

Assessment of Evidence for COVID-19-Related Treatments: Updated 4/15/2020

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ANTIVIRAL AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Baloxavir 3/20/20	8:18.92 Antiviral	Antiviral active against influenza viruses	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 China: Two randomized clinical trials registered, but not yet recruiting. Chinese Clinical Trial Registry links ¹ : ChiCTR2000029544 ChiCTR2000029548	Protocol in one registered Chinese trial (2000029548) specifies a baloxavir marboxil dosage of 80 mg orally on day 1, 80 mg orally on day 4, and 80 mg orally on day 7 as needed, not to exceed 3 total doses. ¹	No data to date support use in the treatment of COVID-19
Chloroquine Phosphate Updated 4/8/20	8:30.08 Antimalarial	In vitro activity against various viruses, including coronaviruses ^{1-3, 13, 14} In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; some evidence it may block infection in Vero E6 cells exposed to SARS-CoV-2 ^{1, 4, 12} Active in vitro against SARS-CoV-1 and MERS-CoV ^{2, 3, 5, 9} Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections ^{1-3, 13, 15-16} Known pharmacokinetics and toxicity profile	Only limited clinical trial data available to date to evaluate use of chloroquine for treatment or prevention of COVID-19 Multiple clinical trials initiated in China and other countries to evaluate various chloroquine dosages for treatment of pts with COVID-19 ^{4, 10} Clinical experience in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 ⁴⁻⁶ At least one clinical trial is being initiated to evaluate chloroquine for <i>prevention</i> of COVID-19 in the healthcare setting (NCT04303507) ¹⁰	Optimal dosage and duration of treatment not known ^{20, 25} Consider: 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base ¹⁷ Various dosages recommended or being investigated for treatment of COVID-19 Oral chloroquine phosphate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation ²⁵ Oral chloroquine phosphate: 500 mg twice daily for 10 days ⁴ Oral chloroquine phosphate: 500 mg twice daily for 7 days (adults 18-65 years weighing >50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing <50 kg) ¹¹	Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established ^{10, 24} Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in some guidelines for treatment of COVID-19 Emergency use authorization (EUA) for chloroquine: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. ^{24, 25} To request the drug, healthcare providers should contact local or state health departments; ²⁵ distribution to states will be managed

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				<p>Oral chloroquine phosphate: Initial dose of 600 mg (of chloroquine) followed by 300 mg (of chloroquine) 12 hours later on day 1, then 300 mg (of chloroquine) twice daily on days 2-5 ⁴</p>	<p>by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. ²⁹ To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA Med-Watch). ^{24, 25} FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID-19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks. ²⁴ Consult the EUA, ²⁴ EUA fact sheet for healthcare providers, ²⁵ and EUA fact sheet for patients and parent/caregivers ²⁷ for additional information.</p>
<p>Favipiravir (Avigan[®], Favilavir)</p> <p><i>Updated 4/10/20</i></p>	<p>8:18.92 Antiviral</p>	<p>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses ¹⁻⁵</p> <p>In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug ^{1, 5}</p> <p>Licensed in Japan and China for treatment of influenza ^{2, 4, 6}</p>	<p>Only very limited clinical trial data available to date to evaluate use of favipiravir in the treatment of COVID-19</p> <p>Open-label, prospective, randomized, multicenter study in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir (Arbidol[®]; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe disease compared with the group receiving umifenovir. ⁶</p> <p>Italy: Randomized, placebo-controlled multicenter trial (NCT04336904) to evaluate efficacy and safety of favipiravir in pts</p>	<p>Oral favipiravir: 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days ⁶</p> <p>Protocol in one ongoing trial (NCT04336904) specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 600 mg three times daily thereafter for up to 14 days ⁷</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 dose and duration</p>



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			<p>with moderate COVID-19 (started 3/25/20; estimated completion date 7/20)⁷</p> <p>Multiple clinical trials initiated in pts with COVID-19 in China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents:⁷⁻⁹</p> <p>NCT04310228 NCT04319900 NCT04303299 NCT04333589 NCT04336904 ChiCTR2000029544 ChiCTR2000030113 ChiCTR2000029548 ChiCTR2000030894 ChiCTR2000030987 JapicCTI-205238 JPRN-jRCTs031190226 JPRN-jRCTs041190120</p>		
<p>HIV Protease Inhibitors (e.g., LPV/RTV, Kaletra[®])</p> <p>Updated 4/15/20</p>	8:18.08.08 HIV Protease Inhibitors	<p>Lopinavir (LPV): In vitro activity against SARS-CoV-2 in Vero E6 cells;¹⁹ also has in vitro activity against SARS-CoV-1 and MERS-CoV;^{1, 2, 9} some evidence of benefit in animal studies for treatment of MERS-CoV^{2, 7, 9, 11}</p> <p>Atazanavir (ATV): ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero cells,^{17, 19} human epithelial pulmonary cells (A549),¹⁷ and human monocytes¹⁷</p> <p>Darunavir (DRV): In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations in Caco-2 cells;¹⁸</p>	<p>Lopinavir and Ritonavir (LPV/RTV; Kaletra[®]) randomized, open-label trial in China in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, time to clinical improvement was not shorter with LPV/RTV compared with standard care (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group. The 28-day mortality rate was numerically lower in LPV/RTV group (19.2% vs 25% in ITT population; 16.7% vs 25% in modified ITT population). Some evidence that LPV/RTV initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. No significant differences in reduction of viral RNA load,</p>	<p>LPV/RTV (COVID-19): LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days^{3, 16}</p> <p>LPV/RTV (COVID-19): LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol[®] 200 mg every 8 hours)⁶</p> <p>LPV/RTV (COVID-19): LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days¹³ 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^{5, 13}</p> <p>LPV/RTV (SARS): LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours)¹</p>	<p>LPV/RTV: Efficacy for treatment of COVID-19 not definitely established</p> <p>LPV/RTV: Additional study needed to evaluate possible clinical benefits of early use of LPV/RPV in COVID-19</p> <p>LPV/RTV: Additional study needed to evaluate benefits of concomitant use of LPV/RTV with other antivirals for COVID-19; usually used in conjunction with other antivirals (e.g., ribavirin with or without an interferon) for SARS and MERS</p> <p>Darunavir: No data to date to support use in the treatment of COVID-19. Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/cobicistat for treatment of COVID-19 and initial unpublished results from a study in China indicated that a 5-day regimen of DRV/cobicistat was not effective for treatment of COVID-19²¹</p>

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		<p>in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells¹⁹</p> <p>Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV): In vitro activity against SARS-CoV-2 in Vero E6 cells¹⁹</p>	<p>duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death. LPV/RTV stopped early in 13 pts because of adverse effects.³</p> <p>LPV/RTV retrospective cohort study in China evaluated use of LPV/RTV with or without umifenovir (Arbidol®) in adults. Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 6/17 pts (35%) treated with LPV/RTV alone vs 12/16 (75%) treated with both drugs; chest CT scans were improving in 29% of pts treated with LPV/RTV alone vs 69% of pts treated with both drugs.⁶ (See Umifenovir in this Evidence Table.)</p> <p>LPV/RTV Clinical Experience (COVID-19): Only limited data on LPV/RTV used with or without interferon in pts with COVID-19 outside of clinical trials.^{5, 12, 14, 16}</p> <p>LPV/RTV Clinical Experience (SARS and MERS): Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon.^{1, 8, 9, 10, 11}</p> <p>LPV/RTV COVID-19 Clinical Trials at clinicaltrials.gov: NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease)¹⁵ NCT04276688 (LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone)¹⁵ NCT04328012 (LPV/RTV vs hydroxychloroquine vs losartan vs placebo)¹⁵</p> <p>Darunavir COVID-19 Clinical Trials: NCT04252274: Open-label randomized trial in China to evaluate DRV/cobicistat¹⁵ NCT04303299: Open-label randomized trial in Thailand to evaluate DRV/RTV in conjunction with other antivirals¹⁵ ChiCTR2000029541: Open-label randomized trial in China to evaluate DRV/cobicistat vs LPV/RTV²⁰</p>	<p>LPV/RTV (MERS): LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α ; LPV 400 mg/RTV 100 mg orally twice daily with interferon β1b (0.25 mg/mL sub-Q on alternate days) for 14 days^{1, 4, 8}</p>	<p>Atazanavir, Nelfinavir, Saquinavir, Tipranavir: No data to date to support use in the treatment of COVID-19</p>

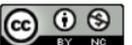


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Hydroxychloroquine (Plaquenil®) <i>Updated 4/8/20</i>	8:30.08 Antimalarial	<p>In vitro activity against various viruses, including coronaviruses^{5, 8, 12-14}</p> <p>In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed^{8, 12}</p> <p>Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections^{3, 8, 13, 15, 16}</p> <p>Known pharmacokinetics and toxicity profile</p> <p>Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects;^{13, 14} may have more favorable dose-related toxicity profile than chloroquine,¹³⁻¹⁶ but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs^{13, 20}</p>	<p>Only limited clinical trial data available to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19</p> <p>Multiple clinical trials initiated in US, China, and other countries to evaluate various hydroxychloroquine dosages for treatment of pts with COVID-19^{4, 10}</p> <p>Clinical experience in treating pts with COVID-19 accumulating; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19^{7, 18}</p> <p>Hydroxychloroquine small pilot study conducted in China: 15 treatment-naïve pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone;¹⁸ both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV.³⁰ Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).¹⁸</p> <p>Hydroxychloroquine randomized, parallel-group study in adults in China (ChiCTR2000029559): 31 pts with COVID-19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 5 days) and standard treatment (O₂, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids)</p>	<p>Optimal dosage and duration of treatment not known^{20, 26}</p> <p>Various dosages recommended or being investigated for treatment of COVID-19</p> <p>Oral hydroxychloroquine sulfate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation²⁶</p> <p>Oral hydroxychloroquine sulfate: 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5^{8, 20}</p> <p>Oral hydroxychloroquine sulfate: 400 mg once or twice daily for 5-10 days^{10, 18}</p> <p>Oral hydroxychloroquine sulfate: 600 mg twice daily on day 1, then 400 mg daily on days 2-5²⁰</p> <p>Oral hydroxychloroquine sulfate: 100-200 mg twice daily for 5-14 days⁴</p> <p>Oral hydroxychloroquine sulfate: 200 mg 3 times daily for 10 days^{7, 34}</p>	<p>Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established^{10, 24}</p> <p>Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19</p> <p>Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration</p> <p>Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.)</p> <p>Data needed regarding toxicity profile when used in patients with COVID-19</p> <p>Hydroxychloroquine suggested as possible option and included in some guidelines for treatment of COVID-19</p> <p>Emergency use authorization (EUA) for hydroxychloroquine: FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use only in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible.^{24, 26} To request the drug, healthcare providers should contact local or state health departments; ²⁶ distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA.²⁹ To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including</p>

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			<p>and 31 other pts received standard treatment alone (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group).³¹ Note: This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery,³² data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported.³¹</p> <p>Hydroxychloroquine with azithromycin open-label, nonrandomized study in France: 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</p>		<p>adverse event reporting to FDA Med-Watch).^{24,26} FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID-19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks.²⁴ Consult the EUA,²⁴ EUA fact sheet for healthcare providers,²⁶ and EUA fact sheet for patients and parent/caregivers²⁸ for additional information.</p>



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			<p>was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6.⁷ Note: This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented.</p> <p>Hydroxychloroquine with azithromycin open-label, uncontrolled study in France: 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O₂. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested.³³ Note: In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.</p>		



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			<p>Hydroxychloroquine with azithromycin uncontrolled, observational study in France: 80 adults with confirmed COVID-19 were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O₂ saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O₂; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested.³⁴ Note: Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease.</p> <p>Efficacy measures: Initial studies evaluating hydroxychloroquine based efficacy of</p>		



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			<p>the drug on negative conversion in nasopharyngeal samples at day 6 or 7.^{7, 18} RT-PCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19;^{19, 21} however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined.^{22, 23}</p> <p>Various clinical trials are being initiated in the US and elsewhere to evaluate hydroxychloroquine for <i>prevention</i> of COVID-19 in the healthcare setting or in household contacts of pts with the disease:¹⁰ NCT04328961 NCT04303507 NCT04318444 NCT04318015 NCT04330144</p>		
<p>Neuraminidase inhibitors (e.g., oseltamivir)</p> <p>3/20/20</p>	<p>8:18.28</p>	<p>Antivirals active against influenza viruses</p>	<p>In a retrospective case series of 99 patients with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of patients received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died.¹</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-19.²</p> <p>Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture.⁴</p> <p>Clinicaltrials.gov trials for COVID-19 that include oseltamivir⁵: NCT04303299 (not yet recruiting) NCT04261270 (recruiting) NCT04255017 (recruiting)</p>	<p>Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours.¹</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).⁵</p>	<p>No data to date support use in the treatment of COVID-19</p>



Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Remdesivir <i>Updated 4/15/20</i>	8:18.92 Antivirals, Miscellaneous	<p>Broad-spectrum antiviral with activity against various viruses, including coronaviruses</p> <p>In vitro evidence of activity against SARS-CoV-2 ¹</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 ¹⁻⁸</p> <p>Pharmacokinetic data available from evaluations for Ebola</p>	<p>Various clinical trials initiated in US, China, and other countries</p> <p>Phase 3 randomized, open-label trial (NCT04292899) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care in pts with severe COVID-19 ¹⁰</p> <p>Phase 3 randomized, open-label trial (NCT04292730) initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- or 10-day regimens of remdesivir in conjunction with standard of care in pts with moderate COVID-19 compared with standard of care alone ¹¹</p> <p>Phase 3 adaptive, randomized, placebo-controlled trial (NCT04280705) sponsored by NIAID initiated to evaluate safety and efficacy of remdesivir in hospitalized pts with laboratory-confirmed COVID-19 ¹³</p> <p>Expanded access and compassionate use access: The manufacturer (Gilead) is transitioning from individual compassionate use requests to an expanded access program for emergency access to the drug for severely ill pts with confirmed COVID-19. During this transition, new individual compassionate use requests cannot be accepted, with the possible exception of requests for pregnant women and children <18 years of age with confirmed infections and severe manifestations of the disease. ¹⁵ https://rdvcu.gilead.com/</p> <p>Compassionate use access (NCT04302766): May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command ¹²</p> <p>Data from the manufacturer's compassionate use program: 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</p>	<p>Optimal dosage and duration of treatment not known</p> <p>Phase 3 trial protocol (severe COVID-19): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) ¹⁰</p> <p>Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) ¹¹</p> <p>NIAID adaptive study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total ¹³</p> <p>Compassionate use access protocol: 200 mg IV on day 1, then 100 mg IV on days 2-10 ¹⁶</p>	<p>Not commercially available; most promising antiviral currently being investigated for COVID-19</p> <p>Safety and efficacy not established; additional data needed</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
			<p>with remdesivir; 40 pts received the full 10-day regimen (200 mg IV on day 1, then 100 mg IV on days 2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects.¹⁶ Note: Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load</p>		
<p>Umifenovir (Arbidol®)</p> <p><i>Added 4/3/20</i></p>	<p>8:18.92 Antiviral</p>	<p>Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses⁴</p> <p>Although data limited, in vitro activity against SARS-CoV-1⁴ and SARS-CoV-2⁵ reported</p> <p>Licensed in China and Russia for prophylaxis and treatment of influenza⁴</p>	<p>Retrospective cohort study in 33 adults with COVID-19 in China suggests more favorable outcome with LPV/RTV plus umifenovir vs LPV/RTV alone: Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 12/16 pts (75%) treated with LPV/RTV plus umifenovir vs 6/17 pts (35%) treated with LPV/RTV alone; at 14 days, undetectable in 15/16 pts (94%) treated</p>	<p>Dosage recommended for treatment of COVID-19 in China: Adults, 200 mg orally 3 times daily for no more than 10 days^{5,7}</p> <p>Dosage used or being investigated in COVID-19 clinical trials: 200 mg orally 3 times daily for duration of 7-10 days or longer^{2,3,6}</p>	<p>Not commercially available in the US</p> <p>Included in some guidelines for treatment of COVID-19⁷</p> <p>Published data to support use in treatment of COVID-19 currently are limited</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
			<p>with both drugs vs 9/17 pts (53%) treated with LPV/RTV alone. At 7 days, chest CT scans were improving in 11/16 pts (69%) treated with both drugs vs 5/17 pts (29%) treated with LPV/RTV alone ¹</p> <p>Open-label, prospective, randomized, multicenter study in 236 adults with COVID-19 in China (ChiCTR200030254): When favipiravir was compared with umifenovir, clinical recovery rate was greater in those treated with favipiravir than in those treated with umifenovir. ⁶ (See Favipiravir in this Evidence Table.)</p> <p>Clinical trials initiated in China: NCT04252885: Randomized, single-center, open-label trial evaluating efficacy of umifenovir in conjunction with standard of care vs LPV/RTV in conjunction with standard of care in adults with COVID-19 ²</p> <p>NCT04260594: Randomized, open-label trial evaluating efficacy and safety of umifenovir in conjunction with standard of care in adults with COVID-19 ³</p>		



SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Anakinra <i>Added 4/1/20</i>	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant human interleukin-1 (IL-1) receptor antagonist; ¹ may potentially combat cytokine release syndrome (CRS) symptoms in severely ill patients ^{2,3,4}	Currently no known published clinical trial evidence supporting efficacy or safety of anakinra in treating COVID-19 Encouraging preliminary results reported in China with another disease-modifying antirheumatic drug, tocilizumab ^{5,6} Italy: Phase 3 randomized, open-label, multicenter trial (NCT04324021) to be initiated by the manufacturer (Swedish Orphan Biovitrum) to evaluate efficacy and safety of anakinra or emapalumab with standard of care in reducing hyperinflammation and respiratory distress in patients with COVID-19 (estimated start date 3/20) ³	Phase 3 trial protocol (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days ³ (Note: Anakinra is approved only for subcutaneous administration in the U.S.) ¹	No data to date support use in the treatment of COVID-19
Ascorbic acid <i>Updated 4/8/20</i>	88:12 (Vitamin C)	Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress ^{3-5,7} Presence of infection may decrease vitamin C concentrations ²⁻⁵	Phase 2 randomized, placebo-controlled trial (NCT04264533) initiated in China to evaluate high-dose IV ascorbic acid in ICU patients with severe COVID-19-associated pneumonia ¹ Other infections: Sepsis: Meta-analysis of several small studies suggested beneficial effects from IV ascorbic acid; however, primary end points not improved in CITRIS-ALI study (NCT02106975) in patients with sepsis and ARDS or in VITAMINS study (NCT0333278) in patients with septic shock; additional studies under way ^{4,6,8,9,10} Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia ^{2,3} Common cold: Effect of oral supplementation studied extensively; decreases duration of symptoms, may decrease incidence of common cold in individuals under heavy physical stress but not in overall population ^{2,3}	Phase 2 trial protocol (NCT04264533): Ascorbic acid 12 g IV every 12 hours for 7 days (12 g of drug diluted in sterile water for injection to total volume of 50 mL and infused IV at rate of 12 mL/hour) ¹ 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 until shock resolution or for up to 10 days used in VITAMINS study ^{4,8,9,10} Note: May interfere with laboratory tests based on oxidation-reduction reactions (e.g., blood and urine glucose testing, nitrite and bilirubin concentrations, leukocyte counts). Manufacturer states to delay oxidation-reduction reaction-based tests until 24 hours after infusion, if possible ¹¹	Current data not specific to COVID-19; additional study needed ⁶

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Azithromycin <i>Updated 4/8/20</i>	8:12.12 Macrolides	<p>Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) ^{1, 3-5}</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 ^{2, 6, 8, 9, 11-14, 17}</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) ^{10, 13}</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) ^{6, 8, 17}</p>	<p>Adjunctive therapy in certain respiratory viral infections: Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza). ^{10, 12, 13} However, in a retrospective cohort study in critically ill pts with laboratory-confirmed MERS, there was no statistically significant difference in 90-day mortality rates or clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not. ¹²</p> <p>Adjunctive therapy in certain respiratory conditions: Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS). ⁸ In a retrospective cohort study in pts with moderate or severe ARDS, a statistically significant improvement in 90-day survival was reported in those who received adjunctive azithromycin. ⁸</p> <p>Clinical experience in pts with COVID-19: Has been used for antibacterial coverage in hospitalized pts with COVID-19 ¹⁵</p> <p>Use in conjunction with hydroxychloroquine in pts with COVID-19: Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), ⁷ open-label uncontrolled study in France (11 pts), ¹⁸ and uncontrolled observational study in France (80 pts).¹⁹ 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>Adjunctive treatment in certain viral infections: 500 mg once daily has been used ¹³</p> <p>COVID-19: 500 mg on day 1, then 250 mg daily on days 2-5 in conjunction with 10-day regimen of hydroxychloroquine has been used ^{7, 18, 19}</p>	<p>Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19</p> <p>Additional data needed before any conclusions can be made regarding possible benefits of using a combined regimen of hydroxychloroquine and azithromycin in pts with COVID-19</p> <p>Because both azithromycin and hydroxychloroquine are associated with QT prolongation, caution is advised if considering use of both drugs in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias and in those with chronic medical conditions (e.g., renal failure, hepatic disease); ^{16, 20} diagnostic testing and monitoring recommended to minimize risk of drug-induced cardiac effects ²⁰</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Corticosteroids (general) Updated 4/15/20	68:04 Adrenals	<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.^{3,9}</p> <p>Evidence suggests that cytokine storm, a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), is a contributing factor in COVID-19-associated mortality.^{8,18} Immunosuppression from corticosteroids has been proposed as a treatment option for such hyperinflammation.¹⁸</p> <p>May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low.^{4,11}</p>	<p>Observational studies: Evidence suggests that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes).¹</p> <p>Uncontrolled observational data from the recent COVID-19 outbreak in China suggest a possible treatment benefit of methylprednisolone in COVID-19 patients with ARDS.^{6,13} (See Methylprednisolone in this Evidence Table.)</p> <p>No randomized controlled clinical studies specifically evaluating corticosteroids for COVID-19 or other coronaviruses have been conducted; however, indirect evidence from studies in patients with community-acquired pneumonia, acute respiratory distress syndrome (ARDS), and other viral infections has been used to inform treatment decisions for COVID-19 patients.^{3,5,8,9,12,15,16,17}</p> <p>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 the prelung protection strategy era.^{5,8,9,14,17}</p> <p>In a recent multicenter, randomized controlled study (DEXA-ARDS trial), the effects of dexamethasone were evaluated in patients with moderate-to-severe ARDS receiving lung-protective mechanical ventilation.¹⁷ Treatment with IV dexamethasone at a dosage of 20 mg once daily on days 1-5, followed by 10 mg once daily on days 6-10 resulted in reduced duration of mechanical ventilation and reduced overall mortality compared with placebo treatment.¹⁷</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.^{3,4}</p>	<p>In general, low to moderate dosages of corticosteroids are recommended in intubated patients with ARDS.⁸</p> <p>Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days.⁸ Some experts suggest that equivalent dosages of dexamethasone (i.e., 7-15 mg daily, typically 10 mg daily) may have an advantage of producing less fluid retention, since dexamethasone has less mineralocorticoid activity.⁸ This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial.^{8,17}</p> <p>Higher dosages have been suggested for cytokine storm.⁸ (See Comments column.)</p>	<p>Existing evidence is inconclusive for use of corticosteroids in the treatment of COVID-19 patients.^{3,5,7}</p> <p>WHO and CDC recommend that corticosteroids not be routinely used in patients with COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock).^{1,2,3,8,9}</p> <p>Benefits and risks of corticosteroid therapy should be carefully weighed before using in patients with COVID-19.^{1,7}</p> <p>Corticosteroids generally should not be used in early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding.^{3,8}</p> <p>Based on limited information from observational studies with methylprednisolone^{6,13} (see Methylprednisolone in this Evidence Table), some experts state that corticosteroid therapy may be considered in severe cases of COVID-19 with ARDS provided the drugs are given in low doses over a short duration.^{7,8,10,12}</p> <p>There is no well-established or evidence-based treatment for cytokine storm in patients with COVID-19.⁸ However, some experts suggest that use of more potent immunosuppression with corticosteroids may be beneficial in such patients.⁸ These experts suggest higher dosages of corticosteroids (e.g., IV methylprednisolone 60-125 mg every 6 hours for up to 3 days) followed by tapering of the dose when inflammatory markers (e.g., C-reactive protein levels) begin to decrease.⁸</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
					<p>The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS).¹² However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS.¹²</p> <p>The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different than the effects seen in those with ARDS.¹² The Surviving Sepsis Campaign suggests a weak recommendation to use low-dose corticosteroid (e.g., hydrocortisone 200 mg daily as an IV infusion or intermittent doses) therapy over no corticosteroid therapy in adults with COVID-19 and refractory shock.¹² Other international clinical practice guidelines also make a weak recommendation for use of corticosteroids in patients with sepsis.⁴ Recommendation applies to all patients with sepsis with no meaningful difference in efficacy of corticosteroids in different patient populations, including those with septic shock, pneumonia, or ARDS.⁴</p> <p>For treatment of sepsis, clinicians considering corticosteroids for such patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding.¹ If corticosteroids are prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia.^{1,4}</p>



Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
<p>Epoprostenol (inhaled)</p> <p><i>Added 4/3/20</i></p>	<p>48:48 Vasodilating Agent</p>	<p>Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19¹⁻⁹</p> <p>Inhaled epoprostenol has been suggested as an alternative to inhaled nitric oxide due to its similar efficacy, lower potential for systemic adverse effects, lower cost, and ease of delivery^{1,2,9}</p>	<p>No studies evaluating use specifically in COVID-19 patients¹⁰</p> <p>Experience in patients with ARDS indicates that inhaled epoprostenol can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients; however, data demonstrating clinical benefit are lacking^{3,6-9}</p>	<p>Various dosages of inhaled epoprostenol have been used in ARDS studies^{2,9}</p> <p>Dosages up to 50 ng/kg per minute have been used (titrated to response).^{1-4,6,9} To provide a clinically important increase in PaO₂ and reduction in pulmonary artery pressure, data from these studies suggest that the most effective and safe dosage appears to be 20-30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients⁹</p> <p>(Note: Epoprostenol is labeled only for IV administration in the US.)</p>	<p>Additional studies are needed to evaluate the potential role of inhaled epoprostenol in the treatment of ARDS⁶⁻⁹</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 use of inhaled prostacyclins in COVID-19 patients with severe ARDS¹⁰</p>
<p>Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®)</p> <p><i>Updated 4/15/20</i></p>	<p>68:04 Adrenal</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^{3,9}</p>	<p>Retrospective, observational, single-center study: In 201 patients with confirmed COVID-19 pneumonia who developed ARDS, methylprednisolone appeared to reduce the risk of death.⁶ Among patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46%) patients died, while of those who did not receive methylprednisolone, 21 of 34 (61.8%) died.⁶</p> <p>Retrospective, observational, single-center study: In 46 patients with confirmed severe COVID-19 pneumonia that progressed to acute respiratory failure, use of methylprednisolone was associated with improvement in clinical symptoms (i.e., fever, hypoxia) and a shortened disease course in patients who received the drug compared with those who did not.¹³ Death occurred in 3 patients during hospitalization; 2 of these patients received methylprednisolone.¹³</p>	<p>Dosage used in the retrospective study (Wu et al) not provided.⁶</p> <p>Dosage used in the retrospective study (Wang et al) was 1-2 mg/kg daily IV for 5-7 days.¹³</p>	<p>Findings from observational studies suggest that for patients with COVID-19 pneumonia who progress to ARDS, methylprednisolone treatment may be beneficial. However, results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Confirmation from randomized controlled studies is needed.^{6,13}</p> <p>(See Corticosteroids in this Evidence Table.)</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
<p>Nitric oxide (inhaled)</p> <p><i>Updated 4/3/20</i></p>	48:48 Vaso-dilating Agent	<p>Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19^{2,3,9}</p> <p>In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and COVID-19 suggests potential effectiveness for COVID-19¹</p>	<p>No studies evaluating use specifically in COVID-19 patients¹⁰</p> <p>In a small pilot study conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support^{2,3}</p> <p>Randomized controlled studies of inhaled nitric oxide in ARDS patients generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment)^{4,5,6,9}</p>	<p>Inhaled nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) in a pilot study in SARS-CoV patients²</p> <p>Phase 2 clinical trial protocol (NCT04306393) for treatment of severe ARDS in ventilated patients: 80 ppm for the first 48 hours, followed by 40 ppm and then subsequently wean³</p>	<p>Therapeutic guidelines for the treatment of ARDS state that inhaled nitric oxide may be considered in patients with severe hypoxemia not responsive to conventional ventilation strategies; however, routine use not recommended^{4,5,6,9,10}</p> <p>The Surviving Sepsis Campaign suggests a trial of inhaled pulmonary vasodilator therapy as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if rapid improvement in oxygenation is not observed, treatment should be tapered off¹⁰</p> <p>Clinical trials evaluating inhaled nitric oxide for treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243)^{3,7}</p> <p>On March 20th, 2020, Bellerophon Therapeutics announced that the FDA granted emergency expanded access allowing its inhaled nitric oxide delivery system (INOpulse®) to be immediately used for the treatment of COVID-19⁸</p>
<p>Ruxolitinib (Jakafi®)</p> <p><i>Added 4/10/20</i></p>	10:00 Antineoplastic Agents	<p>Janus kinase (JAK) 1 and 2 inhibitor;⁷ may potentially combat cytokine release syndrome (CRS) in severely ill patients^{4,5}</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^{5,7}</p>	<p>Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19</p> <p>Phase 3 clinical trial evaluating ruxolitinib plus standard of care vs standard of care alone is being initiated pending FDA approval of the protocol in patients with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.)¹</p> <p>Expanded-access (managed-access, compassionate use) program (NCT04337359) being initiated for eligible adults and children ≥6 years of age with severe or very</p>	<p>Various dosages are being evaluated^{2,3,6}</p>	

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
			<p>severe COVID-19 illness; address inquiries to Incyte (855-463-3463 or me-dinfo@incyte.com)^{1,2}</p> <p>Other noncomparative, open-label clinical trials registered but not yet recruiting (NCT04331665, NCT04334044, NCT04338958); small parallel-group or uncontrolled studies also registered in Chinese Clinical Trial Registry (ChiCTR2000029580, ChiCTR2000030170)^{3,6}</p>		
<p>Sarilumab (Kefzara®)</p> <p><i>Updated 3/27/20</i></p>	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients ^{1,2,5}	<p>Currently no known published clinical trial evidence supporting efficacy or safety against Coronavirus.</p> <p>However, based on encouraging results in China with a similar drug, tocilizumab, a U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently under way^{3,4}</p> <p>Clinicaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4</p> <p>For information on compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)⁶</p>	Not available (see Trials or Clinical Experience)	
<p>Sirolimus</p> <p><i>3/20/20</i></p>	92:44 Immunosuppressive agent (mTOR inhibitor)	mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus ^{1,2,5}	<p>In vitro studies demonstrated inhibitory activity against MERS-CoV infection²</p> <p>In an open-label prospective randomized study in 38 patients with confirmed H1N1 pneumonia, treatment with sirolimus 2 mg daily in conjunction with corticosteroids for 14 days was associated with improved patient outcomes (e.g., shortened duration of mechanical ventilation, improved hypoxia and multiorgan function)³</p> <p>Currently a registered clinical trial (NCT03901001 not yet recruiting) designed to evaluate adjunctive use of sirolimus and oseltamivir in patients hospitalized with influenza^{4,6}</p>	Dosage of sirolimus in the open-label trial was 2 mg daily orally, administered in conjunction with oral prednisolone 20 mg daily for 14 days; patients also received oseltamivir 75 mg twice daily for 10 days ³	Although possible clinical application, current data not specific to 2019-nCoV/SARS-CoV2-2; additional study needed ⁵

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
<p>Tocilizumab (Actemra®)</p> <p><i>Updated 4/3/20</i></p>	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients ^{1, 2, 3, 6}	<p>Case study/series describing use of tocilizumab in patients with COVID-19 reported from various areas of the world^{1, 3}</p> <p>In preliminary data from a non-peer-reviewed, single-arm Chinese trial involving 21 patients with severe or critical COVID-19 infection, patients demonstrated rapid fever reduction and a reduced need for supplemental oxygen within several days after receiving tocilizumab (initially given as a single 400-mg dose by IV infusion; this dose was repeated within 12 hours in 3 patients because of continued fever)³</p> <p>Currently no other known clinical trial evidence supporting efficacy and safety of tocilizumab against Coronavirus¹</p> <p>China: Randomized, multicenter, controlled clinical trial evaluating efficacy & safety in 188 patients with COVID-19 under way through 5/10/20. Results not yet available. Chinese Clinical Trial Registry link: http://www.chictr.org.cn/showprojen.aspx?proj=49409</p> <p>US/Global randomized, placebo-controlled trial: Manufacturer (Roche) conducting a randomized, double-blind, placebo-controlled phase 3 trial (NCT04320615) in collaboration with the US Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA); the study will evaluate safety and efficacy of tocilizumab in combination with standard of care compared with placebo. Expected to enroll about 330 patients globally, including in the U.S., beginning in April 2020^{7, 8}</p> <p>Multiple other clinical trials planned or initiated using tocilizumab in COVID-19 patients in China and Europe⁵</p>	<p>IV infusion: China recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg²</p> <p>US/Global randomized, placebo-controlled trial (manufacturer sponsored): Will evaluate an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose may be given if symptoms worsen or show no improvement⁸</p>	<p>In China, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels²</p> <p>Published data to support use currently are limited^{1, 7}</p>

OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
<p>ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)</p> <p>Updated 4/3/20</p>	24:32 Renin-Angiotensin-Aldosterone System Inhibitor	<p>Hypothetical harm: Human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2).^{1, 4, 5} Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs.^{1, 4, 8} Increased expression of ACE2 may potentially facilitate COVID-19 infections.¹</p> <p>Hypothetical benefit: ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.^{1, 2, 6}</p>	<p>Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection.^{1, 2, 3}</p> <p>Clinical trial underway: Initiation of losartan in adult patients with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009)⁷</p>		<p>American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend to continue treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.^{2, 3}</p> <p>Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.^{1, 4}</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.⁸</p>
<p>Ibuprofen</p> <p>Updated 4/15/20</p>	28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)	<p>Speculative link between ibuprofen and increased ACE2 expression leading to worse outcomes in COVID-19 patients, and should NOT be used in patients with COVID-19¹</p>	None; anecdotal ¹		<p>A letter published in The Lancet Respir Med stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2; however, this appears to be based on animal studies.^{1, 4}</p> <p>A statement attributed to WHO spokesperson Christian Lindmeier recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position could not be found on the WHO website or other official sources. WHO has stated "after a rapid review of the literature, is not aware of published clinical or population-based data on this topic." As of 3/18/20 (via Twitter) "WHO does not recommend against the use of ibuprofen." https://twitter.com/WHO/status/1240409217997189128</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
					<p>In addition, there have been unsubstantiated reports of younger, healthy patients who took ibuprofen and suffered severe outcomes with COVID-19. Official case reports are lacking.</p> <p>On 3/19/20, FDA issued a statement that it is not aware of scientific evidence connecting the use of NSAIDs, such as ibuprofen, with worsening COVID-19 symptoms. FDA stated that it is investigating this issue further and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that by reducing inflammation, and possibly fever, these drugs may diminish the utility of diagnostic signs in detecting infections. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19</p> <p>Therefore, currently no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19. However, some experts have recommended preferentially using acetaminophen for treatment of fever ^{2, 3, 4}</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) ²</p>
Indomethacin 3/20/20	28:08.04 Nonsteroidal Anti-inflammatory Agents (NSAIA)	Possible antiviral activity against other coronaviruses SARS-CoV & CanineCoV (interferes with viral RNA synthesis) ¹	Speculative; one in vitro & animal model study with other coronaviruses SARS-CoV & CanineCoV ¹		



Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
Ivermectin <i>Added 4/8/20</i>	8:08 Anthelmintic	In vitro activity against some human and animal viruses ¹⁻⁶ In vitro evidence of activity against SARS-CoV-2 in Vero-hSLAM cells infected with the virus ¹	Currently no known published data regarding efficacy or safety in the treatment of COVID-19		No data to date to support use in the treatment of COVID-19 Only data available to date are results of a single in vitro study
Nebulized drugs <i>Added 3/27/20</i>		Potential harm: Concern that use of nebulized drugs (e.g., albuterol) for the management of respiratory conditions in patients with COVID-19 infection may distribute the virus into the air and expose close contacts. ^{1,2}	Nebulizer treatment used in clinical practice to treat influenza and other respiratory infections is thought to generate droplets or aerosols. In one study, nebulized saline delivered droplets in the small- and medium-size aerosol/droplet range. These results may have infection control implications for airborne infections, including severe acute respiratory syndrome and pandemic influenza infection. ³		American College of Allergy, Asthma & Immunology (ACAAI) recommends that nebulized albuterol should be administered in a location that minimizes exposure to close contacts who do not have COVID-19 infection. In the home, choose a location where air is not recirculated (e.g., porch, patio, or garage) or areas where surfaces can be cleaned easily or may not need cleaning. ¹ In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose inhalers because of the risk of the virus becoming airborne when treating patients infected with COVID-19. ²
Niclosamide <i>3/20/20</i>	8:08 Anthelmintic	Broad antiviral activity In vitro evidence of activity against SARS-CoV and MERS-CoV ^{1,2}	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 In drug repurposing screens, was found to inhibit replication and antigen synthesis of SARS-CoV; did not interfere with virion's attachment into cells ^{1,2}		Not commercially available in the US No data to date support use in treatment of COVID-19
Nitazoxanide <i>Added 4/1/20</i>	8:30.92 Antiprotozoal	In vitro activity against various viruses, including coronaviruses ^{4,5} Structurally similar to niclosamide ^{3,5} In vitro evidence of activity against SARS-CoV-2 ¹	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 Other infections (influenza): In a randomized, placebo-controlled phase 2b/3 study in 624 otherwise healthy adult and adolescent patients with acute uncomplicated influenza, treatment with nitazoxanide reduced duration of symptoms by approximately 1 day ⁶	Dosages investigated for treatment of influenza and influenza-like illness or being investigated for other viral infections: Adults and adolescents (≥12 years of age): 500 or 600 mg orally twice daily for 5 days ^{6,7,8}	Current data not specific to COVID-19; additional study needed ¹

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
		<p>In vitro activity against MERS-CoV⁴</p> <p>Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice⁴</p>	<p>Other infections (influenza-like illness): In two phase 2 studies for the treatment of influenza-like illness symptoms associated with viral respiratory infection in 186 adults and pediatric pts, treatment with nitazoxanide reduced duration of symptoms (4 days versus ≥7 days with placebo).⁷ In another phase 2 study in 260 adults and pediatric pts hospitalized with influenza-like illness (≥50% with pneumonia at presentation), treatment with nitazoxanide did not reduce the duration of hospital stay (primary end point) or duration of symptoms⁷</p>		
<p>Tissue Plasminogen Activator (t-PA; alteplase)</p> <p>Added 4/15/20</p>	<p>20:12.20 Thrombolytic agents</p>	<p>Experience from China and Italy suggests that patients with severe COVID-19 infection may develop a hypercoagulable state contributing to their risk of respiratory failure and acute respiratory distress syndrome (ARDS).^{1, 2, 3, 5, 6, 7, 8, 9}</p> <p>Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular thrombosis and occlusion in</p>	<p>Results of a small phase 1 study conducted in 2001 suggest possible benefit for treatment of ARDS.^{1, 2, 3} 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 a plasminogen activator (urokinase or streptokinase); such therapy improved PaO₂ and also appeared to improve survival.^{1, 2, 3}</p>	<p>An initial t-PA (alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg of t-PA over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg, has been tested in patients with COVID-19 in an ongoing study by Beth Israel Deaconess et al; however, the optimum dose, route of administration, and duration of treatment remain to be determined.^{1, 9}</p>	<p>t-PA has been proposed as a salvage treatment for COVID-19 patients with decompensating respiratory function when mechanical ventilation or extracorporeal membrane oxygenation (ECMO) is not available.¹ However, there is currently no clinical trial data to inform this practice and a lack of clinical experience with the use of fibrinolytic agents in ARDS patients in general.¹¹</p> <p>Several institutions (Beth Israel Deaconess, University of Colorado Anschutz Medical Campus, Denver Health) are planning to test this approach under the FDA compassionate use program.^{2, 4} Initial findings from the first few cases reported initial, transient improvement in PaO₂/FiO₂ (P/F) ratio.⁹</p>

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage ^a	Comments
		<p>the pulmonary vasculature; potential use of t-PA is based on these findings.^{1, 2, 9, 10}</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.⁸</p>

^a 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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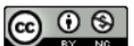
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