Assessment of Evidence for COVID-19-Related Treatments: Updated 5/8/2020

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Select entries were updated on 5/8/2020; these can be identified by the date that appears in the Drug(s) column.

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ANTIVIRAL AGENTS

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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 4/29/20*	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 **Clinical experience** in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 [4-6] **Double-blind randomized phase 2b study in Brazil (Borba et al)** to evaluate two different chloroquine dosages as adjunctive therapy in hospitalized adults with severe COVID-19 (NCT04323527): The first 81 enrolled pts were randomized 1:1 to receive high-dose chloroquine (600 mg twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. By day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QT_c >500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). The high-dose arm	**Optimal dosage and duration of treatment not known** [20, 25] **Consider:** 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base [17] **Various dosages recommended or being investigated for treatment of COVID-19** **Oral chloroquine phosphate dosage suggested in the EUA:** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation [25] **Oral chloroquine phosphate:** 500 mg twice daily for 7 days (adults 18-65 years weighing >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] **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]	Efficacy and safety of chloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. [11] NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of chloroquine for the *treatment* of COVID-19.[35] IDSA recommends that chloroquine be used for the *treatment* of COVID-19 in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including chloroquine, for

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			included more pts prone to cardiac complications than the lower-dose arm. Data were insufficient to evaluate efficacy. Study continuing using only the lower dosage. [37] Multiple clinical trials to evaluate chloroquine for the *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10] NCT04323527 NCT04328493 NCT04331600 NCT04333628 NCT04353336 NCT04360759 NCT04362332 Several clinical trials to evaluate chloroquine for *prevention* of COVID-19 in the healthcare setting are registered at clinicaltrials.gov: [10] NCT04303507 NCT04333732 NCT04349371		preexposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for *prevention* of SARS-CoV-2 infection outside of clinical trials. [35] Because chloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; [36, 39] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. [35, 36, 39] FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. [39] **Emergency use authorization (EUA) for chloroquine:** FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use **only** in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. [24, 25] To request the drug, healthcare providers should contact local or state health departments; [25] 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 .

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					adverse event reporting to FDA MedWatch). [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
Favipiravir (Avigan®, Favilavir) ***Updated 5/8/20***	8:18.32 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [1–5] In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug [1, 5, 16] Licensed in Japan and China for treatment of influenza [2, 4, 6]	**Only very limited clinical trial data available** to date to evaluate use of favipiravir in the treatment of COVID-19 **Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir (Arbidol®; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe to critical COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe to critical disease compared with the group receiving umifenovir. [6] **In a small, open-label, nonrandomized study** in patients with non-severe COVID-19 in China (ChiCTR2000029600), favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (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 α-1b. [15]	A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days was used in one open-label COVID-19 study [6] A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 14 days was used in one open-label COVID-19 study [15] Protocol in one ongoing trial (NCT04336904) for treatment of moderate COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 600 mg three times daily thereafter for up to 14 days [7] Protocol in one ongoing trial (NCT04346628) for treatment of mild COVID-19 specifies a favipiravir dosage of 1800 mg on day 1, then 800 mg twice daily on days 2–10 [7] Protocol in one ongoing trial (NCT04349241) for treatment of non-severe COVID-19 specifies a favipiravir dosage of 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10 [7] Protocol in one ongoing trial NCT04358549 for treatment of COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 [7]	Not commercially available in the US Efficacy and safety of favipiravir for treatment of COVID-19 not established Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dosage and treatment duration Given the lack of pharmacokinetic and safety data for the high favipiravir dosages proposed for treatment of COVID-19, the drug should be used with caution at such dosages. [19, 20] Some have suggested close cardiac (e.g., QT_c) and hepatic monitoring during treatment, as well as monitoring of plasma and tissue concentrations of the drug and, if possible, the active metabolite. [19, 20] Some data suggest that favipiravir exposure may be greater in Asian populations. [17, 19] 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. [14] If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g [17, 18]

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			Italy: Randomized, placebo-controlled multicenter trial (NCT04336904) to evaluate efficacy and safety of favipiravir in pts with moderate COVID-19 [7] **US**: Randomized, controlled open-label proof-of-concept trial (NCT04358549) of favipiravir for the treatment of COVID-19 [7, 10] **US**: Randomized, open-label trial (NCT04346628) to evaluate efficacy of favipiravir in pts with mild, uncomplicated COVID-19 [7] **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 (some listed below): [7-9] NCT04310228 NCT04319900 NCT04303299 NCT04333589 NCT04336904 NCT04345419 NCT04351295 NCT04349241 NCT04356495 NCT04358549 NCT04359615 NCT04373733 ChiCTR2000029544 ChiCTR2000030113 ChiCTR2000029548 ChiCTR2000030894 ChiCTR2000030987 ChiCTR2000029996 JapicCTI-205238 JPRN-jRCTs031190226 JPRN-jRCTs041190120	Protocol in one ongoing trial (NCT04373733; PIONEER) for early treatment of suspected or confirmed COVID-19 specified a favipiravir dosage of 1800 mg twice daily on day 1, followed by 800 mg twice daily on days 2–10 [7] Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2, [1, 5, 13] 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. [11, 19, 20] One such favipiravir regimen used in the treatment of Ebola virus disease includes a loading dosage of 6000 mg (doses of 2400 mg, 2400 mg, and 1200 mg given 8 hours apart on day 1), then a maintenance dosage of 1200 mg every 12 hours on days 2–10. [12, 13] 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 [19]	
HIV Protease Inhibitors *Updated 4/24/20*	8:18.08.08 HIV Protease Inhibitors	**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]	**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	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days [3, 16] **LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours) [6]	**LPV/RTV:** Efficacy for the treatment of COVID-19, with or without other antivirals, not definitely established **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

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		Atazanavir (ATV): ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells, [17, 19] human epithelial pulmonary cells (A549), [17] and human monocytes [17] **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] in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells [19] **Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):** In vitro activity against SARS-CoV-2 in Vero E6 cells [19]	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, 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] **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.) **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] **LPV/RTV Clinical Experience (SARS and MERS):** Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon. [1, 8, 9, 10, 11]	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days [13] 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] **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] **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]	of DRV/cobicistat for treatment of COVID-19 and initial unpublished results from a study in China indicated that a 5-day regimen of DRV/cobicistat was not effective for treatment of COVID-19 [21] **Atazanavir, Nelfinavir, Saquinavir, Tipranavir:** No data to date to support use in the treatment of COVID-19 NIH COVID-19 Treatment Guidelines Panel recommends against the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial [22] IDSA recommends that LPV/RTV be used for the treatment of COVID-19 only in the context of a clinical trial [23]

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			LPV/RTV COVID-19 Clinical Trials at clinicaltrials.gov: NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease) [15] NCT04276688 (LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone) [15] NCT04328012 (LPV/RTV vs hydroxychloroquine vs losartan vs placebo) [15] **Darunavir COVID-19 Clinical Trials:** NCT04252274: Open-label randomized trial in China to evaluate DRV/cobicistat [15] NTC04303299: Open-label randomized trial in Thailand to evaluate DRV/RTV in conjunction with other antivirals [15] ChiCTR2000029541: Open-label randomized trial in China to evaluate DRV/cobicistat vs LPV/RTV [20]		
Hydroxychloroquine (Plaquenil®) *Updated 4/29/20*	8:30.08 Antimalarial	In vitro activity against various viruses, including coronaviruses [5, 8. 12-14] In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed [8, 12] Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections [3, 8, 13, 15, 16] Known pharmacokinetics and toxicity profile 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]	**Only limited clinical trial data available** to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19 **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] **Hydroxychloroquine small pilot study conducted in China:** 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; [18] **both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV**. [30] Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 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	**Optimal dosage and duration of treatment not known** [20, 26] **Various dosages recommended or being investigated** for treatment of COVID-19 **Oral hydroxychloroquine sulfate dosage suggested in the EUA:** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation [26] **Oral hydroxychloroquine sulfate:** 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 [8, 20] **Oral hydroxychloroquine sulfate:** 400 mg once or twice daily for 5-10 days [10, 18] **Oral hydroxychloroquine sulfate:** 600 mg twice daily on day 1, then 400 mg daily on days 2-5 [20]	Efficacy and safety of hydroxychloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.) Additional data needed regarding toxicity profile when used in patients with COVID-19 Hydroxychloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. [11]

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			treated with the drug (all pts showed improvement at follow-up). [18] **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 (O_2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids)** and 31 other pts received **standard treatment alone** (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >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]	**Oral hydroxychloroquine sulfate:** 100-200 mg twice daily for 5-14 days [4] **Oral hydroxychloroquine sulfate:** 200 mg 3 times daily for 10 days [7, 34]	NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against use of hydroxychloroquine for the *treatment* of COVID-19. [35] IDSA recommends that hydroxychloroquine be used for the *treatment* of COVID-19 in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the *treatment* of COVID-19, except in the context of a clinical trial. [35] IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the *treatment* of COVID-19 only in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for *prevention* of SARS-CoV-2 infection outside of clinical trials. [35] Because hydroxychloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; [36, 39] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects [35, 36, 39] FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions

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			Hydroxychloroquine with azithromycin open-label, nonrandomized study in France (Gautret et al): Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6.[7] **Note:** This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented. **Hydroxychloroquine with azithromycin open-label, uncontrolled study in France (Molina et al):** 11 adults hospitalized with 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 O_2. 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		against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch.[39] **Emergency use authorization (EUA) for hydroxychloroquine:** FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use **only** in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible.[24, 26] To request the drug, healthcare providers should contact local or state health departments;[26] distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA.[29] To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch).[24, 26] FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID-19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks.[24] Consult the EUA,[24] EUA fact sheet for healthcare providers,[26] and EUA fact sheet for patients and parent/caregivers[28] for additional information.

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			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. **Hydroxychloroquine with azithromycin uncontrolled, retrospective, observational study in France (Gautret et al):** 80 adults with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O_2 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_2; 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		

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			infectiousness, especially for pts with more severe disease. **Hydroxychloroquine (with or without azithromycin) in a retrospective analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers (Magagnoli et al):** Data for 368 males (median age >65 years) treated with hydroxychloroquine in addition to standard supportive management were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in those treated with hydroxychloroquine, 22.1% (25/113) in those treated with hydroxychloroquine and azithromycin, and 11.4% (18/158) in those not treated with hydroxychloroquine; rate of ventilation was 13.3, 6.9, and 14.1%, respectively. Use of hydroxychloroquine alone (but not use of hydroxychloroquine and azithromycin) was associated with increased overall mortality compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation. [40] **Note:** The pt population included only elderly males 59-75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures. **Efficacy measures:** Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. [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] Multiple clinical trials to evaluate hydroxychloroquine for *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			NCT04329923 NCT04332991 NCT04334967 NCT04335552 NCT04341727 NCT04345692 NCT04350450 NCT04351620 NCT04353037 NCT04362332 Multiple clinical trials to evaluate hydroxychloroquine for *prevention* of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed below): [10] NCT04303507 NCT04318015 NCT04318444 NCT04328961 NCT04330144 NCT04331834 NCT04333225 NCT04341441 NCT04352946 NCT04359537 NCT04363450		
Neuraminidase inhibitors (e.g., oseltamivir) ***Updated 5/8/20***	8:18.28	Antivirals active against influenza viruses	In a **retrospective case series** of 99 patients with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of patients received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died. [1] 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] Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture. [4]	Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours. [1] 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]	No data to date support use in the treatment of COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Clinicaltrials.gov trials for COVID-19 that include oseltamivir[5]: NCT04303299 NCT04261270 NCT04255017 NCT04338698		
Remdesivir *Updated 5/4/20*	8:18.32 Antiviral	Broad-spectrum antiviral (nucleotide analog prodrug) with activity against various viruses, including coronaviruses [24] In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells [1, 18] 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 viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control [19] 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] Pharmacokinetic data available from evaluations for Ebola	**Various clinical trials** initiated in US, China, and other countries **Randomized, double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al):** Pts were randomized 2:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10) or placebo initiated within 12 days of symptom onset. Primary outcome was time to clinical improvement within 28 days after randomization or hospital discharge, whichever came first. ITT population included 158 pts treated with remdesivir and 78 pts treated with placebo; 32% of pts also received interferon α-2b, 28% also received LPV/RTV, and 66% also received corticosteroids during hospitalization. **Median time to clinical improvement was not significantly different in remdesivir group (21 days) vs placebo group (23 days); 28-day mortality rate was similar in both groups (14 vs 13%).** When remdesivir was initiated within 10 days of symptom onset, median time to clinical improvement was numerically shorter (but not statistically significant) compared with placebo group (18 vs 23 days). Duration of invasive mechanical ventilation was numerically shorter (but not statistically significant) in remdesivir group; only a small percentage of pts (0.4%) were on invasive mechanical ventilation at time of enrollment. Remdesivir did not result in significant reduction in SARS-CoV-2 viral load in nasopharyngeal, oropharyngeal, and sputum samples. Remdesivir was discontinued in 18 pts (12%) because of adverse effects. **Note:** Enrollment was terminated before the pre-specified number of pts was attained (lack of available	**Optimal dosage and duration of treatment not known [25, 26]** 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] 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) [10] Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) [11] NIAID adaptive study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total [13] Compassionate use access protocol: 200 mg IV on day 1, then 100 mg IV on days 2-10 [16] **Emergency use authorization (EUA) dosage recommended for adults and children weighing 40 kg or more:** Loading dose of 200 mg by IV infusion on day 1, followed by 100 mg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 100 mg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts **not** requiring mechanical ventilation and/or ECMO). [26] **Emergency use authorization (EUA) dosage recommended for children weighing 3.5 to less than 40 kg:**	Not commercially available; most promising direct-acting antiviral (DAA) currently being investigated for COVID-19 Efficacy and safety of remdesivir for treatment of COVID-19 not established NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of remdesivir for the treatment of COVID-19 [20] **Emergency use authorization (EUA) for remdesivir:** FDA issued an EUA on May 1, 2020 that permits use of the drug for the treatment of COVID-19 *only* in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 who have severe disease (defined as oxygen saturation [SpO_2] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) and requires that the drug be administered by a healthcare provider in an inpatient hospital setting via IV infusion at dosages recommended in the EUA. [25, 26] Distribution of remdesivir under this EUA is controlled by the US government for use consistent with the terms and conditions of the EUA. The manufacturer (Gilead) will supply remdesivir to authorized distributors, or directly to a US government agency, who will distribute the drug to hospitals and other healthcare facilities as directed by the US government, in collaboration with state and local government authorities, as needed. [25] The EUA requires that healthcare facilities and healthcare providers administering remdesivir comply with certain

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			pts); **trial was insufficiently powered to detect assumed differences in clinical outcome**. [21] **Phase 3 randomized, open-label trial in hospitalized adults with severe COVID-19 (NCT04292899)** sponsored by the manufacturer (Gilead): Initial study protocol designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg once daily for total of 5 or 10 days) in conjunction with standard of care in pts not receiving mechanical ventilation; [10] protocol subsequently modified to add extension arms to evaluate safety and efficacy of 10-day regimen of remdesivir in conjunction with standard of care in pts who are or are not receiving mechanical ventilation. [10] **Manufacturer announced** that data available for the initial 397 pts **not** requiring mechanical ventilation at study entry (200 received a 5-day regimen and 197 received a 10-day regimen) indicate similar clinical improvement with both treatment durations. **Time to clinical improvement for 50% of pts was 10 days in the 5-day treatment group vs 11 days in the 10-day treatment group. At day 14, 129/200 pts (64.5%) in the 5-day group and 106/197 pts (53.8%) in the 10-day group achieved clinical recovery.** Pts who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms. [23] **Note:** Data regarding this initial pt population (e.g., disease severity and comorbidities at study enrollment, additional supportive treatment received) not provided to date. **Phase 3 randomized, open-label trial in pts with moderate COVID-19 (NCT04292730)** sponsored by the manufacturer (Gilead) is evaluating safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care compared with standard of care alone [11]	5 mg/kg by IV infusion on day 1, followed by 2.5 mg/kg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 2.5 mg/kg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts **not** requiring mechanical ventilation and/or ECMO). [26]	mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). [25, 26] Consult the EUA, [25] EUA fact sheet for healthcare providers, [26] and EUA fact sheet for patients and parent/caregivers [27] for additional information.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Phase 3 adaptive, randomized, placebo-controlled trial (NCT04280705) in hospitalized adults sponsored by NIAID: Pts received remdesivir (200 mg IV on day 1, then 100 mg once daily for duration of hospitalization up to 10 days total) or placebo. [13] **Sponsor announced** that preliminary data analysis (total of 1063 pts) indicated **shorter median time to recovery in remdesivir group (11 days) vs placebo group (15 days)** and suggested that remdesivir treatment may have provided a survival benefit (mortality rate 8% in remdesivir group vs 11.6% in placebo group). [22] **Note:** Data regarding the pt population (e.g., disease severity and comorbidities at study enrollment, time to initiation of treatment after symptom onset, additional supportive treatment received) not provided to date. **Expanded access IND protocol (NCT04323761):** The manufacturer (Gilead) has established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19 [17] **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. 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/ **Compassionate use access (NCT04302766):** May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command [12] **Data from the manufacturer's compassionate use program:** Preliminary data are available for a cohort of 53 adults from		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			multiple sites in the US, Italy, Japan, and other countries who were hospitalized with severe COVID-19 and received treatment with remdesivir; 40 pts received the full 10-day regimen (200 mg IV on day 1, then 100 mg IV on days 2-10), 10 pts received 5-9 days and 3 pts received less than 5 days of treatment with the drug. At baseline, 30 pts (57%) were receiving mechanical ventilation and 4 (18%) were receiving extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days after first dose, 36 pts (68%) showed clinical improvement based on oxygen-support status and 8 pts (15%) worsened. There were 7 deaths (13%), including 6 pts receiving invasive ventilation. Adverse effects (e.g., increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (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		
Umifenovir (Arbidol®) ***Updated 5/8/20***	8:18.92 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [4] Although data limited, in vitro activity against SARS-CoV-1 [4] and SARS-CoV-2 [5] reported	**Retrospective cohort study** in 50 adults with COVID-19 in China suggests better viral suppression with umifenovir vs LPV/RTV. All pts received conventional therapy, including interferon α-2b. At 7 days after hospital admission, SARS-CoV-2 was undetectable in 50% of pts treated with umifenovir vs 23.5% treated with LPV-RTV; at 14 days, viral load undetectable in all pts treated with umifenovir vs 44.1% treated with LPV/RTV. Duration of positive	**Dosage recommended for treatment of COVID-19 in China:** Adults, 200 mg orally 3 times daily for no more than 10 days [5, 7] **Dosage used or being investigated in COVID-19 clinical trials:** 200 mg orally 3 times daily for duration of 7-10 days or longer [2, 3, 6, 8]	Not commercially available in the US Included in some guidelines for treatment of COVID-19 [7] Efficacy for the treatment of COVID-19 not established

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza [4]	SARS-CoV-2 RNA positive test was shorter with umifenovir vs LPV-RTV [8] **Retrospective cohort study** in 33 adults with COVID-19 in China suggests more favorable outcome with LPV/RTV plus umifenovir vs LPV/RTV alone: Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 12/16 pts (75%) treated with LPV/RTV plus umifenovir vs 6/17 pts (35%) treated with LPV/RTV alone; at 14 days, undetectable in 15/16 pts (94%) treated with both drugs vs 9/17 pts (53%) treated with LPV/RTV alone. At 7 days, chest CT scans were improving in 11/16 pts (69%) treated with both drugs vs 5/17 pts (29%) treated with LPV/RTV alone [1] **Retrospective cohort study** in 81 hospitalized, non-ICU adults with COVID-19 in China found *no difference* in clearance of SARS-CoV-2 virus between pts receiving umifenovir vs those who did not. At 7 days, SARS-CoV-2 undetectable in pharyngeal specimens in 33/45 pts (73.3%) treated with umifenovir vs 28/36 pts (77.8%) who did not receive umifenovir. No difference in median time from onset of symptoms to negative SARS-CoV-2 test (18 vs 16 days) [9] **Open-label, prospective, randomized, multicenter study** in 236 adults with 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.) **Randomized, single-center, partially blinded trial in China (NCT0425885)** evaluated efficacy of umifenovir in conjunction with standard care vs LPV/RTV in conjunction with standard care vs standard care without an antiviral in hospitalized adults with mild/moderate COVID-19. [2, 10] Data for the		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			86 enrolled pts suggest no difference in mean time for positive-to-negative conversion of SARS-CoV-2 nucleic acid in respiratory specimens and no difference in clinical outcomes between pts treated with umifenovir or LPV/RTV compared with no antiviral therapy [10] NCT04260594 (not yet recruiting): Randomized, open-label trial evaluating efficacy and safety of umifenovir in conjunction with standard of care in adults with COVID-19 [3]		

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Anakinra *Updated 4/24/20*	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) initiated by the manufacturer (Swedish Orphan Biovitrum) to evaluate efficacy and safety of anakinra or emapalumab with standard of care in reducing hyperinflammation and respiratory distress in patients with COVID-19 is recruiting [3] Other noncomparative, open-label trials are recruiting in Greece (NCT04356366, NCT04339712) and Belgium (NCT04330638) [3]	Various dosage regimens are being studied [3] Trial protocol in Italy (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days [3] Some studies under way in Greece and Belgium are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge (Note: Anakinra is approved only for subcutaneous administration in the U.S.) [1, 7]	Insufficient clinical data to recommend either for or against use in the treatment of COVID-19 [7] Safety profile well established in patients with sepsis and has been studied extensively in pediatric patients with rheumatologic conditions [7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Ascorbic acid *Updated 5/6/20*	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]	**IV ascorbic acid:** 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 also registered: [1] NCT04264533 NCT04323514 NCT04363216 NCT04357782 NCT04344184 **Oral ascorbic acid:** 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 [1] Included at lower dosages as an active or placebo-equivalent comparator (control) in other COVID-19 prevention or treatment studies [1] Included as a component of some hydroxychloroquine-based combination regimens being studied for prevention or treatment of COVID-19 [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 (NCT03333278) in patients with septic shock; additional studies under way [4, 6, 8-10] 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]	Various dosages of IV ascorbic acid used in COVID-19 studies; 50 mg/kg IV every 6 hours for 4 days used in NCT03680274 [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, 8-10] NCT04342728: Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses [1] 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 *Updated 4/24/20*	8:12.12 Macrolides	Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) [1, 3-5] No data to date on in vitro activity against coronaviruses, including SARS-CoV-2 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] 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] 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]	**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] **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] **Clinical experience in pts with COVID-19:** Has been used for antibacterial coverage in hospitalized pts with COVID-19 [15] **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.)	**Adjunctive treatment in certain viral infections:** 500 mg once daily has been used [13] **COVID-19:** 500 mg on day 1, then 250 mg daily on days 2-5 in conjunction with 10-day regimen of hydroxychloroquine has been used [7, 18, 19]	Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19 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 NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial. [21] (See Hydroxychloroquine in this Evidence Table.) IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial. [22] 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; [20] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects [20]
Baricitinib (Olumiant®) *Updated 4/24/20*	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]),	Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19 Baricitinib to be included as an arm in NIAID's Adaptive COVID-19 Treatment Trial[3]	Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1 [1, 2, 5] Dosage information not yet available (see Trials or Clinical Experience)	Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and other drugs [4]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		which may help reduce viral entry and inflammation; also may interfere with intracellular virus particle assembly [1, 2] Inhibits JAK1 and JAK2-mediated cytokine release; may combat cytokine release syndrome (CRS) in severely ill patients [1, 2, 4, 5] Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19 [5]	**Adaptive phase 2/3 clinical trial:** Open-label study planned to evaluate safety and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232) [6] 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) [7, 8, 9, 10]		NIH COVID-19 Treatment Guidelines Panel recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit [11]
Colchicine *Added 4/24/20*	92:16 Antigout Agents	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 [2,3,5,6] May combat the hyperinflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines [2] NLRP3 inflammasone activation results in release of interleukins, including IL-1β [3,5,6,8,11]	Minimal anecdotal experience and no clinical trial data reported to date in COVID-19 [4] **Phase 3, randomized, double-blind, placebo-controlled study** (NCT04322682; COLCORONA) initiated in adults with COVID-19 and at least one high-risk criterion to evaluate effect of colchicine on mortality, hospitalization rate, and need for mechanical ventilation; study excludes enrollment of currently hospitalized patients; enrollment target is approximately 6000 pts [1] Other registered randomized, open-label, parallel-group studies (not yet recruiting) will evaluate effects of colchicine plus standard treatment vs standard treatment alone on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in adults with COVID-19: NCT04326790, NCT04322565, NCT04328480, NCT04350320, NCT04355143 [2,3]	Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days [1] Consider possible need for colchicine dosage adjustment; [2] manufacturer-recommended dosages for labeled indications depend on patient's age, renal and hepatic function, and concomitant use of interacting drugs, including protease inhibitors (e.g., lopinavir/ritonavir), other moderate or potent CYP3A4 inhibitors, and P-glycoprotein (P-gp) inhibitors [5] Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated [5]	Safety and efficacy for treatment of COVID-19 not established

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		In experimental models of acute respiratory distress syndrome/acute lung injury (ARDS/ALI), the NLRP3 inflammasome had a major role in the development of lung injury [3,11] Potential to limit COVID-19-related myocardial damage also has been hypothesized [2,3] based on the drug's mechanisms of action and promising results of ongoing research on colchicine in various cardiac conditions [3,6-10] SARS-CoV-1 envelope (E) protein, a viroporin involved in replication and virulence, activates the NLRP3 inflammasome in vitro in Vero E6 cells by forming calcium-permeable ion channels, leading to increased IL-1β production [2,12,13]			
Corticosteroids (general) *Updated 5/1/20*	68:04 Adrenals	Potent anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9] 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]	**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, 25] Uncontrolled observational data from the recent COVID-19 outbreak in China suggest a possible treatment benefit of methylprednisolone in COVID-19 patients with acute respiratory distress syndrome (ARDS). [6, 13] (See Methylprednisolone in this Evidence Table.) Pending results of randomized controlled clinical studies specifically evaluating corticosteroids for COVID-19, indirect evidence from studies in patients with community-acquired pneumonia, ARDS, and other viral infections has been used to inform treatment decisions for COVID-19 patients. [3, 5, 8, 9, 12, 15-17, 25]	In general, low to moderate dosages of corticosteroids are recommended in intubated patients with ARDS. [8] 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] Higher dosages have been suggested for cytokine storm. [8] (See Comments column.)	Data on the use of corticosteroids in COVID-19 are limited. [3, 5, 7, 24, 25] The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19. [1, 7] 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. [1, 2, 8, 12, 24, 25] **General recommendations:** WHO, CDC, NIH, and IDSA generally recommend against the routine use of corticosteroids for the treatment of COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock). [1, 2, 3, 8, 9, 24, 25]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low [4, 11]	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] In a recent multicenter, unblinded, randomized controlled study (DEXA-ARDS trial), the effects of dexamethasone in conjunction with conventional care were evaluated in hospitalized patients with moderate-to-severe ARDS receiving lung-protective mechanical ventilation. [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 (i.e., 15% increase in 60-day survival) compared with conventional treatment alone. [17] Based on results of this study, a clinical trial (NCT04325061) has been initiated to specifically evaluate the use of dexamethasone in patients with ARDS due to COVID-19. [21] Other clinical trials have been initiated in various countries to evaluate use of IV corticosteroids (e.g., dexamethasone, hydrocortisone), oral corticosteroids (e.g., prednisone), or inhaled corticosteroids (e.g., budesonide) for treatment of COVID-19 pneumonia or ARDS, including the following trials registered at clinicaltrials.gov: [22] NCT04327401 NCT04344288 NCT04344730 NCT04348305 NCT04355637 NCT04359511 NCT04360876 (For registered clinical trials evaluating use of methylprednisolone, see Methylprednisolone in this Evidence Table.) Randomized controlled studies evaluating use of corticosteroids (e.g., hydrocortisone, dexamethasone, methylprednisolone, prednisolone) in septic shock suggest a small, but uncertain mortality reduction. [3, 4]		**Non-critical patients:** Corticosteroids generally should not be used in the treatment of early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding. [3, 8, 24] NIH recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients unless they are in the intensive care unit. [24] **Critically ill patients:** The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and 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] NIH also recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated COVID-19 patients without ARDS. However, the NIH panel states that there is insufficient evidence for or against the use of systemic corticosteroids in mechanically ventilated patients with COVID-19 and ARDS. [24] IDSA suggests against using corticosteroids in hospitalized patients with COVID-19 pneumonia; however, in those with ARDS due to COVID-19, systemic corticosteroids may be used in the context of a clinical trial. [25] **Cytokine storm:** There is no well-established or evidence-based treatment for cytokine storm in patients with COVID-19. [8] However, some experts

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					suggest that use of more potent immunosuppression with corticosteroids may be beneficial in such patients. [8] These experts suggest higher dosages of corticosteroids (e.g., IV methylprednisolone 60-125 mg every 6 hours for up to 3 days) followed by tapering of the dose when inflammatory markers (e.g., C-reactive protein levels) begin to decrease. [8] The decision to use corticosteroids in patients with early signs of cytokine storm should be balanced with the known adverse effects. [24] **Septic shock:** The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different than the effects seen in those with ARDS. [12] The Surviving Sepsis Campaign and NIH suggest the use of low-dose corticosteroid therapy (e.g., hydrocortisone 200 mg daily as an IV infusion or intermittent doses) over no corticosteroid therapy in adults with COVID-19 and refractory shock. [12, 24] 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] **Patients receiving corticosteroid therapy for chronic conditions**: NIH states that oral corticosteroids used for the treatment of an underlying condition prior to COVID-19 infection (e.g., primary or secondary adrenal insufficiency, rheumatologic diseases) should not be discontinued. Supplemental or stress dosages of corticosteroids may be indicated on an individual basis in patients with such conditions. The guidelines also recommend that inhaled corticosteroids used daily for the management of asthma and COPD to control airway

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					inflammation should not be discontinued in patients with COVID-19. [24] 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. [19, 26] 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. [19] These guidelines also apply to patients who are receiving prolonged therapy (> 3 months) with corticosteroids for underlying inflammatory conditions, including asthma, allergy, and rheumatoid arthritis. [19] In such patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral corticosteroids may be necessary. [19, 26] Administration of physiologic stress doses of corticosteroids (e.g., IV hydrocortisone 50-100 mg 3 times daily) and not pharmacologic doses should be considered in all cases to avoid potentially fatal adrenal failure.[19, 20] Additional study is needed to determine the optimum corticosteroid stress dosage regimens in patients with COVID-19. [26, 27] There is some evidence suggesting that continuous IV infusion of hydrocortisone (following an initial IV bolus dose) may provide more stable circulating cortisol concentrations in patients with adrenal insufficiency and reduce the potentially harmful effects of peak and trough concentrations of cortisol on the immune system. [26, 27] **Pregnancy considerations:** For pregnant women with COVID-19, NIH guidelines state that the antenatal use of corticosteroids that cross the placenta

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					(i.e., betamethasone, dexamethasone) is generally reserved for when administration is required for fetal benefit. Other systemic corticosteroids do not cross the placenta, and pregnancy is not a reason to restrict their use if otherwise indicated. ACOG recommends against administration of antenatal corticosteroids for fetal benefit in the late preterm period (i.e., 34 weeks and 0 days through 36 weeks and 6 days) in patients with suspected or confirmed COVID-19 because the benefits of such therapy in late preterm are less well established. Treatment should be individualized, weighing the neonatal benefits of antenatal corticosteroid therapy with the risks of potential harm to the pregnant patient. [24]
COVID-19 Convalescent Plasma ***Updated 5/8/20***		Plasma obtained from patients who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2, including neutralizing antibodies, may provide short-term *passive* 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. [1-5, 24] Convalescent plasma therapy has been used historically for the treatment of various viral diseases, including some that have caused other pandemics. [16, 20, 22, 24] In patients with SARS-CoV-1 infection, use of convalescent plasma was reported to shorten the duration of hospitalization	**Uncontrolled pilot study of COVID-19 convalescent plasma in China:** 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 α) and 6 patients also received methylprednisolone. The median time from onset of symptoms to transfusion of convalescent plasma was 16.5 days. COVID-19 symptoms (fever, cough, shortness of breath, chest pain) improved in all patients within 1-3 days after the transfusion and all patients showed radiological 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. [9] **Uncontrolled case series in China: 5** critically ill adults with rapidly progressing severe COVID-19 and acute respiratory		Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. [11] Most appropriate criteria for selection of patients to receive investigational COVID-19 convalescent plasma, optimal time during the course of the disease to receive such therapy, and appropriate dosage (e.g., volume, number of doses) not determined. [1-5, 9] Theoretically, convalescent plasma should be more effective if given during the early course of the disease.[1, 2, 16, 17, 20, 24] Optimal timing of donor plasma collection in relation to recovery from COVID-19, most appropriate methods of antibody testing, and minimum titers of SARS-CoV-2 antibody in convalescent plasma that may be associated with clinical benefits in pts with COVID-19 not determined. [1-5] Logistics of obtaining, processing, storing, and distributing COVID-19 convalescent plasma evolving. [1-5, 11, 14, 15] FDA does not collect COVID-19 convalescent plasma and does not provide such plasma; healthcare providers and acute care

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		and decrease mortality; [6-8, 14] SARS patients who received convalescent plasma less than 14 days after onset of symptoms had better outcomes than those who received such plasma later in the course of the disease. [1, 2, 6-8]	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 α-1b) and methylprednisolone. Patients received the convalescent plasma transfusions 10-22 days after hospital admission. Following the transfusions, body temperature normalized within 3 days in 4/5 patients, sequential organ failure assessment (SOFA) scores improved in all patients (decreased from initial scores of 2-10 to 1-4 on day 12), titers of SARS-CoV-2 IgG, IgM, and neutralizing antibody increased in all patients, and viral loads decreased and became negative within 12 days. [10] **Retrospective observational study in China**: 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 out of 6 patients. [16] **Uncontrolled descriptive study in China:** 6 adults with COVID-19 received convalescent plasma initiated at a relatively late stage of the disease (most patients received 2 or 3 plasma transfusions); various laboratory, radiologic, and clinical improvements were reported. [18] **Although there is some evidence that suggests possible benefits from use of convalescent plasma in patients with COVID-19, available data to date are largely from case reports or series; confirmation from randomized controlled studies is required.** [1, 20-23]		facilities obtain COVID-19 convalescent plasma from FDA-registered establishments. [11] Potential risks associated with COVID-19 convalescent plasma therapy (e.g., inadvertent transmission of other infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], antibody-dependent enhancement of infection) and steps to mitigate such risks not fully determined and require further evaluation. [1-5, 9, 23, 24] **FDA issued a guidance for industry to provide recommendations to healthcare providers and investigators regarding administration and study of investigational COVID-19 convalescent plasma**. This guidance document includes recommendations regarding pathways for access to COVID-19 convalescent plasma, patient eligibility to receive such plasma, collection of such plasma (including donor eligibility and qualifications), product labeling, and recordkeeping. [11] **FDA states that COVID-19 convalescent plasma is regulated as an investigational product and there currently are 3 available pathways for administering or studying use of such plasma**: 1). **Clinical Trials:** Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional investigational new drug (IND) regulatory pathway. [11] 2). **Expanded Access IND:** For patients with serious or immediately life-threatening COVID-19 who are not eligible or are unable to participate in randomized clinical trials, an expanded access IND can be used. A National Expanded Access Treatment Protocol has been established to facilitate access

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Multiple clinical trials have been initiated in the US and other countries to evaluate use of COVID-19 convalescent plasma in various settings (e.g., postexposure prophylaxis, treatment of different stages of the disease). [19, 22] Some of the trials that are currently recruiting are listed below. For additional trials, see clinicaltrials.gov: NCT04374370 (Expanded Access) NCT04358211 (Expanded Access) NCT04338360 (Expanded Access) NCT04363034 (Expanded Access) NCT04343261 (US) NCT04372368 (US) NCT04343755 (US) NCT04344535 (US) NCT04364737 (US) NCT04340050 (US) NCT04344015 (US) NCT04376034 (US) NCT04359810 (US) NCT04362176 (US) NCT04360486 (US ARMY) NCT04347681 NCT04346446 NCT04345523 NCT04342182 NCT04352751 NCT04375098 NCT04357106 NCT04327349 NCT04292340		through participation of acute care facilities under an IND that is already in place. [11] Information on a protocol that is currently in place is available at https://www.uscovidplasma.org. [12] 3). **Single Patient Emergency IND (eIND)**: Licensed physicians seeking to administer COVID-19 convalescent plasma to individual patients with serious or life-threatening disease may request an eIND from the FDA. Consult the FDA guidance document for specific information on applying for an eIND. [11] **Donor eligibility**: FDA guidance suggests that COVID-19 convalescent plasma be collected from individuals with laboratory-confirmed evidence of COVID-19 infection and complete resolution of symptoms for at least 14 days before donation (a negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor). [11] **Antibody titers in donor plasma:** If measurement of antibody titers is available, FDA recommends a neutralizing antibody titer of at least 1:160 (a titer of 1:80 may be considered acceptable if an alternative matched unit of plasma is not available). [11] **Patient eligibility**: For healthcare providers seeking an eIND for the treatment of patients with severe or life-threatening disease, consideration should be given to following the patient eligibility criteria used in the National Expanded Access Treatment Protocol https://www.uscovidplasma.org. [11] According to the protocol, **severe** disease is defined as one or more of the following: shortness of breath, respiratory frequency 30/minute or greater, blood oxygen saturation 93% or lower, PaO_2/FiO_2 ratio less than 300, lung infiltrates greater than 50% within 24-48 hours, and **life-threatening disease** is defined as one or more of the following: respiratory failure, septic shock, multiple organ dysfunction or failure. [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Epoprostenol (inhaled) *Added 4/3/20*	48:48 Vasodilating Agent	Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19 [1-9] **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]	No studies evaluating use specifically in COVID-19 patients [10] 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]	Various dosages of inhaled epoprostenol have been used in ARDS studies [2, 9] 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 PaO_2 and reduction in pulmonary artery pressure, data from these studies suggest that the most effective and safe dosage appears to be 20-30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients [9]	Additional studies are needed to evaluate the potential role of inhaled epoprostenol in the treatment of ARDS [6-9] The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against use of inhaled prostacyclins in COVID-19 patients with severe ARDS [10]
Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®) *Updated 5/1/20*	68:04 Adrenal	Potent anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9] (See Corticosteroids in this Evidence Table.)	**Retrospective, observational, single-center study:** In 201 patients with confirmed COVID-19 pneumonia who developed ARDS, methylprednisolone appeared to reduce the risk of death. [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] **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] **Open-label, multicenter, randomized controlled study** (NCT04244591) was recently completed in China that compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to acute respiratory failure; results have not yet been posted. [23]	Dosage used in the retrospective study (Wu et al) not provided. [6] Dosage used in the retrospective study (Wang et al) was 1-2 mg/kg daily IV for 5-7 days. [13] Dosage used in the randomized, controlled study (NCT04244591) was 40 mg IV every 12 hours for 5 days. [23]	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] (See Corticosteroids in this Evidence Table.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Multiple clinical trials have been initiated in various countries to evaluate use of methylprednisolone for *treatment* of COVID-19 pneumonia or severe acute respiratory syndrome, including the following trials registered at clinicaltrials.gov: [22] NCT03852537 NCT04263402 NCT04323592 NCT04329650 NCT04343729 A non-randomized pilot study registered at clinicaltrials.gov (NCT04355247) has been initiated to evaluate use of methylprednisolone for the *prevention* of COVID-19 cytokine storm and progression to respiratory failure. [22]		
Nitric oxide (inhaled) *Updated 4/22/20*	48:48 Vasodilating Agent	Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19 [2, 3, 9] In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential effectiveness for COVID-19 [1]	No studies evaluating use specifically in COVID-19 patients [10] In a small pilot study (Chen et al.) conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide in ICU patients with SARS reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support [2, 3] Randomized controlled studies of inhaled nitric oxide in ARDS patients generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment) [4, 5, 6, 9]	In the Chen et al. study in severe SARS patients, inhaled nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) [2] Phase 2 clinical trial protocol (NCT04306393) for treatment of mechanically ventilated COVID-19 patients: 80 ppm for the first 48 hours, followed by 40 ppm and then subsequently wean [3]	Therapeutic guidelines for the treatment of ARDS state that inhaled nitric oxide may be considered in patients with severe hypoxemia not responsive to conventional ventilation strategies; however, routine use not recommended [4, 5, 6, 9, 10] The Surviving Sepsis Campaign suggests a trial of inhaled pulmonary vasodilator therapy as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if rapid improvement in oxygenation is not observed, treatment should be tapered off [10] Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway (NCT04338828, NCT04305457, NCT04306393, NCT04312243) [3, 7] 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-19 [8]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Ruxolitinib (Jakafi®) *Updated 5/6/20*	10:00 Antineoplastic Agents	Janus kinase (JAK) 1 and 2 inhibitor; [7] may potentially combat cytokine release syndrome (CRS) in severely ill patients [4, 5] Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19 [5, 7]	Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19 **Phase 3 randomized, double-blind, placebo-controlled clinical trial** (NCT04362137; RUXCOVID) evaluating ruxolitinib plus standard of care vs standard of care alone is being initiated in patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.) [1, 10] **Expanded-access (managed-access, compassionate use) program** (NCT04337359) available for eligible adults and children ≥6 years of age with **severe or very severe COVID-19** illness; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) [1, 2] **Expanded-access program** (NCT04355793) available for emergency treatment of **cytokine storm** from COVID-19 infection in adults and pediatric patients ≥12 years of age; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) [9] Other earlier-phase, smaller, and/or open-label clinical trials registered: NCT04331665 NCT04334044 NCT04338958 NCT04348071 NCT04359290 NCT04354714 NCT04348695 ChiCTR2000029580 (in Chinese Clinical Trial Registry) [3, 6]	Various dosages are being evaluated [3, 6, 10] Phase 3 study (NCT04362137): Ruxolitinib 5 mg twice daily for 14 days with possible extension to 28 days [10]	NIH COVID-19 Treatment Guidelines Panel recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit [8]
Sarilumab (Kefzara®) *Updated 5/1/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients [1, 2, 5]	Currently no known published clinical trial evidence supporting efficacy or safety in treatment of patients with COVID-19 However, based on encouraging results in China with a similar drug, tocilizumab, a U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently under way [3, 4]	Not available (see Trials or Clinical Experience)	NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of sarilumab in the treatment of COVID-19 [7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Clinicaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4 **For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)** [6]		
Sirolimus (Rapamune®) *Updated 4/22/20*	92:44 Immunosuppressive agent (mTOR inhibitor)	mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus [1, 2, 5] In vitro studies demonstrated inhibitory activity against MERS-CoV infection [2]	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] A randomized, double-blind, placebo-controlled trial (NCT04341675) has been initiated to evaluate the use of sirolimus in hospitalized patients with COVID-19 [4]	Dosage being investigated in NCT04341675 trial: 6 mg orally on day 1 followed by 2 mg daily for a maximum treatment duration of 14 days or until hospital discharge [4]	Although possible clinical application, current data not specific to COVID-19; additional study needed [5]
Tocilizumab (Actemra®) *Updated 5/1/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients [1-3, 6, 10, 14]	Case reports and observational studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world [1, 3, 10, 12] 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) [3] 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. [10]	IV infusion: **China** recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg [2] **US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA):** Will evaluate an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose may be given if symptoms worsen or show no improvement [8]	**In China**, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels [2] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of tocilizumab in the treatment of COVID-19 [9] The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study [14]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			A single-center, retrospective observational study of 20 kidney transplant recipients in Italy with COVID-19 hospitalized for pneumonia included 6 patients who received tocilizumab. Half of the patients experienced reduced oxygen requirements and 2 (33%) showed improved radiologic findings following administration; 2 (33%) of the 6 tocilizumab-treated patients died. [12] Zhang et al. from China reported on a patient with COVID-19 and multiple myeloma who appeared to be successfully treated with tocilizumab [13] Currently, there are no well-controlled published studies on the efficacy and safety of tocilizumab for the treatment of COVID-19; however, numerous clinical trials are planned or under way globally [1, 5, 7, 8] **China**: Randomized, multicenter, controlled clinical trial evaluating efficacy & safety in 188 patients with COVID-19 under way through 5/10/20. **Results not yet available.** Chinese Clinical Trial Registry link: http://www.chictr.org.cn/showprojen.aspx?proj=49409 **US/Global randomized, placebo-controlled trial:** Manufacturer (Roche) conducting a randomized, double-blind, placebo-controlled phase 3 trial (COVACTA; NCT04320615) in collaboration with the US Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA); the study will evaluate safety and efficacy of tocilizumab in combination with standard of care compared with placebo. Expected to enroll about 330 patients globally, including in the U.S., beginning in April 2020 [7, 8]		

OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) *Updated 4/29/20*	24:32 Renin-Angiotensin-Aldosterone System Inhibitor	**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] **Hypothetical benefit:** ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.[1, 2, 6]	Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection.[1,2,3] Clinical trial underway: Initiation of losartan in adult patients with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009)[7]		American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend to continue treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.[2, 3] NIH COVID-19 Treatment Guidelines Panel states patients who are receiving an ACE inhibitor or ARB for cardiovascular disease (or other indications) should continue receiving these drugs; recommends against use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial. [9] Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.[1, 4] Abrupt withdrawal of RAAS inhibitors in high-risk patients (e.g., heart failure patients, patients with prior myocardial infarction) may lead to clinical instability and adverse health outcomes. [8]
Anticoagulants (low molecular weight heparin [LMWH], unfractionated heparin [UFH]) *Updated 5/6/20*	20:12.04.16 Heparins	There is increasing evidence that patients with severe COVID-19 develop a hypercoagulable state, which has been associated with poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-6, 14, 16] Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular	Limited data from a retrospective study in China suggest that patients with severe COVID-19 infection or markedly elevated levels of D-dimer (>6 x ULN) may have decreased mortality when given prophylactic doses of LMWH or UFH.[4, 19] However, prospective studies are needed to confirm these findings.[19] A randomized open-label clinical trial (NCT04345848) is currently being conducted to evaluate prophylactic- and therapeutic-dose anticoagulation in hospitalized adults with severe COVID-19 infection. [12]		Additional study is needed to understand the anticoagulant needs of COVID-19 patients. [9, 11, 27] Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy. [4, 5, 9, 25, 27] The International Society for Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) recommend that all hospitalized COVID-19 patients, including non-ICU patients, receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, platelet count <25×10^9/L, fibrinogen less than 0.5 g/L). [4, 5] Abnormal PT or aPTT is not a contraindication for prophylaxis. [4, 5] WHO recommends pharmacologic

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		thrombosis. [1-6, 8, 11, 16, 18] Early anticoagulation in patients with severe COVID-19 infection may reduce the risk of thrombotic complications and improve clinical outcomes. [2, 4, 5, 14, 25, 27] An additional benefit of heparins is their anti-inflammatory effects. [5, 7, 8, 17]			prophylaxis with LMWH (preferred) or UFH (5000 units sub-Q twice daily) in adults and adolescents without contraindications. [25] Although LMWH is generally preferred, [4, 5, 25] UFH also has been used for thromboprophylaxis; practical concerns (e.g., need for frequent monitoring, convenience of administration, risk of medical staff exposure) may influence institutional choice of anticoagulant. [8, 9, 14, 20, 27] Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of thrombotic complications that have continued to occur despite standard prophylaxis with LMWH or UFH, some clinicians suggest that higher prophylactic doses or even therapeutic doses be considered; however, high-quality randomized controlled studies are needed to evaluate these approaches. [11, 14, 17, 20-24, 26, 27] The American Society of Hematology (ASH) states that therapeutic anticoagulation is not required in COVID-19 patients unless there is documented VTE or atrial fibrillation. [4] The efficacy of intermediate or full therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is being evaluated. [4] In patients already on anticoagulation for VTE or atrial fibrillation, therapeutic doses of anticoagulant therapy should continue but may need to be held if the platelet count is less than 30-50 x 10^9/L or if fibrinogen is less than 1 g/L. [4] The risk of venous thromboembolism and anticoagulation requirements should be assessed in all patients on an individual basis. [4, 5, 10, 17, 18] Bleeding appears to be infrequent in COVID-19 patients. [5] However, standard risk factors for bleeding should be considered and patients should be individually assessed to balance risk of thrombosis with risk of bleeding. [4]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Famotidine *Added 5/6/20*	56:28.12 Histamine H_2 Antagonists	Computer-aided, structure-based, virtual screening of libraries of compounds against SARS-CoV-2 proteins suggested potential for famotidine to interact with viral proteases involved in coronavirus replication [1-4] Anecdotal observations, including observations based on retrospective medical record review, indicated that many Chinese COVID-19 survivors had received famotidine for chronic heartburn; mortality rate appeared to be lower in hospitalized COVID-19 patients receiving famotidine than in patients not receiving the drug (14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors [3]	Currently no known published clinical trial evidence supporting efficacy or safety for treatment of COVID-19 Randomized, double-blind, historical-controlled, comparative trial (NCT04370262) initiated in New York in hospitalized adults with moderate to severe COVID-19; trial includes 2 active treatment groups (high-dose IV famotidine with oral hydroxychloroquine, IV placebo with oral hydroxychloroquine) and a historical control group receiving neither of these drugs (patients treated during early stages of the COVID-19 pandemic in New York); targeted enrollment is 600 patients in each active treatment group; 2 interim analyses planned [5]	Dosage in NCT04370262: Famotidine is being given IV in 120-mg doses (proposed total daily dosage of 360 mg) for maximum of 14 days or until hospital discharge, whichever comes first [5] Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage; [6] the study excludes patients with creatinine clearance (Cl_{cr}) ≤50 mL/minute, including dialysis patients; [5] renally impaired patients may be at increased risk of adverse CNS effects since drug half-life is closely related to Cl_{cr} [6]	Safety and efficacy for treatment of COVID-19 not established
HMG-CoA Reductase Inhibitors (statins) *Added 4/29/20*	24:06 Antilipemic Agents	In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects which may prevent acute lung injury. [1] Statins affect ACE2 as part of their function in reducing endothelial dysfunction. [2, 8]	Data are lacking on the use of statins in patients with COVID-19. Preliminary findings have shown mixed results with other respiratory illnesses; some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients hospitalized with influenza and/or pneumonia. [3-6] Clinical trials are evaluating the effectiveness of statins (with and without other potential treatment agents) for the treatment of COVID-19. [9, 10] (NCT04348695, NCT04333407)		NIH COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy; [2] recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. [2] Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections. [3] In patients with active COVID-19 who may develop severe rhabdomyolysis, it may be advisable to withhold statin therapy for a short period of time. [3] Most statins are substrates for the CYP450 system; potential for drug interactions. [7] Clinicians should ensure that their high-risk primary prevention (for ASCVD) patients are on guideline-directed statin therapy. [3]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Immune Globulin (IGIV, IVIG, γ-globulin) *Added 4/17/20*	80:04 Immune Globulin	Commercially available immune globulin (IGIV, IVIG, γ-globulin) is derived from pooled plasma; contains many antibodies normally present in adult human blood; used for replacement therapy in pts with primary humoral immunodeficiency unable to produce sufficient IgG antibodies and also used to provide *passive* immunity to certain viral infections in other individuals. [1] May modulate immune responses to infections. [2] Commercially available preparations of immune globulin (IGIV, IVIG, γ-globulin) may contain antibodies against some previously circulating coronaviruses; [2] however, depending on time of donor plasma collection, such preparations may not contain antibodies against SARS-CoV-2. [3, 13]	**SARS Experience:** IGIV has been used in some pts for the treatment of SARS. [4-7, 15] Benefits in such pts were unclear because of comorbidities, differences in stage of illness, and effect of other treatments; [5] IGIV may have contributed to hypercoagulable state and thrombotic complications in some pts. [6, 7] **COVID-19 case reports in China (Cao et al):** 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 pts also received antivirals and 1 pt also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration. [8] **COVID-19 clinical experience in China:** IGIV has been used as an adjunct in the treatment of COVID-19. [9-11] **Efficacy data not available from controlled clinical studies to date.** **COVID-19 clinical trial in China (NCT04261426):** Open-label randomized trial initiated to evaluate efficacy and safety of IGIV with standard care for treatment of severe COVID-19 [12]	IGIV dosage of 0.3-0.5 g/kg daily for 5 days has been used in some pts with COVID-19; [8] IGIV dosage of 0.5 g/kg daily for 5 days being investigated in a clinical trial in China. [12]	Role of commercially available immune globulin (IGIV, IVIG, γ-globulin) in the treatment of COVID-19 unclear. The Surviving Sepsis Campaign COVID-19 subcommittee suggests that IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, currently available IGIV preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury). [13] IGIV mentioned in Chinese guidelines as other therapeutic measure for treatment of severe and critical cases of COVID-19 in children. [14]
Ivermectin *Updated 4/24/20*	8:08 Anthelmintic	In vitro activity against some human and animal viruses [1-6] In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug [1]	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 Ivermectin plasma concentrations attained with dosages recommended for treatment of parasitic infections are substantially lower than concentrations associated with in vitro inhibition of SARS-CoV-2 [7] FDA issued a warning concerning possible inappropriate use of ivermectin products intended for animals as an attempt to self-medicate for the treatment of COVID-19 [8]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Nebulized drugs *Added 3/27/20*		**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 ***Updated 5/8/20***	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] Randomized, open-label, controlled trial in France (NCT04372082; HYdiLIC) to evaluate niclosamide in adults with SARS-CoV-2 infection (asymptomatic or onset of symptoms less than 8 days previously) and comorbidities[3]	Protocol in one ongoing trial (NCT04372082) for treatment of COVID-19 specifies a niclosamide dosage of 2 g on day 1, then 500 mg twice daily for 10 days[3]	Not commercially available in the US No data to date support use in treatment of COVID-19
Nitazoxanide *Updated 5/1/20*	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] In vitro activity against MERS-CoV[4]	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 **Experience in treating influenza:** In a randomized, placebo-controlled study in 624 otherwise healthy adult and adolescent patients with acute uncomplicated influenza, treatment with nitazoxanide reduced duration of symptoms by approximately 1 day[6] **Experience in treating influenza-like illness:** In two studies for the treatment of	**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] Protocol in one ongoing trial (NCT04348409) for treatment of moderate COVID-19 specifies a nitazoxanide dosage of 600 mg twice daily for 7 days[8]	Current data not specific to COVID-19; additional study needed[1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice [4]	influenza-like illness symptoms associated with viral respiratory infection in 186 adults and pediatric pts, treatment with nitazoxanide reduced duration of symptoms (4 days versus ≥7 days with placebo). [7] In another study in 260 adults and pediatric pts hospitalized with influenza-like illness (≥50% with pneumonia at presentation), treatment with nitazoxanide did not reduce the duration of hospital stay (primary end point) or duration of symptoms [7] **COVID-19**: Randomized, double-blind, placebo-controlled proof-of-concept trial (NCT04348409) initiated to evaluate nitazoxanide for treatment of moderate COVID-19 [8] **Two randomized, double-blind, placebo-controlled clinical trials** have been initiated by the manufacturer (Romark) to evaluate efficacy and safety for pre- or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers (NCT04359680) and post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (NCT04343248) [8] **Multiple other clinical trials planned or initiated** to evaluate nitazoxanide in combination with other drugs (chloroquine, hydroxychloroquine, or ivermectin) or alone for treatment of COVID-19 [8]	Protocol in two ongoing trials (NCT04343248, NCT04359680) evaluating pre- and/or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks [8]	
Nonsteroidal Anti-inflammatory Agents (NSAIAs) *Updated 4/29/20*	28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)	**Ibuprofen:** Speculative link between ibuprofen and increased ACE2 expression **leading to worse outcomes** in COVID-19 patients, and should NOT be used in patients with COVID-19 [1] **Indomethacin:** Possible antiviral activity against **other** coronaviruses SARS-CoV & CanineCoV (interferes with viral RNA synthesis) [6]	**Ibuprofen:** None; anecdotal [1] **Indomethacin:** Speculative; one **in vitro & animal model** study with other coronaviruses SARS-CoV & CanineCoV [6]		**Ibuprofen:** A letter published in The Lancet Respir Med stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2; however, this appears to be based on animal studies. [1, 4] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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 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. On 3/19/20, FDA issued a statement that it is not aware of scientific evidence connecting the use of NSAIAs, such as ibuprofen, with worsening COVID-19 symptoms. FDA stated that it is investigating this issue further and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that by reducing inflammation, and possibly fever, these drugs may diminish the utility of diagnostic signs in detecting infections. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19 Therefore, currently no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19. **However, some experts have recommended preferentially using acetaminophen for treatment of fever** [2, 3, 4] NIH COVID-19 Treatment Guidelines Panel states that patients who are receiving NSAIAs for other conditions should continue receiving the drugs; states antipyretic strategy (e.g., use of acetaminophen or NSAIAs) should be no different between patients with or without COVID-19. [5]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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]
Tissue Plasminogen Activator (t-PA; alteplase) *Updated 4/29/20*	20:12.20 Thrombolytic agents	A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which may contribute to their risk of poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-3, 5-9, 14, 16] Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), a high incidence of venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. [1, 2, 5-10, 13, 14, 16] In patients with ARDS (regardless of the cause), pathologic findings include fibrin deposition in the alveoli and formation of microthrombi in the pulmonary vasculature. [1, 11, 14] Treatment with t-PA may restore microvascular patency and limit progression of ARDS in patients with COVID-19 [1, 14]	Results of a small phase 1 study conducted in 2001 suggest possible benefit of plasminogen activators for the treatment of ARDS.[1-3] 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 urokinase or streptokinase; such therapy improved PaO_2 and also appeared to improve survival. [1-3] A registered open-label randomized trial (NCT04357730) will evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure [12] A registered open-label nonrandomized pilot study (NCT04356833) will evaluate an inhaled formulation of t-PA (via nebulization) in patients with ARDS due to COVID-19; [12] the inhaled formulation of t-PA is investigational at this time [15]	The open-label systemic fibrinolytic therapy trial (NCT04357730) will evaluate t-PA (alteplase) dosages of 50 mg (administered as a 10-mg IV bolus followed by IV administration of the remaining 40 mg over a total time of 2 hours) and 100 mg (administered as a 10-mg IV bolus dose followed by IV administration of the remaining 90 mg over a total time of 2 hours); a heparin infusion will be initiated immediately following completion of the alteplase infusion [12] Other dosage regimens have been evaluated in patients with ARDS associated with COVID-19, including an initial t-PA (alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg of t-PA over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg (Beth Israel Deaconess et al study); however, the optimum dose, route of administration, and duration of treatment remain to be determined. [1, 9, 14]	t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). [1, 13, 14] However, there are currently no clinical trial data to inform this practice and a lack of clinical experience with the use of fibrinolytic agents in ARDS patients in general. [11] Several institutions (Beth Israel Deaconess, University of Colorado Anschultz Medical Campus, Denver Health) are currently testing the use of t-PA as salvage therapy in patients with severe COVID-19 under the FDA compassionate use program. [2, 4] Preliminary findings from the first few cases reported an initial, but transient improvement in PaO_2/FiO_2 (P/F) ratio. [9] 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]

[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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Anticoagulants

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