25, 27</sup></p> <p>Association also suggested between vitamin D and diabetes mellitus (a condition also associated with worse COVID-19 outcomes).<sup>20, 22, 27</sup></p> <p>Clinical trials are evaluating the relationship between vitamin D concentration and COVID-19 disease severity and mortality (e.g., NCT04394390, NCT04403932, NCT04487951);<sup>4</sup> some preliminary retrospective observational data suggest an association between vitamin D concentration and COVID-19 risk or severity/mortality,<sup>15-18</sup> but may not account for potential confounding factors.<sup>17-19</sup></p>	<p>vitamin D deficiency (but not with COVID-19) indicated that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D<sub>3</sub>; patients in VITdAL-ICU also received oral maintenance doses (90,000 units monthly for 5 months).<sup>6, 7</sup></p> <p><b>Ongoing COVID-19 trials:</b> Clinical trials are evaluating effects of vitamin D supplementation on COVID-19-associated clinical outcomes, including NCT04344041, NCT04386850, NCT04407286, NCT04482673, NCT04435119, NCT04449718, and NCT04411446.<sup>4</sup></p> <p>Clinical trials also are evaluating efficacy of vitamin D supplementation for prevention of COVID-19, including NCT04386850, NCT04483635, NCT04482673, and NCT04535791.<sup>4</sup></p>	<p>meet the needs of 97.5% of the population and concentrations &lt;30 nmol/L are associated with clinical deficiency.<sup>26</sup></p>	<p>supplemental vitamin D. The joint guidance states that current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19.<sup>2</sup></p> <p>Advisory statement from the UK National Institute for Health and Care Excellence (NICE) states that there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. However, all individuals should continue to follow current recommendations on daily vitamin D supplementation to maintain bone and muscle health during the pandemic.<sup>3</sup></p>
Zinc <i>Updated 8/6/20</i>		Trace mineral involved in immune function, including antibody and white blood cell production; an important cofactor for many enzymes; <sup>1, 3</sup> may improve wound healing <sup>8</sup>	<p>No evidence from controlled trials that zinc is effective in the prevention or treatment of COVID-19.<sup>5, 6</sup></p> <p>Because of its role in immune function and potential to decrease coronavirus replication, zinc is being evaluated in a number of clinical trials in both the prophylaxis and</p>	<p>Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day<sup>3, 8</sup></p> <p>Some clinicians have recommended an elemental zinc intake of 30-50 mg/day in the short-term treatment of influenza and coronavirus infections<sup>3, 4</sup></p>	Despite some anecdotal claims in the media that zinc is effective in treating COVID-19, <sup>6</sup> unclear whether zinc supplementation is beneficial in the prophylaxis and/or treatment of COVID-19; further study is needed <sup>1, 3, 6</sup>

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		<p>Zinc deficiency increases proinflammatory cytokine concentrations (interleukin -1 [IL-1], IL-6, TNF alpha) and decreases antibody production; zinc supplementation increases the ability of polymorphonuclear cells to fight infection<sup>1</sup></p> <p>Possible antiviral activity; zinc appears to inhibit virus RNA polymerase activity and viral replication in an in vitro and cell culture model of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1).<sup>1,7</sup> High-dose zinc supplementation reduced the duration but not severity of common cold symptoms compared with placebo in a meta-analysis<sup>1,3,7</sup></p> <p>Zinc enhances cytotoxicity and induces apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine): chloroquine can enhance intracellular zinc uptake in vitro<sup>9</sup></p> <p>Elderly patients and patients with certain concurrent medical conditions are at higher risk of zinc deficiency<sup>2,3,8</sup></p>	<p>treatment of COVID-19, sometimes in combination with other supplements (including vitamin C, vitamin D, and selenium) and drugs (including hydroxychloroquine)<sup>1,2,5,6</sup></p> <p><b>Retrospective observational study in New York City (Carlucci et al; non-peer-reviewed):</b> Data were collected from electronic medical records to compare outcomes between hospitalized patients with COVID-19 who received hydroxychloroquine, azithromycin, and zinc (411 patients) and those who received hydroxychloroquine and azithromycin alone (521 patients). Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or duration of ICU stay, but patients in the treatment group that included zinc were discharged home more frequently and the need for ventilation, ICU admission, and mortality or transfer to hospice for patients not admitted to the ICU were all reduced in univariate analyses. After adjusting for the timing of when zinc was added to the protocol, findings remained significant for increased frequency of being discharged home and reduction in mortality or transfer to hospice in the zinc-treated patients. Because of the study design and its limitations, the authors state that this study should not be used to guide clinical practice, but that the observations do support initiation of randomized controlled trials investigating zinc in patients with COVID-19.<sup>10</sup></p>	<p>Appropriate dosage regimens not established in either the prophylaxis or treatment of COVID-19; various supplementation regimens being evaluated in clinical trials, with a maximum dosage of zinc sulfate of 220 mg (50 mg of elemental zinc) twice daily<sup>2,5,6,9,10</sup></p> <p>Oral zinc supplementation likely safe in dosages up to 40 mg of elemental zinc daily in adults; safety of dosages exceeding those used in the management of the common cold not known<sup>3,6,8</sup></p>	<p>NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of zinc in the <i>treatment</i> of COVID-19<sup>9</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel <i>recommends against</i> using zinc supplementation above the RDA for the <i>prevention</i> of COVID-19, except in a clinical trial<sup>9</sup></p> <p>Zinc concentrations are difficult to measure accurately since it is distributed as a component of various proteins and amino acids<sup>9</sup></p> <p>Adverse effects may include nausea (possibly dose dependent), vomiting, and changes in taste<sup>1,6,7,8</sup></p> <p>Long-term zinc supplementation may cause copper deficiency with adverse hematologic and neurologic effects; zinc supplementation for as little as 10 months has been associated with copper deficiency<sup>9</sup></p> <p>Intranasal administration should be avoided because of reports of prolonged or permanent loss of the sense of smell; intranasal zinc formulations are no longer commercially available in the US<sup>6,8</sup></p> <p>Potential for interactions with iron and copper, certain antibiotics (e.g., quinolones, tetracyclines), and other medications<sup>8</sup></p>

## OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
<p>ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)</p> <p><b>Updated 10/1/20</b></p>	<p>24:32 Renin-Angiotensin-Aldosterone System Inhibitor</p>	<p><b>Hypothetical harm:</b> Human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2).<sup>1,4,5</sup> Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs.<sup>1,4,8</sup> Increased expression of ACE2 may potentially facilitate COVID-19 infections.<sup>1</sup></p> <p><b>Hypothetical benefit:</b> ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.<sup>1,2,6</sup></p>	<p>Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection.<sup>1-3,9</sup></p> <p><b>Large, observational study analyzed a cohort of pts tested for COVID-19 to evaluate the relationship between previous treatment with 5 common classes of antihypertensive agents (including ACE inhibitors, ARBs) and the likelihood of a positive or negative test result for COVID-19 as well as the likelihood of severe COVID-19 illness among pts who tested positive:</b> Study included data obtained from a large health network in New York City for 12,594 pts who were tested for COVID-19 from Mar 1 to Apr 15, 2020. Among these pts, 4357 (34.6%) had a history of hypertension. Of these patients, 2573 (59.1%) tested positive for COVID-19. Among the 2573 pts with hypertension and positive results for COVID-19, 634 pts (24.6%) had severe disease (i.e., indicated by ICU admission, mechanical ventilation, or death). Results of COVID-19 testing were stratified in propensity-score-matched patients with hypertension according to previous treatment with selected antihypertensive agents. Propensity-score matching was based on age, sex, race, BMI, medical history, various comorbidities, and other classes of medications. The authors stated that no substantial increase was observed in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive in association with any single antihypertensive class (including ACE inhibitors, ARBs).<sup>13</sup></p> <p><b>Large, population-based case-control study was conducted to evaluate the association between the use of RAAS blockers (including ACE inhibitors, ARBs) and the risk of COVID-19:</b> Study included data obtained from a regional healthcare database in the Lombardy region of Italy for 6272 case pts with confirmed severe COVID-19 acute respiratory syndrome from Feb 21 to Mar 11, 2020 who were</p>		<p>American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) recommend continuation of treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.<sup>2,3</sup> These experts state there is a lack of experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients receiving ACE inhibitors or ARBs. Further study is needed.<sup>2,3</sup></p> <p>NIH COVID-19 Treatment Guidelines Panel states patients who are receiving an ACE inhibitor or ARB for cardiovascular disease (or other indications) should continue receiving these drugs. The panel <b>recommends against</b> use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial. These experts state there is a lack of sufficient clinical evidence demonstrating that ACE inhibitors or ARBs have any impact on the susceptibility of individuals to SARS-CoV-2 or on the severity or outcomes of COVID-19 infection.<sup>9</sup></p> <p>Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.<sup>1,4</sup></p> <p>Abrupt withdrawal of RAAS inhibitors in high-risk patients (e.g., heart failure patients, patients with prior myocardial infarction) may lead to clinical instability and adverse health outcomes.<sup>8</sup></p>

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			<p>matched to 30,759 controls based on sex, age, and place of residence. Information about use of selected drugs and clinical profiles was obtained from regional healthcare databases. Use of ACE inhibitors or ARBs was more frequent in patients with COVID-19 than among controls because of their higher prevalence of cardiovascular disease. Percentage of patients receiving ACE inhibitors was 23.9% for case pts and 21.4% for controls. Percentage of patients receiving ARBs was 22.2% and 19.2% for case and control pts, respectively. The authors concluded that there was no evidence that treatment with ACE inhibitors or ARBs significantly affected the risk of COVID-19 or altered the course of infection or resulted in more severe disease.<sup>14</sup></p> <p><b>Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to evaluate the relationship between cardiovascular disease and preexisting treatment with ACE inhibitors or ARBs with COVID-19 (Mehra et al; now retracted):</b> Original publication included multinational data for 8910 pts hospitalized with COVID-19 between Dec 20, 2019 and Mar 15, 2020 that were obtained from a global healthcare data collaborative. The authors concluded that those data confirmed previous observations suggesting that underlying cardiovascular disease is independently associated with an increased risk of death in hospitalized pts with COVID-19. They also stated that they were not able to confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital mortality.<sup>10</sup> <b>Note: This published study has now been retracted by the publisher at the request of the original authors. Concerns were raised with respect to the veracity of the data and analyses that were the basis of the authors' conclusions.</b><sup>11,12</sup></p> <p>Clinical trials underway (losartan): Initiation of losartan in adults with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009).<sup>7</sup></p>		

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			<p>Initiation of the drug in adults with COVID-19 not requiring hospitalization; primary outcome measure: treatment failure resulting in hospital admission (NCT04311177).<sup>7</sup></p> <p>Other clinical trials have been initiated in various countries to evaluate the effect of continuing or discontinuing treatment with ACE inhibitors or ARBs on clinical outcomes in patients with COVID-19, including the following trials registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>:<sup>7</sup></p> <p>NCT04329195 NCT04331574 NCT04338009 NCT04351581 NCT04353596 NCT04357535</p>		
<p>Anticoagulants</p> <p><i>Updated 9/3/20</i></p>	<p>20:12.04 Anti-coagulants</p>	<p>Patients with COVID-19, particularly those with severe disease, may develop a hypercoagulable state, which has been associated with poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).<sup>1-6, 14, 16, 28, 29</sup></p> <p>Most common pattern of coagulopathy in hospitalized COVID-19 patients is characterized by elevated D-dimer levels, high fibrinogen levels, minimal prolongation of aPTT and/or PT, and mild thrombocytopenia; microvascular and macrovascular thrombosis also have been reported.<sup>1-6, 9, 11, 13, 16, 26, 27, 29</sup> In addition, high rates of VTE have been observed in critically ill patients with COVID-19.<sup>7, 8, 11, 15, 18, 28, 36</sup></p> <p>Pathogenesis of COVID-19-related coagulopathy not completely known, but may be related to an</p>	<p>Limited data from a retrospective study in China showed reduced mortality in COVID-19 patients with severe sepsis-induced coagulopathy or markedly elevated D-dimer levels (&gt;6 x ULN) who received prophylactic anticoagulation (low molecular weight heparin [LMWH] or unfractionated heparin [UFH]).<sup>4, 19</sup></p> <p>Observational data derived from a single health system in the US suggested possible association between therapeutic-dose anticoagulation and decreased mortality. Among 786 patients who received systemic anticoagulation during their hospital course, mortality rate was 22.5% and median survival was 21 days compared with mortality rate of 22.8% and median survival of 14 days in those who did not receive systemic anticoagulation. In patients who required mechanical ventilation, mortality rate was 29.1% and median survival was 21 days for those receiving anticoagulation compared with a 62.7% mortality rate and a median survival of 9 days for those who did not receive anticoagulation. However, the study had important limitations (e.g., indications for anticoagulation initiation and details on patient characteristics not reported).<sup>28, 31</sup></p> <p>In a subsequent retrospective study involving a larger cohort of patients (n=4389)</p>	<p>See Comments column for available dosage-related information.</p>	<p>Additional study is needed to understand the anticoagulant needs of COVID-19 patients.<sup>9, 11, 27-29</sup> VTE risk should be assessed in all patients on an individual basis.<sup>4, 5, 10, 17, 18, 27, 28, 32</sup></p> <p>Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy.<sup>4, 5, 9, 25, 27, 28, 30, 32</sup></p> <p>The NIH COVID-19 Treatment Guidelines Panel recommends VTE prophylaxis according to the usual standard of care in all hospitalized adults with COVID-19 unless contraindicated.<sup>28</sup></p> <p>WHO recommends pharmacologic prophylaxis (e.g., LMWH) according to local and international standards for prevention of VTE in adults and adolescents hospitalized with COVID-19 unless contraindicated.<sup>25</sup></p> <p>The International Society for Thrombosis and Haemostasis and American Society of Hematology recommend that all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, severe thrombocytopenia, fibrinogen &lt;0.5 g/L).<sup>4, 5</sup></p>

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		<p>uncontrolled immuno-thrombotic response to viral infection.<sup>16, 17, 27-29, 32</sup></p> <p>Potential benefits of anti-coagulant therapy include prevention and treatment of thromboembolic complications; some anticoagulant agents also may have antiviral and anti-inflammatory properties.<sup>2, 4, 5, 14, 25, 27, 40</sup></p>	<p>from the same health system, use of prophylactic or therapeutic anticoagulation was associated with lower in-hospital mortality compared with no anticoagulant therapy (adjusted hazard reductions of 50 and 47%, respectively). In addition, the risk of intubation was about 30% lower in patients treated with either prophylactic or therapeutic anticoagulation. Overall bleeding rates were low, but higher in the therapeutic anticoagulation group (3%) compared with the prophylactic anticoagulation (1.7%) and no anticoagulation (1.9%) groups. Among 26 autopsies performed in this cohort of patients, 42% had evidence of thromboembolic disease not otherwise suspected premortem; the majority of these patients were not treated with therapeutic anticoagulation. Because a variety of anticoagulants were used in these patients including LMWH, UFH, and direct oral anticoagulants, no conclusions can be drawn regarding optimal choice of anticoagulant. The study is limited by its observational design; randomized controlled studies are needed to confirm findings.<sup>40</sup></p> <p>In a retrospective study in 2075 patients with COVID-19 who were admitted to one of 17 hospitals in Spain, use of heparin appeared to be associated with reduced mortality (adjusted for age and gender), and the association remained significant when adjusted for oxygen saturation, temperature, and other concomitant drug therapy; however, the dose, duration, and method of administration of heparin were not reported.<sup>38</sup></p> <p>NIH is planning to evaluate safety and efficacy of various types of anticoagulants in the treatment of adults with COVID-19 in a series of adaptive trials (The Accelerating COVID-19 Therapeutic Interventions and Vaccines [ACTIV-4] studies).<sup>41</sup></p> <p>Additional clinical trials have been initiated or currently are underway to evaluate anti-coagulant strategies in patients with COVID-19, including the following:<sup>12</sup> NCT04512079 (FREEDOM), NCT04406389 (IMPACT), NCT04362085,</p>		<p>LMWH or UFH may be preferred over oral anticoagulants in critically ill hospitalized patients with COVID-19 because of their shorter half-lives, ability to be administered parenterally, and fewer drug-drug interactions.<sup>28</sup> Patient-specific factors (e.g., renal function) and practical concerns (e.g., need for frequent monitoring, convenience of administration, risk of medical staff exposure) may influence choice of anticoagulant.<sup>14, 15, 20, 27, 30, 32</sup></p> <p>Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, some clinicians have used (or suggested the use of) higher prophylactic doses or even therapeutic doses of anticoagulants to prevent thromboembolic complications in such patients; however, prospective studies are needed to evaluate these approaches.<sup>8, 11, 14-17, 20-24, 26-28, 30, 31, 32, 34, 36, 39</sup> Pending additional data, use of higher-intensity nonstandard VTE prophylaxis or therapeutic-dose anticoagulation should ideally be done in the context of a clinical trial.<sup>28, 30</sup></p> <p>Based on expert opinion, the Anticoagulation Forum suggests increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, heparin 7500 units sub-Q 3 times daily, or low-intensity heparin infusion) for critically ill patients (e.g., in the ICU) with confirmed or suspected COVID-19.<sup>32</sup></p> <p>NIH and other experts state that the current data are insufficient to recommend for or against the use of therapeutic anticoagulation in COVID-19 patients in the absence of confirmed or suspected thrombosis.<sup>4, 28, 30</sup> The efficacy of intermediate or full-dose therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is currently being evaluated.<sup>4, 12</sup> Patients who are already on anticoagulant therapy for an existing condition (e.g., VTE, atrial fibrillation) should</p>

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			<p>NCT04486508 (INSPIRATION), NCT04373707 (COVI-DOSE), NCT04372589 (ATTACC), NCT04345848 (COVID-HEP), NCT04412304, NCT04416048 (COVID-PREVENT), NCT04359277, NCT04367831 (IMPROVE), NCT04377997, NCT04354155 (COVAC-TP), NCT04394377 (ACTION), NCT04360824, NCT04444700 (RAPID-BRAZIL), NCT04466670, NCT04401293, NCT04393805 (HETHICO)</p>		<p>continue to receive such treatment unless significant bleeding occurs or other contraindications are present.<sup>4, 28</sup></p> <p>Extended VTE prophylaxis after hospital discharge is not routinely recommended in patients with COVID-19, but may be considered based on the same protocols and risk-benefit analysis as for patients without COVID-19.<sup>15, 27, 28, 30, 32</sup></p> <p>Although a relationship between markedly elevated D-dimer levels and mortality has been shown, whether this can be applied to predicting or managing VTE risk is not known.<sup>5, 6, 7, 30, 32, 33</sup></p> <p>Bleeding appears to be infrequent in COVID-19 patients.<sup>5, 30</sup> However, standard risk factors for bleeding should be considered and patients should be individually assessed to balance risk of thrombosis with risk of bleeding.<sup>4, 32</sup></p>
<p>COVID-19 Convalescent Plasma</p> <p><i>Updated 9/24/20</i></p>		<p>Plasma obtained from patients who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2 may provide short-term <i>passive</i> immunity to the virus; theoretically, such immunity may prevent or contribute to recovery from the infection, possibly as the result of viral neutralization and/or other mechanisms.<sup>1-5, 24, 25</sup></p> <p>Convalescent plasma therapy has been used in the treatment of other viral diseases with various degrees of success.<sup>16, 20, 22, 24, 25</sup></p> <p>In patients with SARS-CoV-1 infection, use of convalescent plasma was reported to shorten the duration of hospitalization and decrease mortality.<sup>6-8, 14</sup> SARS patients who received</p>	<p><b>Study with retrospectively matched control in US (Liu et al):</b> Preliminary (non-peer-reviewed) data from a study of 39 hospitalized adults with severe to life-threatening COVID-19 who received ABO-compatible COVID-19 convalescent plasma (2 units [total volume approximately 500 mL] infused IV over 1-2 hours), obtained from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 or greater, suggest that stable or improved supplemental oxygen requirements by post-transfusion day 14 were more likely in these convalescent plasma recipients than in the matched control group not treated with convalescent plasma (odds ratio: 0.86); this effect appeared to be confounded by use of therapeutic anticoagulants, but not by other types of drugs (i.e., azithromycin, broad-spectrum antibiotics, hydroxychloroquine, corticosteroids, antivirals, interleukin-1 [IL-1] and IL-6 inhibitors) or duration of symptoms before admission. Overall, survival was improved in patients in the convalescent plasma group compared to the control group; after adjusting for covariates, data suggest a significant improvement in survival in non-intubated patients (hazard ratio: 0.19) receiving convalescent plasma,</p>	<p><b>Emergency use authorization (EUA) COVID-19 convalescent plasma dosage and administration for hospitalized patients:</b> Consider initiating therapy with one unit (approximately 200 mL) of COVID-19 convalescent plasma given IV through a peripheral or central venous catheter according to standard institutional transfusion guidelines. Additional COVID-19 convalescent plasma units may be administered based on the prescribing physician's medical judgment and the patient's clinical response.<sup>37, 38</sup></p> <p>Smaller volumes or prolonged transfusion times may be necessary in patients with impaired cardiac function and heart failure.<sup>38</sup></p>	<p>Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established.<sup>11, 25</sup></p> <p><b>There are no convalescent blood products currently licensed by the FDA.<sup>25, 37</sup> COVID-19 convalescent plasma is regulated as an investigational product.<sup>11, 37</sup></b></p> <p><b>Emergency use authorization (EUA) for COVID-19 convalescent plasma:</b> FDA issued an EUA on August 23, 2020 that permits use of the biological product for the treatment of hospitalized patients with COVID-19. This EUA is based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) for COVID-19 convalescent plasma sponsored by the Mayo Clinic.<sup>37</sup> The EUA requires healthcare providers to provide convalescent plasma recipients with the Fact Sheet for Patients and Parents/Caregivers and to inform recipients of</p>

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		<p>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.<sup>1, 2, 6-8</sup></p>	<p>but not in the small cohort of intubated patients (hazard ratio: 1.24). No significant transfusion-related morbidity or mortality was observed in patients receiving convalescent plasma.<sup>32</sup></p> <p><b>Uncontrolled pilot study in China (Duan et al):</b> 10 adults with severe COVID-19 received a single transfusion of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody titers of 1:640 or greater) with standard care; all patients received antiviral therapy (e.g., umifenovir [Arbidol®], ribavirin, oseltamivir, peramivir, interferon <math>\alpha</math>) and 6 patients also received methylprednisolone. The median time from onset of symptoms to transfusion of convalescent plasma was 16.5 days. COVID-19 symptoms (fever, cough, shortness of breath, chest pain) improved in all patients within 1-3 days after the transfusion and all patients showed radiologic improvement in pulmonary lesions. Titers of neutralizing antibody increased in 5 patients after the transfusion, but remained the same in 4 patients. Prior to the transfusion, RT-PCR tests for SARS-CoV-2 RNA were positive in 7 patients and negative in 3 patients; after transfusion, SARS-CoV-2 RNA was undetectable in 3 patients on day 2, 3 patients on day 3, and 1 patient on day 6.<sup>9</sup></p> <p><b>Uncontrolled case series in China (Shen et al):</b> 5 critically ill adults with rapidly progressing severe COVID-19 and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation who had high viral loads despite antiviral treatment received 2 transfusions of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody end point dilution titers of 80-480 depending on the donor); patients continued to receive antiviral treatments (e.g., LPV/RTV, favipiravir, umifenovir [Arbidol®], darunavir, interferon <math>\alpha</math>-1b) and methylprednisolone. Patients received the convalescent plasma transfusions 10-22 days after hospital admission. Following the transfusions, body temperature normalized within 3 days in 4/5 patients, sequential organ failure assessment (SOFA) scores improved in all patients (decreased from</p>		<p>the significant known and potential risks and benefits of emergency use of COVID-19 convalescent plasma.<sup>37, 38</sup> Healthcare facilities and healthcare providers administering COVID-19 convalescent plasma must comply with certain mandatory record keeping and reporting requirements (including adverse event reporting).<sup>38</sup> Consult the EUA,<sup>37</sup> EUA fact sheet for healthcare providers,<sup>38</sup> and EUA fact sheet for patients and parents/caregivers<sup>41</sup> for additional information.</p> <p>The EUA states that COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. FDA states that adequate and well-controlled randomized trials remain necessary to determine optimal product attributes and to identify appropriate subpopulations for its use and that ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on issuance of the EUA.<sup>37</sup></p> <p>The NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend for or against the use of convalescent plasma in patients with COVID-19 and that COVID-19 convalescent plasma should not be considered a standard of care for the treatment of patients with COVID-19.<sup>25</sup></p> <p>The Surviving Sepsis Campaign COVID-19 subcommittee suggests that convalescent plasma not be used routinely in critically ill adults with COVID-19 because efficacy and safety not established and uncertainty surrounding optimal preparation of convalescent plasma.<sup>30</sup></p> <p>Appropriate criteria for selection of patients to receive investigational COVID-19 convalescent plasma, optimal time during the course of the disease to receive such therapy, and appropriate dosage (e.g., volume, number of doses)</p>

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			<p>initial scores of 2-10 to 1-4 on day 12), titers of SARS-CoV-2 IgG, IgM, and neutralizing antibody increased in all patients, and viral loads decreased and became negative within 12 days.<sup>10</sup></p> <p><b>Retrospective observational study in China (Zeng et al):</b> 6 critically ill adults with COVID-19 were treated with convalescent plasma at a median of 21.5 days after first detection of viral shedding. Although viral clearance was observed in all patients following transfusion, death occurred in 5 of 6 patients.<sup>16</sup></p> <p><b>Uncontrolled descriptive study in China (Ye et al):</b> 6 adults with COVID-19 received convalescent plasma at a relatively late stage of the disease (most patients received 2 or 3 plasma transfusions); various laboratory, radiologic, and clinical improvements were reported.<sup>18</sup></p> <p><b>Uncontrolled case series in China (Chen et al; non-peer-reviewed):</b> 16 adults with COVID-19 as determined by a SARS-CoV-2 nucleic acid amplification (NAA) test and rapidly progressive, severe, or life-threatening disease received ABO-compatible COVID-19 convalescent plasma (up to 2-3 IV transfusions; each transfusion 200 – 400 mL); no minimum titer of neutralizing antibody was specified for the convalescent plasma. Patients also received multiple other treatments (e.g., antivirals, antibacterials, traditional Chinese medicine). The average time from symptom onset to plasma transfusion was 23 days. Prior to convalescent plasma transfusion, 10/16 patients had consistently positive SARS-CoV-2 results. Time to SARS-CoV-2 negativity following convalescent plasma transfusion was 2-8 days in 8/10 patients, including 5 critically ill patients and 3 with severe COVID-19 disease. SARS-CoV-2 positivity persisted in 2 critically ill patients; these patients died on day 3 and day 6 post-transfusion.<sup>35</sup></p> <p><b>Uncontrolled case series in US (Salazar et al):</b> 25 adults with severe and/or life-threatening COVID-19 disease received</p>		<p>not determined.<sup>1-5,9</sup> Current data suggest that convalescent plasma is more effective if given during the early course of the disease.<sup>1, 2, 16, 17, 20, 24, 37, 38, 41</sup></p> <p>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.<sup>1-5</sup> Current data suggest that the clinical benefit is greatest when high-titer convalescent plasma is given early in the course of the disease.<sup>36, 37, 38</sup></p> <p>Logistics of obtaining, processing, storing, and distributing COVID-19 convalescent plasma evolving.<sup>1-5,11, 14, 15</sup> 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.<sup>11</sup></p> <p>Analysis of key safety indicators in 20,000 adults who participated in a US FDA Expanded Access Program (NCT04338360) suggests that IV transfusion of COVID-19 convalescent plasma is safe in hospitalized patients with COVID-19;<sup>31</sup> however, potential risks associated with COVID-19 convalescent plasma therapy (e.g., inadvertent transmission of other infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], antibody-dependent enhancement of infection) and steps to mitigate such risks not fully determined and require further evaluation.<sup>1-5, 9, 23, 24, 25</sup></p> <p>May be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.<sup>38</sup> Safety and effectiveness in pediatric patients have not been evaluated; a</p>

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			<p>convalescent plasma in addition to multiple other treatments (e.g., antivirals, anti-inflammatory agents).<sup>26</sup> The median time from symptom onset to plasma transfusion was 10 days and 24/25 patients received a single transfusion.<sup>26</sup> Convalescent plasma was well tolerated and no transfusion-related adverse events were reported. At day 7 post-transfusion, 9 patients (36%) had clinical improvement (defined as at least a 1-point improvement based on a 6-point ordinal scale); by day 14 post-transfusion, 19 patients (76%) had clinical improvement or were discharged. The contribution of convalescent plasma to clinical improvement in these patients is unclear since there was no control group and patients also received other treatments.<sup>26</sup></p> <p><b>Cochrane systematic review:</b> Analysis of 20 published studies (1 RCT, 3 controlled non-randomized studies of interventions [NRSIs], 16 non-controlled NRSIs) evaluating convalescent plasma in adults with COVID-19 (total of 5443 study participants, of whom 5211 received COVID-19 convalescent plasma) found very low confidence in the efficacy and safety of this treatment approach. There was a high risk of bias within and across the studies and great variability in terms of study design, donor and recipient characteristics, and other previous or concurrent treatments.<sup>42</sup></p> <p><b>Systematic review (Joyner et al; non-peer-reviewed):</b> Analysis of pooled data (total of 804 COVID-19 patient outcomes) from 12 studies (3 RCT, 5 matched-control, 4 case series) evaluating convalescent plasma in hospitalized adults with severe or life-threatening COVID-19 found evidence favoring efficacy of this therapeutic approach. The risk of death was substantially reduced in hospitalized COVID-19 patients transfused with convalescent plasma compared to matched patients receiving standard therapy (OR: 0.43, <math>p &lt; 0.001</math>). <b>Note:</b> There were several limitations to this analysis including aggregating mortality data across study populations that varied by dose and timing of convalescent plasma administration, geographic region, and duration of follow-up.<sup>34</sup></p>		<p>decision to use COVID-19 convalescent plasma in patients &lt;18 years of age should be based on an individualized assessment of risks and benefits.<sup>38</sup></p> <p><b>FDA issued a guidance for industry to provide recommendations to healthcare providers and investigators regarding administration and study of investigational COVID-19 convalescent plasma.</b> This guidance document includes recommendations regarding pathways for access to COVID-19 convalescent plasma, collection of such plasma (including donor eligibility and qualifications), product labeling, and record-keeping.<sup>11</sup></p> <p><b>Additional pathways (outside of the EUA) for administering or studying the use of investigational COVID-19 convalescent plasma:</b></p> <ol style="list-style-type: none"> <li>1). <b>Clinical Trials:</b> Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional investigational new drug (IND) regulatory pathway.<sup>11</sup></li> <li>2). <b>Expanded Access IND:</b> FDA is accepting requests for expanded access INDs for use of COVID-19 convalescent plasma in patients with serious or immediately life-threatening COVID-19 who are not eligible or are unable to participate in randomized clinical trials. Consult the FDA guidance document for specific information on applying for an expanded access IND for more than a single patient.<sup>11</sup></li> <li>3). <b>Single Patient Emergency IND (eIND):</b> Licensed physicians seeking to administer COVID-19 convalescent plasma to individual patients with serious or life-threatening disease may request an eIND from the FDA. Consult the FDA guidance document for specific information on applying for an eIND.<sup>11</sup></li> </ol> <p><b>Donor eligibility:</b> FDA guidance suggests that COVID-19 convalescent plasma be collected from individuals with laboratory-confirmed evidence of</p>

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			<p><b>Open-label, randomized, controlled study in Netherlands (Gharbharan et al; Con-COVID study):</b> Preliminary (non-peer-reviewed) data from a study of 86 hospitalized adults with COVID-19 found no significant difference in mortality, duration of hospital stay, or disease severity on day 15 in patients treated with convalescent plasma (300 mL of convalescent plasma containing anti-SARS-CoV-2 neutralizing antibody titers of <math>\geq 1:80</math>) compared with standard of care.<sup>44</sup> <b>Note:</b> Anti-SARS-CoV-2 antibodies were detected at baseline in 53/66 patients who had been symptomatic for 10 days prior to study enrollment. Neutralizing antibodies were detected in 44/56 (79%) patients tested with median titers comparable to the donors (1:160). These findings raised concerns about the potential benefit of convalescent plasma in the study population and the study was terminated.<sup>44</sup></p> <p><b>Open-label, randomized, controlled study in China (Li et al):</b> Results of this study in 103 adults with severe or life-threatening COVID-19 found no significant difference in time to clinical improvement within 28 days, mortality, or time to hospital discharge in patients treated with convalescent plasma (containing a high titer of antibody to SARS-CoV-2) plus standard of care compared with standard of care alone.<sup>28</sup> Convalescent plasma therapy was well tolerated by the majority of patients; 2 cases of transfusion-associated adverse events were reported.<sup>28</sup> There was a signal of possible benefit in the subgroup of patients with severe COVID-19 disease.<sup>28, 29</sup> However, the study had several limitations that preclude any definite conclusions, including the possibility of being underpowered as the result of early termination because of the lack of available patients.<sup>28, 29</sup> In addition, most patients received convalescent plasma treatment at least 14 days after symptom onset and it is unclear whether earlier treatment would have resulted in greater benefit.<sup>28, 29</sup></p> <p><b>Open-label, single-arm, phase 2 study (Ibrahim et al):</b> Preliminary (non-peer-reviewed) data from a study of 38 severely</p>		<p>COVID-19 infection and complete resolution of symptoms for at least 14 days before donation (a negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor).<sup>11</sup></p> <p><b>Antibody titers in donor plasma: According to the EUA, COVID-19 convalescent plasma with an S/Co value of <math>\geq 12</math> (as determined by the Ortho VITROS SARS-CoV-2 IgG test) qualifies as high-titer COVID-19 convalescent plasma.</b><sup>37</sup> Low-titer COVID-19 convalescent plasma must be labeled accordingly and may be considered for use following assessment of the potential benefits and risks of convalescent plasma therapy for the individual patient.<sup>37, 38</sup></p>

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			<p>or critically ill hospitalized adults with COVID-19 who received convalescent plasma (up to 2 transfusions of 200 mL of convalescent plasma containing IgG titers of 1:320) found a significant reduction in mortality (13 versus 55%, respectively) and hospital length of stay (15.4 versus 33 days, respectively) in those who were severely ill compared with those who were critically ill.</p> <p><b>Note:</b> Severely ill patients received convalescent plasma approximately 4.6 days following hospital admission and 12.6 days following symptom onset while on high-flow oxygen supplementation without evidence of acute respiratory distress syndrome (ARDS). Critically ill patients received convalescent plasma approximately 16.4 days following hospital admission and 23.1 days following symptom onset after developing ARDS; these patients also had been on ventilation support for an average of 10.6 days prior to transfusion of convalescent plasma. Transient transfusion reaction (fever and hematuria) was observed within 2 hours of transfusion of convalescent plasma in one patient with severe illness.<sup>45</sup></p> <p><b>Open-label, randomized, controlled study in India (Agarwal et al; PLACID trial):</b> Preliminary (non-peer-reviewed) data from a study of 464 moderately ill adults hospitalized with COVID-19 found no significant difference in 28-day mortality or progression to severe disease in patients treated with convalescent plasma (2 transfusions of 200 mL) plus standard of care compared with standard of care alone. Convalescent plasma therapy was well tolerated by the majority of patients; adverse effects included local infusion site reaction, chills, nausea, bradycardia, dizziness, pyrexia, tachycardia, dyspnea, and IV catheter blockage.<sup>46</sup></p> <p><b>Open-label, randomized, controlled study in Chile (Balcells et al):</b> Preliminary (non-peer-reviewed) data from a study of 58 adults hospitalized within 7 days of COVID-19 symptom onset with risk factors for disease progression and without mechanical ventilation found no significant</p>		

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			<p>difference in composite outcome of death, mechanical ventilation, or prolonged hospital admission (&gt;14 days) in patients who received convalescent plasma (up to two transfusions of 200 mL) immediately following hospital admission compared with those who received convalescent plasma at clinical deterioration. Two patients developed severe respiratory deterioration within 6 hours after transfusion of convalescent plasma and were categorized as possible transfusion-associated acute lung injury (TRALI) type II.<sup>47</sup></p> <p><b>Expanded access IND protocol (Joyner et al):</b> Analysis of 35,322 adults hospitalized with laboratory-confirmed SARS-CoV-2 infection who had or were considered at high risk of progression to severe or life-threatening COVID-19 who participated in a US FDA Expanded Access Program (NCT04338360) suggests that 7- and 30-day mortality rates are substantially reduced in patients transfused with convalescent plasma within 3 days of COVID-19 diagnosis. Patients received at least one unit (approximately 200 mL) of ABO-compatible COVID-19 convalescent plasma IV according to institutional transfusion guidelines. A statistically significant difference in crude 7-day mortality was observed between patients transfused with convalescent plasma within 3 days of COVID-19 diagnosis compared with those transfused with convalescent plasma 4 or more days after COVID-19 diagnosis (8.7 vs 11.9%). Similar findings were observed for 30-day mortality rate (21.6 vs 26.7%). A reduction in 7- and 30-day mortality rate also was observed in patients transfused with convalescent plasma containing higher IgG antibody levels (&gt;18.45 signal-to-cut-off [S/Co] ratio) compared with those transfused with convalescent plasma containing IgG antibody levels ≤18.45 S/Co.<sup>36</sup> Analysis of key safety indicators in 20,000 adults who participated in this Expanded Access Program suggests that IV transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. Within the first 4 hours after transfusion, 146 serious adverse events (i.e., transfusion-associated circulatory overload,</p>		



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			<p>transfusion-related acute lung injury [TRALI], severe allergic transfusion reaction) were reported (incidence of &lt;1% of all transfusions with a mortality rate of 0.3%); however, only 13/146 serious adverse events were judged by the treating clinician as related to convalescent plasma transfusion.<sup>31</sup> Within 7 days after transfusion, 1136 other serious adverse events were reported (i.e., thromboembolic or thrombotic event, sustained hypotensive event requiring IV vasopressor, cardiac event); however, 55/87 thromboembolic or thrombotic complications and 569/643 cardiac events were judged to be unrelated to convalescent plasma transfusion.<sup>31</sup></p> <p><b>Open-label, prospective study (Madariaga et al; non-peer-reviewed):</b> The relationship between clinical and serologic parameters in a group of COVID-19 convalescent plasma donors and antibody responses in recipients of convalescent plasma was evaluated. SARS-CoV-2 anti-receptor binding domain (anti-RBD) and anti-spike antibody titers ranged from 0 to 1:3892 and 0 to 1:3289, respectively, in 103 convalescent plasma donors; mean duration of COVID-19 symptoms in the plasma donors was 11.9 days and mean interval between symptom onset and convalescent plasma donation was 45.1 days; predictors of higher antibody titers in the donors included advanced age, fever, absence of myalgia, fatigue, ABO blood type, and previous hospitalization. In this study, 10 hospitalized adults with severe or life-threatening COVID-19 received 1 or 2 units (approximately 300 mL per unit administered IV over 4 hours) of ABO-compatible COVID-19 convalescent plasma (units had SARS-CoV-2 anti-RBD antibody titers of 1:73 to 1:3892 and anti-spike antibody titers of 1:69 to 1:2921) within 21 days after symptom onset and 80% of these patients had a significant increase in SARS-CoV-2 anti-spike and anti-RBD antibody titer by post-transfusion day 3 and were discharged after clinical improvement; antibody titers in the convalescent plasma recipients were independent of donor antibody titer. SARS-CoV-2 antibody titers in</p>		



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			<p>the convalescent plasma recipients continued to increase for up to 14 days in 4 recipients; however, 2 severely ill patients receiving extracorporeal membrane oxygenation (ECMO) who received convalescent plasma on day 20-21 of illness and had SARS-CoV-2 anti-spike antibody titers of up to 1:13,833 on day 0 had a decrease in antibody titer after receiving convalescent plasma. No convalescent plasma recipients experienced toxicity associated with the transfusion or clinical deterioration or worsening of disease status immediately related to plasma transfusion. Convalescent plasma transfusion was safe in high-risk individuals in this study (i.e., immunosuppressed, end-stage renal disease).<sup>33</sup></p> <p><b>Retrospective matched cohort study (Rogers et al; non-peer-reviewed)</b> of hospitalized COVID-19 patients at 3 Rhode Island medical centers indicated no significant difference in in-hospital mortality or rate of hospital discharge in patients who received convalescent plasma within a median of 7 days after symptom onset; however, subgroup analysis suggested a significantly increased hospital discharge rate among convalescent plasma recipients 65 years of age or older.<sup>43</sup></p> <p><b>Although there is some evidence suggesting possible benefits of convalescent plasma in patients with COVID-19, available data to date are largely from case reports or series; confirmation from additional randomized controlled studies is required.</b><sup>1, 20-23, 27-29</sup></p> <p><b>Multiple clinical trials have been initiated globally</b> to evaluate use of COVID-19 convalescent plasma in various settings (e.g., postexposure prophylaxis, treatment of different stages of the disease).<sup>19, 22</sup> Some trials are listed below. For additional trials, see <a href="https://clinicaltrials.gov">clinicaltrials.gov</a>:</p> <p>NCT04374370 (Expanded Access)  NCT04358211 (Expanded Access)  NCT04363034 (Expanded Access)  NCT04389710 (Expanded Access)  NCT04420988 (Expanded Access)</p>		

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			<p>NCT04458363 (US Pediatric)            NCT04343261 (US)            NCT04343755 (US)            NCT04344535 (US)            NCT04364737 (US)            NCT04344015 (US)            NCT04376034 (US)            NCT04359810 (US)            NCT04362176 (US)            NCT04411602 (US)            NCT04388527 (US)            NCT04397757 (US)            NCT04412486 (US)            NCT04392232 (US)            NCT04353206 (US)            NCT04421404 (US)            NCT04360486 (US ARMY)            NCT04347681            NCT04346446            NCT04345523            NCT04342182            NCT04352751            NCT04375098            NCT04357106            NCT04327349            NCT04292340</p>		
<p>Famotidine</p> <p><i>Updated 9/17/20</i></p>	<p>56:28.12 Histamine H<sub>2</sub> Antagonists</p>	<p>Computer-aided, structure-based, virtual screening of libraries of compounds against SARS-CoV-2 proteins suggested potential for famotidine to interact with viral proteases involved in coronavirus replication.<sup>1-4</sup></p> <p>However, in vitro data suggest famotidine does not bind to SARS-CoV-2 proteases, although antiviral activity was not tested in cell lines that express H<sub>2</sub> receptors.<sup>11, 12</sup></p> <p>No in vitro antiviral activity against SARS-CoV-2 observed in infected Vero E6 cells.<sup>11</sup></p> <p>A possible role for dysfunctional mast cell activation and histamine release in</p>	<p>Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19.</p> <p>Randomized, double-blind, placebo-controlled, comparative trial (NCT04370262) is evaluating high-dose IV famotidine plus standard care vs placebo plus standard care in <b>hospitalized adults with moderate to severe COVID-19</b>; targeted enrollment is at least 942 patients.<sup>5</sup></p> <p>Other randomized clinical trials also evaluating famotidine for treatment of COVID-19, including NCT04504240.<sup>5</sup></p> <p>Retrospective cohort study of 10 <b>outpatients self-medicating with high-dose famotidine</b> following onset of symptoms consistent with COVID-19: No hospitalizations reported; all patients reported symptomatic improvement within 1-2 days, with continued improvement over 14-day period. Patients were symptomatic for 2-26 days before initiating famotidine. Total of 7 patients had PCR-confirmed COVID-19,</p>	<p>Dosage in NCT04370262: Famotidine is being given IV in 120-mg doses (proposed total daily dosage of 360 mg) for maximum of 14 days or until hospital discharge, whichever comes first.<sup>5</sup></p> <p>Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage;<sup>6</sup> the study excludes patients with creatinine clearance (Cl<sub>cr</sub>) ≤50 mL/minute, including dialysis patients;<sup>5</sup> renally impaired patients may be at increased risk of adverse CNS effects since drug half-life is closely related to Cl<sub>cr</sub>.<sup>6</sup></p>	<p>Safety and efficacy for treatment of COVID-19 not established.</p> <p>IDSA suggests against using famotidine for the sole purpose of treating COVID-19 in hospitalized patients with severe COVID-19 outside of the context of a clinical trial.<sup>9</sup></p>

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		<p>mediating clinical manifestations of COVID-19 has been postulated; it is further postulated that the principal action of famotidine in COVID-19 may relate to activity at H<sub>2</sub> receptors.<sup>10,11</sup></p> <p><b>Anecdotal observations:</b> Observations based on retrospective medical record review indicated that many Chinese COVID-19 survivors had received famotidine for chronic heartburn; mortality rate appeared to be lower in hospitalized COVID-19 patients receiving famotidine than in patients not receiving the drug (14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors<sup>3</sup></p>	<p>2 had serologic confirmation of antibodies against SARS-CoV-2, and 1 had clinical diagnosis only. Famotidine dosage of 80 mg 3 times daily was reported by 6 patients (range: 20-80 mg 3 times daily); median reported duration of use was 11 days (range: 5–21 days); high-dose famotidine generally was well tolerated. Data were collected by telephone interviews and written questionnaires. Patients retrospectively provided symptom scores on a 4-point ordinal scale. Potential exists for placebo effect, recall bias, and enrollment bias; symptomatic improvement also could reflect treatment-independent convalescence.<sup>8</sup></p> <p><b>Retrospective matched cohort study</b> of COVID-19 patients hospitalized, but not requiring intubation within the first 48 hrs, at a single New York medical center indicated that <b>the risk for the composite outcome of death or intubation was reduced (mainly due to difference in mortality) in patients who received famotidine within 24 hours of hospital admission (n = 84) vs those who did not receive the drug (n = 1536); overall, 21% of patients met the composite outcome (8.8% were intubated and 15% died); the finding appeared to be specific to the H<sub>2</sub> antagonist and to COVID-19, as the investigators reported observing no protective effect with proton-pump inhibitors or in non-COVID-19 patients. Home use of famotidine was documented on admission in 15% of patients who received the drug in hospital vs 1% of those who did not; 28% of all famotidine doses were IV; 47% of doses were 20 mg, 35% were 40 mg, and 17% were 10 mg; the median duration of use was 5.8 days, and the total median dose was 136 mg (63-233 mg).</b><sup>7</sup></p> <p><b>Retrospective, matched, single-center, observational study</b> in hospitalized patients with RT-PCR-confirmed COVID-19: <b>In-hospital mortality (14.5 vs 26%) and the combined end point of death or intubation (7.2 vs 13.8%) were reduced in patients who received famotidine (n = 83) compared with a propensity score-matched</b></p>		

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			<p>group of patients who did not receive the drug (n = 689). Famotidine use was identified from electronic medical records and was defined as IV or oral use at any dosage within 7 days before or after COVID-19 screening and/or hospitalization; in the famotidine group, 66% received the drug in hospital only, and 29% received the drug both before and during hospitalization. Median total in-hospital dose was 80 mg (range: 40-160 mg) given over a median of 4 days (range: 2-8 days). There were no significant differences between the groups with respect to baseline demographics, comorbidities, or severity of illness or in concomitant use of hydroxychloroquine, remdesivir, azithromycin, or corticosteroids.<sup>10</sup></p> <p>Uncontrolled series of hospitalized patients with COVID-19 receiving open-label, <b>combined H<sub>2</sub> and H<sub>1</sub> antagonist therapy (famotidine and cetirizine)</b> for ≥48 hours (not peer reviewed): Total of 110 patients at a single hospital received famotidine 20 mg and cetirizine hydrochloride 10 mg orally or IV every 12 hours; concomitant therapy included hydroxychloroquine (85%), tocilizumab (51%), methylprednisolone (31%), and convalescent plasma (30%). Findings included a 16.4% overall rate of intubation, 7.3% rate of intubation after ≥48 hours of treatment, 15.5% mortality rate, and 11-day average hospital stay. <b>Note:</b> Comparisons were limited to published outcome data from other locales for patients receiving “standard-of-care” regimens.<sup>13</sup></p>		
<p>HMG-CoA Reductase Inhibitors (statins)</p> <p><i>Updated 10/1/20</i></p>	<p>24:06 Antilipemic Agents</p>	<p>In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects, which may prevent acute lung injury.<sup>1</sup></p> <p>Statins affect ACE2 as part of their function in reducing endothelial dysfunction.<sup>2,8</sup></p>	<p>Data from randomized controlled trials are lacking on the use of statins in patients with COVID-19. Retrospective cohort studies in various settings have indicated potential beneficial effects of statin treatment on disease severity, mortality, and/or recovery time in patients with COVID-19.<sup>10-13,16</sup> Meta-analyses conducted using data from retrospective studies have conflicting results.<sup>14,15</sup></p> <p>In a <b>retrospective cohort study</b> in 13,981 patients in China hospitalized with COVID-19, statin use during hospitalization was</p>		<p>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.<sup>2</sup> The panel <b>recommends against</b> use of statins for the treatment of COVID-19 except in the context of a clinical trial.<sup>2</sup></p> <p>Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.<sup>3</sup></p>

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			<p>associated with lower risk of mortality. The 28-day all-cause mortality was 22% lower in patients who received statins during hospitalization compared with patients who did not receive statins. Among propensity-score-matched patients (861 patients in the statin group vs. 3444 matched patients in the no-statin group), the risk of 28-day all-cause mortality was 42% lower in patients who received statins during hospitalization compared with those who did not receive statins. In addition, lower incidence of invasive mechanical ventilation was observed in the statin-treated patients. The authors note that patients in the statin group were older and had a higher prevalence of comorbidities and more severe symptoms at baseline; matched non-statin patients therefore had more severe baseline symptoms and comorbidities than unmatched patients, which could account for the increased mortality in the non-statin group after propensity score matching.<sup>11</sup></p> <p>In a <b>retrospective cohort study</b> in 154 nursing home residents in Belgium with clinically suspected COVID-19 and/or positive PCR test for SARS-CoV-2, statin use was associated with absence of symptoms (i.e., asymptomatic infection) in this cohort; 45% of the 31 patients receiving statin therapy remained asymptomatic compared with 22% of the 123 patients not receiving statins.<sup>10</sup></p> <p>In a <b>retrospective cohort study</b> in 170 patients hospitalized for COVID-19 at a single US center, statin use prior to admission was associated with reduced risk of developing severe disease and, among those without severe disease, faster time to recovery. In this study, 27% of pts reported using statins within 30 days prior to hospitalization for COVID-19. Statin use was associated with a 71% lower risk of severe outcome (i.e., death or ICU admission). In addition, rate of recovery in patients without severe disease was higher (hazard ratio for recovery: 2.69) and median time to recovery was shorter for those who received statins. The beneficial effect</p>		<p>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.<sup>3</sup></p> <p>Most statins are substrates for the CYP450 system; potential for drug interactions.<sup>7</sup></p> <p>Clinicians should ensure that their high-risk primary prevention (for ASCVD) patients are on guideline-directed statin therapy.<sup>3</sup></p>

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			<p>of statin use on reduction of severe outcomes in patients with COVID-19 was greater than that observed in a large control cohort of COVID-19-negative patients.<sup>12</sup></p> <p>In another <b>retrospective study</b> of 249 patients hospitalized with COVID-19 at multiple US centers, statin use prior to hospitalization was associated with lower risk of invasive mechanical ventilation in some models, but there was no substantial association between statin use and in-hospital death or ICU admission.<sup>16</sup></p> <p>In a <b>retrospective cohort study</b> in 87 patients admitted to the ICU with COVID-19 at a single US center, treatment with atorvastatin (40 mg daily) was associated with a reduced risk of death (adjusted hazard ratio: 0.38).<sup>13</sup></p> <p>Preliminary findings from a <b>meta-analysis</b> (Kow &amp; Hasan) of 4 cohort or case-control studies which included a total of 8990 patients with COVID-19 suggest that statin use is associated with a 30% reduction in risk of severe or fatal outcome in patients with COVID-19.<sup>14</sup> However, another <b>meta-analysis</b> of 9 cohort or case-control studies (Hariyanto &amp; Kurniawan) did not find an association between statin use and improved severity or mortality outcomes in patients with COVID-19. This meta-analysis included a total of 3449 pts with COVID-19 and included 2 of the same studies used in the Kow &amp; Hasan analysis.<sup>15</sup></p> <p>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.<sup>3-6</sup></p> <p><b>Clinical trials evaluating statin use in COVID-19:</b> Multiple trials registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a> (some listed below):<sup>9</sup> NCT04333407 NCT04343001 NCT04348695 NCT04426084 NCT0440727 (STACOV)</p>		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
Immune Globulin  <i>Updated 9/3/20</i>	80:04 Immune Globulin	<p>Commercially available immune globulin (IGIV, IVIG, <math>\gamma</math>-globulin) is derived from pooled plasma and contains many antibodies normally present in adult human blood; used for replacement therapy in patients with primary humoral immunodeficiency who are unable to produce sufficient IgG antibodies and also used to provide <i>passive</i> immunity to certain viral infections in other individuals.<sup>1</sup></p> <p>Investigational SARS-CoV-2 immune globulin is a concentrated immune globulin preparation containing specific antibody derived from the plasma of individuals who have recovered from COVID-19.<sup>16</sup></p> <p>Immune globulin preparations containing antibodies specific to SARS-CoV-2 may theoretically help suppress the virus and modulate the immune response to COVID-19 infection.<sup>2, 16</sup></p> <p>Commercially available preparations of immune globulin (IGIV, IVIG, <math>\gamma</math>-globulin) may contain antibodies against some previously circulating coronaviruses.<sup>2, 3, 13, 18</sup> Antibodies that cross-react with SARS-CoV-1, MERS-CoV, and SARS-CoV-2 antigens have been detected in some currently available IGIV products;<sup>18</sup> however, further evaluation is necessary to assess potential in vivo activity of such anti-SARS-CoV-2 antibodies using functional tests such as neutralization assays.<sup>18</sup></p>	<p><b>SARS Experience:</b> IGIV has been used in the treatment of SARS.<sup>4-7, 15</sup> Benefits were unclear because of patient comorbidities, differences in stage of illness, and effect of other treatments;<sup>5</sup> IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients.<sup>6, 7</sup></p> <p><b>Open-label, prospective, randomized, controlled study in the US (Sakoulas et al; NCT04411667):</b> Preliminary (non-peer-reviewed) data from a study of 33 adults with COVID-19 and moderate to severe hypoxia (defined as SpO<sub>2</sub> <math>\leq</math>96% requiring <math>\geq</math>4 liters O<sub>2</sub> by nasal cannula) but not on mechanical ventilation found that IGIV significantly improved hypoxia and reduced hospital length of stay and progression to mechanical ventilation in patients with alveolar-arterial (A-a) gradient <math>\leq</math>200 mm Hg treated with IGIV (Octagam® 10% 0.5 g/kg daily for 3 days) plus standard of care compared with standard of care alone. All 16 patients in the IGIV group received premedication with methylprednisolone (40 mg IV) prior to each IGIV dose and 5 of these received additional glucocorticoid therapy; 10/17 patients in the standard of care group received some glucocorticoid therapy.<sup>20</sup></p> <p><b>COVID-19 case reports in China (Cao et al):</b> Treatment with IGIV at the early stage of clinical deterioration was reported to provide some clinical benefit in 3 adults with severe COVID-19; 2 patients also received antivirals and 1 patient also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration.<sup>8</sup></p> <p><b>COVID-19 clinical experience in China:</b> IGIV has been used as an adjunct in the treatment of COVID-19 and has been mentioned in Chinese guidelines as a possible treatment option for severe and critically ill children with COVID-19.<sup>9-11, 14</sup></p> <p><b>Multicenter retrospective study in China:</b> Among a cohort of 325 patients with severe or critical COVID-19 disease, no difference</p>	IGIV dosage of 0.3-0.5 g/kg daily for 3-5 days has been used or is being investigated in patients with COVID-19. <sup>8, 12, 20</sup>	<p>Role of commercially available immune globulin (IGIV, IVIG, <math>\gamma</math>-globulin) and investigational SARS-CoV-2 immune globulin in the treatment of COVID-19 unclear.<sup>16</sup></p> <p>The NIH COVID-19 Treatment Guidelines Panel recommends against the use of commercially available IGIV (i.e., non-SARS-CoV-2-specific IGIV) for the treatment of COVID-19 except in the context of a clinical trial and states that current IGIV preparations are not likely to contain SARS-CoV-2 antibodies.<sup>16</sup> This does not preclude the use of IGIV when it is otherwise indicated for the treatment of complications arising during the course of COVID-19 disease.<sup>16</sup></p> <p>NIH states that there are insufficient data to recommend for or against the use of investigational SARS-CoV-2 immune globulin for the treatment of COVID-19.<sup>16</sup></p> <p>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, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury).<sup>13</sup></p>

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			<p>in 28-day or 60-day mortality was observed between patients who were treated with IGIV and those who were not treated with IGIV. However, patients who received IGIV were older and more likely to have coronary heart disease and critical status at study entry; patients also received numerous other treatments which limit interpretation of these findings.<sup>16, 19</sup></p> <p><b>Retrospective study in China:</b> 58 cases of severe or critical COVID-19 illness in ICU patients were reviewed.<sup>17</sup> Patients received IGIV in addition to other treatments (e.g., antiviral and anti-inflammatory agents). A statistically significant difference in 28-day mortality was observed between patients who received IGIV within 48 hours of admission compared with those who received IGIV after 48 hours (23 vs 57%). Treatment with IGIV within 48 hours also was associated with reduced duration of hospitalization and reduced ICU length of stay and need for mechanical ventilation.<sup>17</sup></p> <p><b>Efficacy data not available from controlled clinical studies to date.</b></p> <p><b>Several clinical studies have been initiated</b> to evaluate efficacy and safety of IGIV or SARS-CoV-2 immune globulin in patients with COVID-19, including the following trials:<sup>12</sup></p> <p>NCT04264858 NCT04350580 NCT04381858 NCT04261426 NCT04411667 NCT04400058</p>		
Ivermectin  <i>Updated 9/3/20</i>	8:08 Anthelmintic	<p>In vitro activity against some human and animal viruses<sup>1-6</sup></p> <p>In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug<sup>1</sup></p>	<p>Currently no known published data from randomized, controlled clinical trials regarding efficacy or safety in the treatment of COVID-19</p> <p><b>Pilot observational study comparing efficacy of add-on ivermectin in pts with mild to moderate COVID-19 (not peer reviewed):</b> A total of 16 pts received a single dose of oral ivermectin (0.2 mg/kg) given on the day of hospital admission in addition to initiation of treatment with</p>		<p>No data to date to support use in the treatment of COVID-19</p> <p>NIH COVID-19 Treatment Guidelines Panel <b>recommends against</b> use of ivermectin for the treatment of COVID-19, except in a clinical trial<sup>13</sup></p> <p>Ivermectin plasma concentrations attained with dosages recommended for treatment of parasitic infections are substantially lower than concentrations</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>hydroxychloroquine and azithromycin, and results were compared with 71 pts who received hydroxychloroquine and azithromycin alone (matched controls). The primary outcome was percentage of pts cured (defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR tests from nasopharyngeal swabs at least 24 hours apart) within 23 days. The investigators reported that all 16 pts who received ivermectin were cured compared with 97% of pts who did not receive ivermectin and the mean duration of hospitalization was shorter in the ivermectin group (7.6 days) than in the control group (13.2 days). Note: These results need to be validated in a larger prospective trial.<sup>11</sup></p> <p><b>Retrospective observational evaluation of COVID-19 pts treated with ivermectin (not peer reviewed):</b> Outcome data for 173 pts with confirmed COVID-19 who received at least one dose of oral ivermectin (0.2 mg/kg) at any time during hospitalization, at the discretion of the treating physician, in addition to usual care were compared with outcome data for 107 pts who received usual care. The primary outcome measure was all-cause in-hospital mortality. The investigators reported that overall mortality was lower in the ivermectin group (15%) than in the group not treated with ivermectin (25.2%); there was no difference in duration of hospitalization between the groups (median of 7 days for both groups). <b>Note:</b> The effect of ivermectin on viral load was not evaluated and the impact of confounding factors in these patients (e.g., time from diagnosis to initiation of treatment, differences in drugs used for standard care and variances in clinical benefits of such drugs) is not known.<sup>12</sup></p> <p>Several clinical trials evaluating ivermectin for the treatment of COVID-19 are registered at <a href="https://clinicaltrials.gov">clinicaltrials.gov</a><sup>10</sup></p>		<p>associated with in vitro inhibition of SARS-CoV-2;<sup>7,9</sup> pharmacokinetic modeling predicts that plasma concentrations attained with dosages up to 10 times higher than usual dosage also are substantially lower than concentrations associated with in vitro inhibition of the virus<sup>9</sup></p> <p>FDA issued a warning concerning possible inappropriate use of ivermectin products intended for animals as an attempt to self-medicate for the treatment of COVID-19<sup>8</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
Nebulized drugs  <i>Updated 7/16/20</i>		<p><b>Potential harm:</b> 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.<sup>1, 2, 4, 5</sup></p>	<p>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.<sup>3</sup></p>		<p>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.<sup>1, 4</sup></p> <p>In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose or dry powder inhalers in patients who are awake and who can perform specific breathing techniques because of the risk of the virus becoming airborne when treating patients infected with COVID-19.<sup>2, 5</sup></p> <p>There is a lack of published information and guidance on the optimal administration of aerosolized drugs in the treatment of patients with COVID-19. The safe and effective delivery of aerosol therapy to such patients may require modifications in dosage, frequency, and delivery techniques.<sup>5</sup></p> <p>WHO states there is insufficient evidence to classify nebulizer therapy as an aerosol-generating procedure associated with COVID-19 transmission and that further study is needed.<sup>6</sup></p>
Niclosamide  <i>Updated 9/17/20</i>	8:08 Anthelmintic	<p>Broad antiviral activity</p> <p>In vitro evidence of activity against SARS-CoV and MERS-CoV<sup>1, 2</sup></p>	<p>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19</p> <p>In drug repurposing screens, was found to inhibit replication and antigen synthesis of SARS-CoV; did not interfere with virion's attachment into cells<sup>1, 2</sup></p> <p>Randomized, open-label, controlled trial in France (<a href="#">NCT04372082</a>; HYdiLIC) to evaluate niclosamide in adults with SARS-CoV-2 infection (asymptomatic or onset of symptoms less than 8 days previously) and comorbidities<sup>3</sup></p>	<p>Protocol in one ongoing trial (<a href="#">NCT04372082</a>) specifies a niclosamide dosage of 2 g on day 1, then 500 mg twice daily for 10 days for treatment of COVID-19 in adults<sup>3</sup></p> <p>Protocol in one ongoing trial (<a href="#">NCT04399356</a>) specifies a niclosamide dosage of 2 g orally once daily for 7 days for treatment of mild to moderate COVID-19 in adults<sup>3</sup></p> <p>Protocols in two ongoing trials (<a href="#">NCT04436458</a>, <a href="#">NCT04542434</a>) specify a 3-times-daily niclosamide regimen (e.g., 400 mg of niclosamide)<sup>3</sup></p>	<p>Not commercially available in the US</p> <p>No data to date support use in treatment of COVID-19</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>Randomized, double-blind placebo-controlled trial in Boston, (<a href="#">NCT04399356</a>) to evaluate niclosamide in adults with mild to moderate COVID-19<sup>3</sup></p> <p>Randomized, double-blind placebo-controlled trials (<a href="#">NCT04436458</a>, <a href="#">NCT04542434</a>) to evaluate niclosamide in adults with moderate COVID-19 with GI signs and symptoms<sup>3</sup></p>	orally 3 times daily) for 14 days for treatment of moderate COVID-19 in adults with GI signs and symptoms	
Nitazoxanide  <i>Updated 10/8/20</i>	8:30.92 Antiprotozoal	<p>In vitro activity against various viruses, including coronaviruses<sup>4,5</sup></p> <p>Structurally similar to niclosamide<sup>3,5</sup></p> <p>In vitro evidence of activity against SARS-CoV-2<sup>1</sup></p> <p>In vitro activity against MERS-CoV<sup>4</sup></p> <p>Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice<sup>4</sup></p> <p>Some in vitro evidence of potential synergism between nitazoxanide and remdesivir and between nitazoxanide and umifenovir against SARS-CoV-2; additional data needed<sup>10</sup></p>	<p>Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19</p> <p><b>Experience in treating influenza:</b> 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<sup>6</sup></p> <p><b>Experience in treating influenza-like illness:</b> 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).<sup>7</sup> 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<sup>7</sup></p> <p><b>COVID-19:</b> Randomized, double-blind, placebo-controlled proof-of-concept trials initiated to evaluate nitazoxanide for treatment of hospitalized pts with noncritical COVID-19 (<a href="#">NCT04423861</a>) and pts with moderate COVID-19 (<a href="#">NCT04348409</a>)<sup>8</sup></p> <p><b>Two randomized, double-blind, placebo-controlled clinical trials</b> have been initiated by the manufacturer (Romark) to evaluate efficacy and safety for preexposure and postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers and others at increased risk of SARS-CoV-2 infection (<a href="#">NCT04359680</a>) or postexposure</p>	<p><b>Dosages investigated for treatment of influenza and influenza-like illness or being investigated for other viral infections:</b> Adults and adolescents (≥12 years of age): 500 or 600 mg orally twice daily for 5 days<sup>6,7,8</sup></p> <p>Protocols in many registered trials generally specify a nitazoxanide dosage of 500 or 600 mg two, three, or four times daily for 5-14 days or 1 g twice daily for 7 or 14 days for treatment of COVID-19 in adults<sup>8</sup></p> <p>Protocol in two ongoing trials sponsored by the manufacturer (<a href="#">NCT04343248</a>, <a href="#">NCT04359680</a>) evaluating preexposure and/or postexposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks in adults;<sup>8</sup> another study (<a href="#">NCT04435314</a>) specifies a dosage of 600 mg 3 times daily for 7 days for postexposure prophylaxis in adults<sup>8</sup></p> <p>Another study (NCT04561063) evaluating prophylaxis for prevention of symptomatic COVID-19 in healthcare workers at high risk of exposure specifies a nitazoxanide dosage of 500 mg every 12 hours for 7 days, then 1 g every 12 hours thereafter<sup>8</sup></p> <p>Results of a physiologically based pharmacokinetic model predict that nitazoxanide dosages of 1200 mg 4 times daily, 1600 mg 3 times daily, and 2900 mg twice daily in the fasted state and 700 mg 4 times daily, 900 mg 3 times daily, and 1400 mg twice</p>	<p>Current data not specific to COVID-19; additional study needed<sup>1</sup></p> <p>While nitazoxanide is one of several agents currently under investigation for postexposure prophylaxis,<sup>8</sup> NIH COVID-19 Treatment Guidelines Panel recommends against use of any agent for postexposure prophylaxis against SARS-CoV-2, except in a clinical trial<sup>11</sup></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
			<p>prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (<a href="#">NCT04343248</a>)<sup>8</sup></p> <p><b>Multiple other clinical trials planned or initiated</b> to evaluate nitazoxanide in combination with other drugs (e.g., hydroxychloroquine, ivermectin) or alone for treatment of COVID-19<sup>8</sup></p>	<p>daily in the fed state are capable of maintaining plasma and lung nitazoxanide (major metabolite of nitazoxanide) exposures exceeding the EC<sub>90</sub> for SARS-CoV-2<sup>9</sup></p>	
<p>Nonsteroidal Anti-inflammatory Agents (NSAIDs)</p> <p><i>Updated 9/17/20</i></p>	<p>28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)</p>	<p><b>Ibuprofen:</b> Speculative link between ibuprofen and increased ACE2 expression, which possibly could lead to worse outcomes in COVID-19 patients<sup>1</sup></p> <p><b>Indomethacin:</b> In vitro antiviral activity in SARS-CoV-2 pseudovirus-infected Vero E6 cells;<sup>7</sup> also has in vitro activity against <b>other</b> coronaviruses: SARS-CoV-1 (in Vero E6 and human pulmonary epithelial [A549] cells) and canine coronavirus; also has in vivo activity against canine coronavirus in dogs<sup>6,7</sup> (interferes with viral RNA synthesis)<sup>6,8</sup></p>	<p>In a national <b>registry-based cohort study</b> in Denmark, NSAIA use was <i>not</i> associated with increased 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in individuals who tested positive for SARS-CoV-2. In this study, of the 9236 individuals who had a positive PCR test for SARS-CoV-2, 2.7% had used NSAIDs (defined as individuals having filled a prescription for an NSAIA within 30 days prior to a positive SARS-CoV-2 test) based on national community pharmacy records. The authors note that in Denmark, NSAIDs are available only by prescription with the exception of low-dose ibuprofen (200 mg) sold over the counter (OTC) in packages of no more than 20 tablets, and such OTC purchases of ibuprofen constituted 15% of total ibuprofen sales and a smaller proportion of total NSAIA sales. This definition of NSAIA use was a major limitation of the study<sup>14</sup></p> <p><b>Ibuprofen:</b> In a <b>retrospective cohort study</b> of 403 hospitalized patients with COVID-19 at a single center in Israel, use of ibuprofen (1 week prior to diagnosis or during the course of disease) was not associated with increased mortality or the need for respiratory support compared with acetaminophen or no antipyretic drug.<sup>15</sup></p> <p><b>Indomethacin:</b> In vitro studies and animal models only;<sup>6,7</sup> currently no published studies evaluating use specifically in COVID-19 patients</p>		<p>Concerns that anti-inflammatory drugs such as ibuprofen may worsen COVID-19 circulated widely in the early months of the pandemic.<sup>5,12,14</sup> These reports were based largely on a letter published in <i>The Lancet Respir Med</i> stating that increased expression of ACE2 could facilitate infection with COVID-19 and that ibuprofen can increase ACE2.<sup>1,4</sup> In addition, there were unconfirmed reports of younger, healthy patients who had used ibuprofen to treat early symptoms of COVID-19 and later experienced severe outcomes.<sup>10,12,14</sup></p> <p>A statement attributed to the WHO recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position by the WHO has not been substantiated. WHO subsequently performed a rapid review of the literature and concluded that there was no evidence at that time of severe adverse events or effects on acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIDs.<sup>9</sup></p> <p>FDA has stated that it is not aware of scientific evidence connecting the use of NSAIDs, such as ibuprofen, with worsening COVID-19 symptoms and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that by reducing inflammation, and possibly fever, these drugs may diminish the utility of diagnostic signs in detecting infections.<sup>11</sup></p> <p>Although there currently is no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19, <b>some</b></p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
					<p>experts have recommended preferentially using acetaminophen for treatment of fever<sup>2, 3, 4, 10</sup></p> <p><b>NIH COVID-19 Treatment Guidelines Panel</b> states that patients who are receiving NSAIDs for other conditions should continue receiving the drugs; the panel also states that antipyretic strategy (e.g., use of acetaminophen or NSAIDs) should be no different between patients with or without COVID-19.<sup>5</sup></p> <p>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)<sup>2</sup></p> <p>IDSA makes no specific recommendation for or against the use of NSAIDs in patients with COVID-19<sup>12</sup></p> <p><b>Indomethacin:</b> Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy in the treatment of COVID-19</p>
<p>Thrombolytic Agents (t-PA [alteplase], tenecteplase)</p> <p><b>Updated 10/1/20</b></p>	<p>20:12.20 Thrombolytic agents</p>	<p>A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which has been shown to contribute to poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).<sup>1-3, 5-9, 14, 16, 18, 19</sup></p> <p>Coagulation abnormalities observed include prothrombotic disseminated intravascular coagulation (DIC), venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis.<sup>1, 2, 5-10, 13, 14, 16</sup></p>	<p>Results of a small phase 1 study suggested possible benefit of plasminogen activators in the treatment of ARDS.<sup>1-3</sup> In this study, 20 patients with ARDS secondary to trauma and/or sepsis who failed to respond to standard ventilator therapy and were not expected to survive were treated with urokinase or streptokinase; such therapy improved PaO<sub>2</sub> and also appeared to improve survival.<sup>1-3</sup></p> <p>In a case series of 5 COVID-19 patients who had severe hypoxemia, declining respiratory status, and increasing oxygen requirements, administration of t-PA (alteplase) at an initial IV bolus dose of 25 mg over 2 hours followed by a continuous IV infusion of 25 mg over the next 22 hours appeared to improve oxygen requirements in all patients and prevent progression to mechanical ventilation in 3 of the patients.<sup>20</sup></p>	<p>t-PA (alteplase): Dosage regimens being evaluated in the registered NCT04357730 trial: 50 mg (administered as a 10-mg IV bolus followed by IV infusion of the remaining 40 mg over a total time of 2 hours) and 100 mg (administered as a 10-mg IV bolus followed by IV infusion of the remaining 90 mg over a total time of 2 hours); both regimens will be followed by a heparin infusion immediately after completion of the alteplase infusion.<sup>12</sup></p> <p>Other t-PA (alteplase) dosage regimens evaluated in patients with COVID-19 include an initial t-PA (alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg; however, the optimum dose, route</p>	<p>t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who are not responding to or do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).<sup>1, 13, 14, 22</sup></p> <p>Several institutions (e.g., Beth Israel Deaconess, University of Colorado, Denver Health) are currently testing this approach with t-PA (alteplase).<sup>2, 12</sup> Preliminary findings from the first few cases reported an initial, but transient improvement in PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio.<sup>9</sup></p> <p>The NIH COVID-19 Treatment Guidelines Panel states that current data are insufficient to recommend for or against the use of thrombolytic agents in hospitalized COVID-19 patients outside the setting of a clinical trial; patients who develop catheter thrombosis or other</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage <sup>a</sup>	Comments
		<p>A consistent finding in patients with ARDS (regardless of the cause) is fibrin deposition and microthrombi formation in the alveoli and pulmonary vasculature.<sup>1, 11, 14</sup></p> <p>Dysregulation of the clotting system in ARDS is a result of both enhanced activation of coagulation and suppression of fibrinolysis.<sup>12, 19</sup></p> <p>Fibrinolysis shutdown, as evidenced by complete failure of clot lysis on thromboelastography, has been observed in critically ill patients with COVID-19.<sup>23</sup></p> <p>Thrombolytic therapy may restore microvascular patency and limit progression of ARDS in patients with COVID-19.<sup>1, 14, 19, 22</sup></p>	<p>Other case series have described the use of t-PA in COVID-19 patients with severe respiratory failure or ARDS who were rapidly deteriorating and were either already on mechanical ventilation or likely to require intubation. Following IV infusion of t-PA (dosages varied), the majority of patients responded with rapid improvement in oxygenation.<sup>21, 24</sup> However, multiple confounding factors limit interpretation of findings from these case reports.<sup>21, 24</sup></p> <p>An open-label, randomized trial (NCT04357730) is being conducted to evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure.<sup>12</sup></p> <p>An open-label, nonrandomized pilot study (NCT04356833) is being conducted to evaluate an inhaled formulation of t-PA (via nebulization) in patients with ARDS due to COVID-19;<sup>12</sup> the inhaled formulation of t-PA is investigational at this time.<sup>15</sup></p> <p>A phase 3 randomized, double-blind, placebo-controlled study (NCT04453371; AtTAC) has been initiated to evaluate t-PA (alteplase) IV infusion in patients with ARDS due to COVID-19.<sup>12</sup></p> <p>Several randomized, double-blind, placebo-controlled trials have been initiated to evaluate low-dose IV bolus tenecteplase in conjunction with anticoagulation for the treatment of COVID-19-associated respiratory failure, including the following trials:<sup>12</sup> NCT04505592 NCT04558125</p>	<p>of administration, and duration of treatment remain to be determined.<sup>1, 9, 14, 20</sup></p> <p>Tenecteplase: A low-dose IV bolus of tenecteplase (0.25 mg/kg or 0.5 mg/kg) is being evaluated in the registered NCT04505592 trial.<sup>1</sup></p>	<p>indications for thrombolytic therapy should be treated according to the usual standard of care in patients without COVID-19.<sup>17</sup></p> <p>The CHEST guideline for the prevention, diagnosis, and treatment of VTE in patients with COVID-19 states that there is a lack of evidence regarding use of thrombolytic therapies in critically ill patients with COVID-19 without objective evidence of VTE or VTE-associated hypotension; based on indirect evidence from other populations, the expert panel recommends against the use of thrombolytic therapy in COVID-19 patients without objectively confirmed PE and PE-induced hypotension.<sup>25</sup></p> <p>The Anticoagulation Forum recommends against the use of thrombolytic agents in COVID-19 patients outside the setting of a clinical trial unless there is another clinical indication (e.g., STEMI, acute ischemic stroke, high-risk [massive] PE with hemodynamic compromise); in general, thrombolytic therapy is not recommended in the vast majority of patients with PE given limited efficacy data in patients who are hemodynamically stable.<sup>26</sup></p> <p>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.<sup>8</sup></p>

<sup>a</sup> See US prescribing information for additional information on dosage and administration of drugs commercially available in the US for other labeled indications.

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