Assessment of Evidence for COVID-19-Related Treatments: Updated 6/11/2020

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ANTIVIRAL AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Baloxavir *Updated 5/13/20*	8:18.92 Antiviral	Antiviral active against influenza viruses In vitro antiviral activity against SARS-CoV-2 demonstrated in one trial [3]	**Only limited clinical trial data available** to date to evaluate use of baloxavir for treatment of COVID-19 Exploratory, open-label, randomized controlled study at a single center in China (ChiCTR2000029544): 29 adults hospitalized with COVID-19 receiving antiviral treatment with lopinavir/ritonavir, darunavir/cobicistat, or umifenovir (Arbidol®), in combination with inhaled interferon-α, were randomized to treatment with baloxavir marboxil (80 mg orally on day 1 and on day 4, and 80 mg orally on day 7 as needed) (n=10), favipiravir (1600 or 2200 mg orally on day 1, followed by 600 mg three times daily for up to 14 days) (n=9), or control (standard antiviral treatment) (n=10). Percentage of pts with viral conversion (2 consecutive tests with undetectable viral RNA results) after 14 days of treatment was 70, 77, and 100% in the baloxavir, favipiravir, and control groups, respectively, with median time to clinical improvement of 14, 14, and 15 days, respectively. [3] Another randomized controlled trial registered in China: [1] CHiCTR2000029548	Protocol for two registered Chinese trials (ChiCTR2000029544, ChiCTR2000029548) specifies an oral baloxavir marboxil dosage of 80 mg on day 1 and on day 4, and another dose of 80 mg on day 7 (as needed); not to exceed 3 total doses. [1, 3]	No data to date support use in the treatment of COVID-19
Chloroquine Phosphate ***Updated 6/8/20***	8:30.08 Antimalarial (4-aminoquinoline derivative)	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	**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; some reports of possible clinical benefits, including decrease in viral load and duration of illness; [4-6] majority of data to date involves use in pts with mild or moderate COVID-19; [35] only limited clinical data on use in pts with severe disease. [35] **Small, randomized study in hospitalized adults in China compared chloroquine with LPV/RTV (Huang et al):** 10 pts (7 with moderate and 3 with severe COVID-19) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate	**Optimal dosage and duration of treatment not known** [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	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 Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		patients with viral infections [1-3, 13, 15-16] Known pharmacokinetics and toxicity profile based on use for other indications [13, 17]	and 5 with severe COVID-19) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR results for SARS-CoV-2 by day 13 and were discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from the hospital by day 14. **Note:** Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively).[20] **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 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] See Hydroxychloroquine in this Evidence Table for additional information on clinical	total treatment based on clinical evaluation [25] **Oral chloroquine phosphate dosage in Chinese guidelines:** 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]	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; the panel recommends against use of high-dose chloroquine (i.e., 600 mg twice daily for 10 days) because such dosage has been associated with more severe toxicities compared with lower-dose chloroquine. [35] IDSA recommends that chloroquine be used for the *treatment* of COVID-19 in the context of a clinical trial. [38] IDSA recommends that a combined regimen of chloroquine 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 chloroquine, for preexposure prophylaxis (PrEP) or postexposure 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; [13, 17, 36, 39] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. [35, 36, 39] (See Hydroxychloroquine in this Evidence Table.) 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			trials and experience with 4-aminoquinoline antimalarials in the management of COVID-19. 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		(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 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 6/3/20*	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]	**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)	A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days was used in several open-label COVID-19 studies in China [6, 15] Protocol in one ongoing trial (NCT04346628) for treatment of mild COVID-19 specifies a favipiravir dosage of 1800 mg on day 1, then 800	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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Licensed in Japan and China for treatment of influenza [2, 4, 6]	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] **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 NCT04333589 NCT04358549 NCT04373733 NCT04376814 ChiCTR2000030113 ChiCTR2000030894 ChiCTR2000030987	mg twice daily 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] 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] For the treatment of COVID-19, one pharmacokinetic simulation model suggested that a dosage of 2400 mg twice daily on day 1, followed by 1600 mg twice daily on days 2–10 should achieve adequate favipiravir trough plasma concentrations and may be more pharmacologically relevant than lower dosages [19] **Pharmacokinetic data are available from a study in critically ill pts with COVID-19 requiring mechanical ventilation who received a favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–5 (or longer if needed) via NG tube.** Trough serum concentrations of the drug in most samples	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] Favipiravir is associated with QT prolongation. [21] Some have suggested close cardiac and hepatic monitoring during treatment, as well as monitoring of plasma and tissue concentrations of the drug and, if possible, the active metabolite. [19, 20, 21] 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			ChiCTR2000029996 JapicCTI-205238 JPRN-jRCTs031190226 JPRN-jRCTs041190120	were lower than the lower limit of quantification and lower than the in vitro EC_{50} of the drug reported for SARS-CoV-2; trough concentrations in these critically ill pts also were much lower than those previously reported in healthy individuals who received the same dosage [22]	
HIV Protease Inhibitors *Updated 5/21/20*	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] **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]	**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (Cao et al)** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, **time to clinical improvement was not shorter with LPV/RTV compared with standard care** (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group. The 28-day mortality rate was numerically lower in LPV/RTV group (19.2% vs 25% in ITT population; 16.7% vs 25% in modified ITT population). Some evidence that LPV/RTV initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. **No significant differences in reduction of viral RNA load, 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 vs chloroquine in small, randomized study in hospitalized adults with COVID-19 in China (Huang et al):** 10 pts (7 with moderate and 3 with severe disease) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate and 5 with severe disease) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR results for SARS-CoV-2 by day 13 and were	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days [3, 16, 24] **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 (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 β-1b (0.25 mg/mL sub-Q on alternate days) for 14 days [1, 4, 8]	**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 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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			discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only 6/12 (50%) were discharged from the hospital by day 14. **Note:** Results suggest that chloroquine was associated with shorter time to RT-PCR conversion and quicker recovery than LPV/RTV; however, this study included a limited number of pts and the median time from onset of symptoms to initiation of treatment was shorter in those treated with chloroquine than in those treated with LPV/RTV (2.5 vs 6.5 days, respectively). [24] **LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone in open-label, randomized trial in adults with mild to moderate COVID-19 in Hong Kong (Hung et al; NCT04276688):** 127 pts were randomized 2:1 to receive LPV/RTV (LPV 400 mg/RTV 100 mg) twice daily for 14 days) with ribavirin (400 mg twice daily) and interferon β-1b (8 million IU sub-Q on alternate days for up to 3 doses depending on how soon treatment initiated after symptom onset) or a 14-day regimen of LPV/RTV alone. Median time to negative RT-PCR results for SARS-CoV-2 in nasopharyngeal samples was 7 days in pts treated with the 3-drug regimen vs 12 days in those treated with LPV/RTV alone; median duration of hospitalization was 9 or 14.5 days, respectively. Adverse effects reported in 48% of those treated with the 3-drug regimen and in 49% of those treated with LPV/RTV alone. **Note:** Results indicate a 3-drug regimen that included LPV/RTV, ribavirin, and interferon β-1b was more effective than LPV/RTV alone in pts with mild to moderate COVID-19, especially when treatment was initiated within 7 days of symptom onset. [25] **LPV/RTV retrospective cohort study in China (Deng et al)** 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		

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			(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, 8-11] **LPV/RTV COVID-19 Clinical Trials:** Multiple trials registered at clinicaltrials.gov (some listed below): [15] NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease) NCT04255017 (LPV/RTV vs umifenovir vs oseltamivir) NCT04372628 (LPV/RTV vs hydroxychloroquine vs placebo) 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 6/11/20***	8:30.08 Antimalarial (4-aminoquinoline derivative)	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]	**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; majority of data to date involves use in pts with mild or moderate COVID-19; [7, 18, 31, 35, 47, 49] only limited clinical data on use in pts with severe disease. [35] **Hydroxychloroquine small pilot study conducted in China:** 15 treatment-naive pts received hydroxychloroquine sulfate	**Optimal dosage and duration of treatment not known** [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	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 Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of

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		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 based on use for other indications [13] 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, 35]	(400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; [18] **both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV**. [30] Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up). [18] **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	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] **Oral hydroxychloroquine sulfate:** 400 mg once or twice daily for 5-10 days [10, 18] **Oral hydroxychloroquine sulfate with azithromycin (NIAID trial A5395; NCT04358068):** 400 mg twice daily on day 1, then 200 mg twice daily for 6 days) with azithromycin (500 mg on day 1, then 250 mg once daily for 4 days) [10, 48] **Oral hydroxychloroquine sulfate with azithromycin (France):** 200 mg 3 times daily for 10 days with or without azithromycin (500 mg on day 1, then 250 mg once daily on days 2-5) [7, 34, 47]	COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration Additional data needed from randomized, controlled clinical trials 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 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 and because use of hydroxychloroquine with

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			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] **Hydroxychloroquine randomized, parallel-group, open-label study in hospitalized adults with mild to moderate COVID-19 in China (ChiCTR2000029868):** 150 pts (148 with mild to moderate disease and 2 with severe disease) were randomized 1:1 to receive hydroxychloroquine (1200 mg daily for 3 days, then 800 mg daily for total treatment duration of 2-3 weeks) with standard of care or standard of care alone. Mean time from onset of symptoms to randomization was 16.6 days (range: 3-41 days). Standard of care included IV fluids, O_2, various antivirals (e.g., umifenovir, LPV/RTV), antibiotics, and/or glucocorticoid therapy. By day 28, 73% of pts (53 treated with hydroxychloroquine with standard of care and 56 treated with standard of care alone) had converted to negative for SARS-CoV-2. The probability of negative conversion by day 28 in those treated with hydroxychloroquine was similar to that in those treated with standard of care alone; the median time to negative seroconversion (6 and 7 days) also was similar in both groups. Adverse effects reported in 30% of those treated with hydroxychloroquine and 9% of those treated with standard of care alone. **Note: Results indicate that use of hydroxychloroquine in pts with mild to moderate COVID-19 did not provide additional benefits compared with use of standard of care alone.** [49] **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		azithromycin may further increase the risk of QT prolongation, caution is advised when considering use of hydroxychloroquine (with or without azithromycin) in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. [35, 36, 38, 39, 41-44] The benefits and risks of hydroxychloroquine (with or without azithromycin) should be carefully assessed; diagnostic testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects. [35, 36, 38, 39, 41-44] FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. [39] **Emergency use authorization (EUA) for hydroxychloroquine:** FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use **only** in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. [24, 26] To request the drug, healthcare providers should contact local or state health departments; [26] distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. [29] To mitigate risks of this unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch). [24, 26] FDA states that, based on

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			assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6.[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 were 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 was discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. [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		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.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O_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 infectiousness, especially for pts with more severe disease. **Hydroxychloroquine with azithromycin uncontrolled, observational, retrospective analysis in France (Million et al):** Data for 1061 pts with PCR-documented SARS-CoV-2 RNA who were treated with a regimen of hydroxychloroquine sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) were analyzed for clinical		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			outcomes and persistence of viral shedding. Pts were included in the analysis if they received the combined regimen for at least 3 days and were clinically assessable at day 9. There were 56 asymptomatic and 1005 symptomatic pts; the majority (95%) had relatively mild disease and were considered low risk for clinical deterioration; median age was 43.6 years (range: 14-95 years) and mean time between onset of symptoms and initiation of treatment was 6.4 days. Within 10 days of treatment, good clinical outcome reported in 973 pts (91.7%) and poor clinical outcome reported in 46 pts (4.3%). Persistent nasal carriage of SARS-CoV-2 reported at completion of treatment in 47 pts (4.4%); 8 pts died.[47] **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. **Two different retrospective studies analyzed outcome data for hospitalized pts with confirmed COVID-19 in New York to assess the effects of treatment with hydroxychloroquine with or without azithromycin (Rosenberg et al, Geleris et al):**		

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			Results of these studies suggest that use of hydroxychloroquine with or without azithromycin is **not** associated with decreased in-hospital mortality. [45, 46] **Rosenberg et al** analyzed data for 1438 pts (735 received hydroxychloroquine with azithromycin, 271 received hydroxychloroquine alone, 211 received azithromycin alone, 221 received neither drug) and assessed in-hospital mortality (primary outcome). Overall, in-hospital mortality was 20.3%; in-hospital mortality was 25.7, 19.9, 10, or 12.7% in those treated with hydroxychloroquine with azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug, respectively. [45] **Geleris et al** analyzed data for 1376 pts (811 received hydroxychloroquine [486 of these also received azithromycin] and 565 did not receive hydroxychloroquine [127 of these received azithromycin]) and assessed the primary end point of time from study baseline to intubation or death. Overall, 346 pts (25.1%) progressed to a primary end point of intubation and/or death and the composite end point of intubation or death was not affected by hydroxychloroquine treatment (intubation or death reported in 32.3% of pts treated with hydroxychloroquine and 14.9% of pts not treated with the drug). [46] **Large, randomized, controlled, adaptive trial evaluating efficacy of 6 different treatments for prevention of death in hospitalized pts with COVID-19 compared with usual care alone (NCT04381936; RECOVERY):** Study protocol included a treatment arm to evaluate efficacy of hydroxychloroquine sulfate (two 800-mg doses given 6 hours apart followed by two 400-mg doses given 12 and 24 hours after the initial dose on day 1, then 400 mg every 12 hours thereafter for 9 days). [53, 54] **The investigators announced preliminary results** for the hydroxychloroquine treatment arm. A total of 1542 pts were randomized to receive hydroxychloroquine with usual care and 3132 pts were randomized to usual care alone. Data for these pts		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			indicate that hydroxychloroquine did **not** provide a significant difference in the primary end point of 28-day mortality (25.7% in those treated with hydroxychloroquine with usual care compared with 23.5% in those treated with usual care alone). In addition, there was no evidence of beneficial effects on duration of hospitalization or other outcomes. [53] **Note:** Data regarding pt demographics and clinical characteristics (e.g., age, disease severity, comorbidities) and time from diagnosis to study enrollment have not been provided to date. **Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to assess the effects of hydroxychloroquine or chloroquine used with or without a macrolide (Mehra et al; now retracted):** Original publication included data obtained worldwide for 96,032 pts hospitalized with COVID-19 between Dec 20, 2019 and Apr 14, 2020, including 14,888 pts who received chloroquine or hydroxychloroquine with or without a macrolide (azithromycin or clarithromycin) initiated within 48 hours of diagnosis (treatment group) and 81,144 pts who did not receive these drugs (control group). Based on those data, in-hospital mortality rate in the control group was 9.3% compared with 18% in those treated with hydroxychloroquine alone (n=3016), 23.8% in those treated with hydroxychloroquine and a macrolide (n=6221), 16.4% in those treated with chloroquine alone (n=1868), and 22.2% in those treated with chloroquine and a macrolide (n=3783). [50] **Note: This published study has now been retracted by the publisher at the request of 3 of the original authors.** [52] **Concerns were raised with respect to the veracity of the data and analyses conducted by a global healthcare data collaborative.** [51, 52] **Hydroxychloroquine for postexposure prophylaxis of COVID-19 randomized, placebo-controlled trial in the US and Canada (NCT04308668):** Asymptomatic adults with occupational or household exposure to an individual with COVID-19 were		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			randomly assigned 1:1 to receive postexposure prophylaxis with a 5-day regimen of hydroxychloroquine sulfate (initial 800-mg dose followed by a 600-mg dose given 6-8 hours after first dose on day 1, then 600 mg once daily for 4 additional days) or placebo (folate tablets). A total of 821 asymptomatic adults were enrolled within 4 days after COVID-19 exposure (414 randomized to hydroxychloroquine and 407 randomized to placebo); 66% were healthcare workers. Overall, 88% of participants reported high-risk exposures (occurred at a distance of <6 feet for >10 minutes while not wearing a face mask or eye shield) and the others reported moderate-risk exposures (occurred at a distance of <6 feet for >10 minutes while wearing a face mask but no eye shield). **Note: Participants were recruited primarily through social media outreach and traditional media platforms and were enrolled using an internet-based survey. The exposure event and subsequent onset of new symptoms and illness compatible with COVID-19 after enrollment were self-reported using email surveys on days 1, 5, 10, and 14 and at 4-6 weeks.** Results of these surveys and information obtained using additional forms of follow-up indicated that confirmed or probable COVID-19 (based on self-reported symptoms or PCR testing) developed in 13% of participants overall (107/821) and did not differ significantly between those who received hydroxychloroquine prophylaxis (11.8%) and those who received placebo (14.3%). [55] **Note: The various limitations of the trial design should be considered when interpreting the results.** Exposure to someone with confirmed COVID-19, time from the exposure event to initiation of prophylaxis, and all outcome data (including possible COVID-19 symptoms and PCR test results) were self-reported by study participants. COVID-19 was confirmed with PCR testing in only a small percentage (<3%) of participants who self-reported COVID-19 symptoms. Survey results indicated that full adherence to the 5-day prophylaxis regimen was reported by only 75% of patients randomized to hydroxychloroquine and 83% of those		

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			randomized to placebo. In addition, a total of 52 participants did not complete any surveys after study enrollment. [55, 56] **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] **Hydroxychloroquine with azithromycin randomized, double-blind, placebo-controlled trial sponsored by NIAID (A5395; NCT04358068):** Symptomatic adults with COVID-19 not currently requiring hospitalization will be randomized to receive hydroxychloroquine (400 mg twice daily on day 1, then 200 mg twice daily for 6 days) and azithromycin (500 mg on day 1, then 250 mg once daily for 4 days) or placebo and followed for 23 weeks to determine whether the combined regimen will prevent hospitalization and death. [10, 48] Multiple clinical trials to evaluate hydroxychloroquine for *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10] NCT04329923 NCT04332991 NCT04334967 NCT04335552 NCT04341727 NCT04345692 NCT04350450 NCT04351620 NCT04353037 NCT04362332 Multiple clinical trials to evaluate hydroxychloroquine for *prevention* of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed		

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			below): [10] NCT04318015 NCT04318444 NCT04328961 NCT04331834 NCT04334148 NCT04341441 NCT04363450 NCT04372017		
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] Clinicaltrials.gov trials for COVID-19 that include oseltamivir[5]: NCT04303299 NCT04261270 NCT04255017 NCT04338698	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
Remdesivir ***Updated 6/11/20***	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	**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	**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	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 recommends use of remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease; the NIH panel does not recommend remdesivir for the treatment of mild or moderate COVID-19 outside of clinical trials. [20]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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	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 pts); **trial was insufficiently powered to detect assumed differences in clinical outcome**. [21] **Phase 3 randomized, open-label trial in hospitalized pts with severe COVID-19 (NCT04292899; GS-US-540-5773; SIMPLE-Severe)** sponsored by the manufacturer (Gilead): Initial study protocol was designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care in adults with **severe COVID-19** not receiving mechanical ventilation at study entry; [10] protocol was subsequently modified to include pts 12 years of age or older, add an extension phase, and include a cohort of pts receiving mechanical ventilation. [10, 23] Data 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 after adjusting for baseline clinical status. Pt demographics and clinical characteristics at baseline generally were similar in both	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:** 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]	**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. [25, 26] The manufacturer (Gilead) donated remdesivir for use under the EUA; distribution to hospitals and other healthcare facilities is being directed by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state health departments. To request remdesivir for use under the EUA, healthcare providers should contact their state health departments. [28] The EUA requires that healthcare facilities and healthcare providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). [25, 26] Consult the EUA, [25] EUA fact sheet for healthcare providers, [26] and EUA fact sheet for patients and parent/caregivers [27] for additional information.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			groups, although the 10-day group included a higher percentage of pts in the most severe disease categories and a higher proportion of men (who are known to have worse COVID-19 outcomes than women); median duration of symptoms before first dose of remdesivir was similar in both groups (8 or 9 days). **At day 14, 129/200 pts (65%) in the 5-day group and 106/197 pts (54%) in the 10-day group achieved clinical recovery (defined as an improvement of at least 2 points from baseline on a 7-point ordinal scale).** After adjusting for baseline imbalances in disease severity, data indicate that clinical status at day 14, time to clinical improvement, recovery, and death (from any cause) were similar in both groups. Although eligibility criteria according to the initial study protocol excluded pts receiving invasive mechanical ventilation, 4 pts in the 5-day group and 9 pts in the 10-day group were receiving invasive mechanical ventilation or ECMO (need identified after initial screening and before treatment initiation or pts were accepted as protocol deviations). There also were more pts in the 10-day group (30%) who required high-flow oxygen support at baseline compared with the 5-day group (24%). Post-hoc analysis among pts receiving mechanical ventilation or ECMO at day 5 indicate that, by day 14, 40% of such individuals who had received the 5-day regimen had died compared with 17% of those who had received the 10-day regimen. Treatment with remdesivir beyond 5 days did not appear to improve outcomes among pts who were receiving *noninvasive* positive-pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air. **Note:** Results for the initial 397 study pts with severe COVID-19 not requiring mechanical ventilation at study entry cannot be extrapolated to critically ill pts receiving mechanical ventilation. [23] **Phase 3 randomized, open-label trial in hospitalized pts with moderate COVID-19 (NCT04292730; GS-US-540-5774; SIMPLE-Moderate)** sponsored by the manufacturer (Gilead): Initial protocol was designed to evaluate safety and antiviral activity of		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg IV once daily for total of 5 or 10 days) in conjunction with standard of care compared with standard of care alone in adults with **moderate COVID-19** (i.e., hospitalized with evidence of pulmonary infiltrates but without reduced oxygen levels); [11] protocol was subsequently modified to include pts 12 years of age or older and add an extension phase to include additional pts. [11] **Manufacturer announced preliminary data** for the initial group of pts who received a 5-day regimen of remdesivir with standard of care (n=191), 10-day regimen of the drug with standard of care (n=194), or standard of care alone (n=200). At day 11, data indicate that 70, 65, or 61% of pts in the 5-day, 10-day, or standard of care alone group, respectively, had clinical improvement based on at least a 2-point improvement from baseline on a 7-point ordinal scale. When clinical improvement at day 11 was based on at least a 1-point improvement, data indicate a statistically significant improvement in clinical status in those treated with a 5-day regimen of remdesivir compared with standard of care alone (76% of pts in the 5-day group and 66% in the standard of care alone group had clinical improvement). Oxygen support of any kind was required in 11% of pts treated with standard of care alone compared with 6 or 7% of pts in the 5- or 10-day group, respectively. Although the differences were not statistically significant, at least a 1-point *worsening* of clinical status was reported in 11% of pts treated with standard of care alone compared with 3 or 6% of pts in the 5 - or 10-day group, respectively. There were 4 deaths reported in the standard of care alone group compared with none in the 5-day group and 2 in the 10-day group. [30] **Note:** Data regarding pt demographics and clinical characteristics at study enrollment (e.g., age, comorbidities, time to initiation of treatment after symptom onset) and information on any additional supportive treatment received not provided to date. **Phase 3 adaptive, randomized, double-blind, placebo-controlled trial (NIAID**		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Adaptive COVID-19 Treatment Trial 1 [ACTT-1]; NCT04280705) in hospitalized adults with COVID-19: 1063 pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg once daily on days 2-10 or until hospital discharge or death) or placebo. [13, 22] All pts received supportive care according to the standard of care for the trial site hospital. Baseline demographics and clinical characteristics (e.g., age, disease severity, comorbidities at study enrollment, time to initiation of treatment after symptom onset) were similar in both groups. Overall, 88.7% of pts had severe disease at study enrollment and the median time from symptom onset to randomization was 9 days (range: 6-13 days). Preliminary data analysis that included 1059 pts (538 randomized to remdesivir and 521 randomized to placebo) indicated **shorter median time to recovery in the remdesivir group (11 days) vs the placebo group (15 days)** and suggested that remdesivir treatment may have provided a survival benefit (Kaplan-Meier estimates of mortality by day 14 were 7.1% in the remdesivir group vs 11.9% in the placebo group). [22] **Expanded access IND protocol (NCT04323761):** The manufacturer (Gilead) established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19 in hospitalized adults and children 12 years of age or older [17] **Compassionate use access:** The manufacturer (Gilead) has transitioned from individual compassionate use requests to expanded access programs for emergency access to the drug for the treatment of severe COVID-19. The only individual compassionate use requests for the drug still being reviewed by the manufacturer are those for pregnant women and children <18 years of age with confirmed COVID-19 and severe manifestations of the disease. [15] (https://rdvcu.gilead.com/) **Compassionate use access (NCT04302766):** May be available for DoD personnel		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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 **Adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib (ACTT2):** This next iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) will evaluate possible benefits of using baricitinib (a Janus kinase [JAK] inhibitor) in conjunction with remdesivir in hospitalized		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			adults with laboratory-confirmed SARS-CoV-2 infection and evidence of lung involvement (abnormal chest x-rays, need for supplemental oxygen or mechanical ventilation). Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization or up to 10 days total) or the same remdesivir dosage given with oral baricitinib (4 mg once daily for the duration of hospitalization or up to 14 days total). [29]		
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 Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza [4]	**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 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	**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
			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 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 5/28/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant human interleukin-1 (IL-1) receptor antagonist [1] IL-1 levels are elevated in patients with COVID-19; anakinra may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients [2, 3, 4, 7]	Currently no known published controlled clinical trial evidence supporting efficacy or safety of anakinra in treating COVID-19 [7] Encouraging preliminary results reported in China with another disease-modifying antirheumatic drug, tocilizumab [5, 6] **France:** A small case series (9 patients) of open-label anakinra treatment in hospitalized (non-ICU) adults with moderate to severe COVID-19 pneumonia has been published with encouraging results [8] **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]	Various dosage regimens are being studied [3, 8] 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 [3] In a French case series, anakinra was given subcutaneously in a dosage of 100 mg every 12 hours on days 1-3, then 100 mg once daily from day 4-10 [8] (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 adults with sepsis and has been studied extensively in severely ill pediatric patients with complications of rheumatologic conditions; pediatric data on use in acute respiratory distress syndrome/ sepsis are limited [7] **Pregnancy:** Limited evidence to date: unintentional first trimester exposure considered unlikely to be harmful [7]
Ascorbic acid ***Updated 6/11/20***	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 registered, including: [1] NCT04264533 NCT04323514 NCT04363216 NCT04401150 (LOVIT-COVID) NCT04395768 **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; other clinical trials of outpatient oral ascorbic acid treatment registered, including NCT04395768 [1]	**IV ascorbic acid:** Various dosages of IV ascorbic acid used in COVID-19 studies; 50 mg/kg IV every 6 hours for 4 days used in NCT03680274 and NCT04401150 [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] **Oral ascorbic acid:** NCT04342728: Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses [1] NCT04395768 (outpatients): Ascorbic acid 1 g orally 3 times daily for 7 days following initial 200-mg/kg IV dose Note: May interfere with laboratory tests based on oxidation-reduction	Current data not specific to COVID-19; additional study needed [6]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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]	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]	
Azithromycin ***Updated 6/8/20***	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	**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	**Adjunctive treatment in certain viral infections:** 500 mg once daily has been used [13] **COVID-19:** 500 mg on day 1, then 250 mg once daily on days 2-5 in conjunction with a 5-, 7-, or 10-day regimen of hydroxychloroquine has been used or is being investigated [7, 18, 19, 23, 24, 29]	Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19 Additional data needed from randomized, controlled clinical trials 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.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]	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 uncontrolled observational study in France (80 pts),19 and larger uncontrolled observational study in France (1061 pts).23 Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.) **Use in conjunction with hydroxychloroquine in hospitalized pts with COVID-19:** Data from 2 retrospective studies that analyzed outcome data for hospitalized pts in New York treated with hydroxychloroquine with or without azithromycin indicate that use of the 4-aminoquinoline antimalarial with or without azithromycin is not associated with decreased in-hospital mortality. [30, 31] (See Hydroxychloroquine in this Evidence Table.) **Randomized, double-blind, placebo-controlled trial sponsored by NIAID initiated to evaluate efficacy of hydroxychloroquine with azithromycin** for prevention of hospitalization and death in symptomatic adult outpatients with COVID-19 (A5395; NCT04358068). [24, 29] (See Hydroxychloroquine in this Evidence Table.) **Multiple clinical trials to evaluate azithromycin alone or azithromycin with hydroxychloroquine or chloroquine for treatment of COVID-19** are registered at clinicaltrials.gov (some listed below): [29]		IDSA recommends that a combined regimen of hydroxychloroquine (or chloroquine) 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 with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. [20-22, 25-28] The benefits and risks of a combined regimen of azithromycin and hydroxychloroquine (or chloroquine) should be carefully assessed; if the regimen is used, diagnostic testing and monitoring are recommended to minimize risk of adverse effects, including drug-induced cardiac effects. [20, 22, 25-28] (See Hydroxychloroquine in this Evidence Table.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			NCT04329832 NCT04334382 NCT04336332 NCT04370782 NCT04341727 NCT04335552		
Baricitinib (Olumiant®) *Updated 5/15/20*	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]), 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]	Currently no known published controlled clinical trial evidence supporting efficacy or safety in patients with COVID-19 In a small (12 patients) open-label study in Italy (NCT04358614), use of baricitinib (4 mg orally once daily for 2 weeks) in combination with lopinavir/ritonavir was evaluated in patients with moderate COVID-19 pneumonia.[13, 14] Baricitinib was well tolerated with no serious adverse events reported.[13] At week 1 and week 2, patients who received baricitinib had significant improvement in respiratory function parameters and none of the patients required ICU support.[13] Baricitinib is included in the next iteration of **NIAID's Adaptive COVID-19 Treatment Trial (ACTT 2)**. [3, 12] Inclusion criteria: Laboratory- confirmed COVID-19 infection and evidence of lung involvement, including need for supplemental oxygen, abnormal chest X-ray, or need for mechanical ventilation. [12] Patients randomized to receive treatment with remdesivir with or without baricitinib.[12] Remdesivir to be administered as one 200-mg IV dose on day 1 followed by 100 mg IV daily for the duration of hospitalization (up to 10-day treatment course). Baricitinib to be administered as a 4-mg oral dose administered once daily for the duration of hospitalization (up to 14-day treatment course). [12] **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) [7-10]	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, 14] 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Colchicine *Updated 6/3/20*	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] 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]	Minimal anecdotal experience and no clinical trial data reported to date in COVID-19 [4] **Retrospective review** of computerized healthcare database found no difference in baseline use of colchicine (0.53 vs 0.48%) between patients with a positive RT-PCR result for SARS-CoV-2 (n = 1317) and those with a negative result (n = 13,203), suggesting a lack of protective effect for colchicine against SARS-Cov-2 infection; indication for and duration of colchicine use were unknown [15] **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, parallel-group studies are evaluating the effects of colchicine on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in patients with COVID-19: NCT04326790, NCT04322565, NCT04328480, NCT04350320, NCT04355143, NCT04392141, NCT04375202, NCT04360980, NCT04367168, NCT04403243, NCT04363437 [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] Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19 [2] 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 The potential for toxic doses of colchicine to affect alveolar type II pneumocytes (which may inhibit surfactant release and contribute to ARDS) and increase the risk of multiple-organ failure and disseminated intravascular coagulation (DIC) has been raised as a possible concern with the use of colchicine in COVID-19 patients [14]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Corticosteroids (general) *Updated 6/3/20*	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] May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low [4, 11]	**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] 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	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] **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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			corticosteroids (e.g., dexamethasone, hydrocortisone), oral corticosteroids (e.g., prednisone), or inhaled corticosteroids (e.g., budesonide, ciclesonide) for treatment of COVID-19 pneumonia or ARDS, including the following trials registered at clinicaltrials.gov: [22] NCT04327401 NCT04344288 NCT04344730 NCT04348305 NCT04355637 NCT04359511 NCT04360876 NCT04381364 (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]		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 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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 inflammation should not be discontinued in patients with COVID-19. [24] Rheumatology experts, including members of the American College of Rheumatology COVID-19 Clinical Guidance Task Force, state that abrupt discontinuance of corticosteroid therapy in patients with rheumatologic diseases should be avoided regardless of COVID-19 exposure or infection status. These experts also state that if indicated, corticosteroids should be used at the lowest effective dosage to control manifestations, but also acknowledge that higher dosages may be necessary in the context of severe, vital organ-threatening rheumatologic disease even following COVID-19 exposure. [28-30] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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 (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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Epoprostenol (inhaled) *Updated 5/28/20*	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) in patients with ARDS. [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]	The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against the use of inhaled prostacyclins in COVID-19 patients with severe ARDS [10] The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign state that a trial of inhaled pulmonary vasodilator as rescue therapy may be considered in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment [10, 12]
Interferons *Added 5/28/20*	8:18.20 Interferons 10:00 Antineoplastic Agents 92:20 Immunomodulatory Agents	Interferons (IFNs) modulate immune responses to some viral infections; [2, 7, 19] in vitro studies indicate only weak induction of IFN following SARS-CoV-2 infection, and a possible role for IFNs in prophylaxis or early treatment of COVID-19 has been suggested to compensate for possibly insufficient endogenous IFN production [1, 3, 4, 7, 18] **Type 1 IFNs (IFN alfa and IFN beta)** are active in vitro against MERS-CoV in Vero and LLCMK2 cells and in rhesus macaque model of MERS-CoV infection; type I IFNs also active in vitro against SARS-CoV-1 in Vero, fRhK-4, and human cell lines; [8] IFN beta is more active than IFN alfa in vitro against SARS-CoV-1 and MERS-CoV [2, 8, 12] IFN alfa and IFN beta are active in vitro against SARS-COV-2 in Vero cells at	**Only limited clinical trial data available** to date specifically evaluating efficacy of IFNs for treatment of COVID-19; for information on additional studies including IFN alfa or IFN beta as a component of combination therapy (e.g., background regimen), see antiviral entries in this Evidence Table Clinical trials are currently evaluating **IFN beta-1a or IFN beta-1b**, generally added to other antivirals, for treatment of COVID-19, including: [16] NCT04315948 (IFN beta-1a plus lopinavir/ritonavir [LPV/RTV] vs LPV/RTV vs remdesivir vs hydroxychloroquine [each regimen given with standard care] vs standard care) NCT04324463 (IFN beta-1b vs IFN beta-1b plus hydroxychloroquine [or chloroquine] plus azithromycin vs usual care) NCT04343768 (IFN beta-1a plus hydroxychloroquine plus LPV/RTV vs IFN beta-1b plus hydroxychloroquine plus LPV/RTV vs hydroxychloroquine plus LPV/RTV) [16] Open-label, randomized study in Hong Kong in hospitalized adults with COVID-19, mainly mild disease (NCT04276688): Combination regimen of **LPV/RTV, ribavirin, and sub-Q IFN beta-1b** (IFN beta-1b was omitted to avoid proinflammatory effects when treatment was initiated 7-14 days after symptom onset) was associated with	**IFN beta:** Various sub-Q dosages of IFN beta-1a and IFN beta-1b are being evaluated for treatment of COVID-19 [10, 16] Open-label, randomized study in hospitalized adults with COVID-19, mainly mild disease (NCT04276688**):** **IFN beta-1b** 8 million units was given sub-Q on alternate days for 1, 2, or 3 doses (when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset) in conjunction with 14-day regimen of LPV/RTV and ribavirin [10, 16] Open-label, randomized study in hospitalized adults with COVID-19 (NCT04324463) is evaluating **IFN beta-1b** 0.25 mg sub-Q on days 1, 3, 5, and 7, either alone or in conjunction with 7-day regimen of hydroxychloroquine (or chloroquine) and 5-day regimen of azithromycin [16] Adaptive, open-label, randomized study in hospitalized adults with moderate or severe COVID-19 disease (NCT04315948) is evaluating **IFN beta-1a** 44 mcg sub-Q on days 1, 3, and 6 in conjunction with 14-day regimen of LPV/RTV [16]	Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established Relative effectiveness of different IFNs against SARS-CoV-2 not established [12] NIH COVID-19 Treatment Guidelines Panel recommends against use of IFNs for treatment of COVID-19, except in the context of a clinical trial, because no benefit was observed with use of IFNs for treatment of other coronavirus infections (SARS, MERS), clinical trial results for treatment of COVID-19 are lacking, and toxicity of IFNs outweighs the potential for benefit [11] Surviving Sepsis Campaign COVID-19 subcommittee states that there is insufficient evidence to issue a recommendation on use of interferons, alone or in combination with antivirals, in critically ill adults with COVID-19 [12] Interferon alfa via atomization inhalation is included in Chinese guidelines as a possible option for treatment of COVID-19 [13]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		clinically relevant concentrations; [1] in vitro study suggests SARS-CoV-2 is more sensitive than SARS-CoV-1 to IFN alfa [1, 3] However, lack of clinical benefit observed with use of type 1 IFNs, generally in combination with ribavirin, for treatment of SARS and MERS [2, 8, 9, 11, 12] IV IFN beta-1a did not reduce ventilator dependence or mortality in a placebo-controlled trial in patients with acute respiratory distress syndrome (ARDS) [11, 17] **Type 3 IFNs (IFN lambda)** are thought to provide important immunologic defense against respiratory viral infections [3, 4, 6, 7, 19] and may have less potential than type 1 IFNs to produce systemic inflammatory response, including inflammatory effects on respiratory tract; [4, 7, 19] IFN lambda receptor is expressed mainly on epithelial (including respiratory epithelial) cells and neutrophils, and is distinct from the ubiquitous type 1 IFN receptor; [2, 4, 7, 19] despite different receptors and expression patterns, type 1 and type 3 IFNs activate similar signaling cascades; [4, 7, 19] unknown whether limited receptor distribution might also affect efficacy [4]	shorter median time from treatment initiation to negative RT-PCR result in nasopharyngeal swab (7 vs 12 days), earlier resolution of symptoms (4 vs 8 days), and shorter hospital stay (9 vs 14.5 days) compared with control (LPV/RTV). In the subset of patients initiating treatment 7 or more days after symptom onset (i.e., those not treated with IFN beta-1b), there was no significant difference in time to negative RT-PCR result, time to resolution of symptoms, or duration of hospital stay between the combination regimen (LPV/RTV and ribavirin) and control (LPV/RTV). IFN beta-1b (8 million units on alternate days) was administered for 1, 2, or 3 doses when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset (median of 2 IFN beta-1b doses given); 52 of 86 patients (60%) randomized to combination regimen received all 3 drugs, and 41 patients received control LPV/RTV. [10] **Aerosolized IFN alfa** (not commercially available in U.S.) has been used in China in children and adults for treatment of COVID-19, [13, 14, 15] but limited clinical data presented to date. [11] In a retrospective study of 77 hospitalized adults with moderate COVID-19 disease who received aerosolized IFN alfa-2b (5 million units twice daily) (n = 7), umifenovir (Arbidol®) (n = 24), or both drugs (n = 46), time from symptom onset to negative RT-PCR result in throat swab appeared to be shorter in those receiving IFN alfa-2b alone or in combination with umifenovir compared with those receiving umifenovir alone; this exploratory study was small and nonrandomized, and treatment groups were of unequal size and demographically unbalanced in age, comorbidities, and time from symptom onset to treatment. [15] **Sub-Q peginterferon lambda-1a** (not commercially available in U.S.) is being evaluated for *treatment* (e.g., NCT04354259, NCT04388709) and *postexposure prophylaxis* (e.g., NCT04344600) of SARS-CoV-2 infection [5]	**IFN alfa:** Chinese guidelines suggest IFN alfa dosage of 5 million units (or equivalent) twice daily via atomization inhalation for treatment of COVID-19 [13] **Peginterferon lambda-1a:** For *treatment* of COVID-19 in adults (NCT04354259, NCT04388709): Peginterferon lambda-1a 180 mcg sub-Q; number of doses (1 dose or 2 doses given 1 week apart) depends on the protocol [5] For *postexposure prophylaxis* of CoV-2 infection in adults (NCT04344600): Two 180-mcg sub-Q doses of peginterferon lambda-1a given 1 week apart [5]	

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®) *Updated 5/21/20*	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] 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 NCT04273321 NCT04323592 NCT04329650 NCT04343729 NCT04374071 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]	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 for general recommendations on corticosteroid use in patients with COVID-19.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Nitric oxide (inhaled) *Updated 5/28/20*	48:48 Vasodilating Agent	Selective pulmonary vasodilator with bronchodilatory and vasodilatory effects in addition to other systemic effects mediated through cGMP-dependent or independent mechanisms; may be useful for supportive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19 [2, 3, 9, 11, 14] Also has been shown to have antiviral effects. [1, 14] In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV-1) [1, 14] In a small pilot study (Chen et al.) conducted during the SARS outbreak, treatment with inhaled nitric oxide was found to reverse pulmonary hypertension, improve severe hypoxia, and shorten the duration of ventilatory support in critically-ill SARS patients [2, 3] Genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential benefit in patients with COVID-19 [1, 14]	No published studies evaluating use specifically in COVID-19 patients [10] One case report described possible benefit in a SARS-CoV-2-positive outpatient who also had idiopathic pulmonary arterial hypertension [13] 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] Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway, including the following trials: NCT04388683, NCT04383002, NCT04358588 (Expanded Access), NCT04397692, NCT04398290, NCT04338828, NCT04305457, NCT04306393, NCT04312243 [3, 7]	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] Various dosing protocols using different methods of delivery are being evaluated in ongoing studies in COVID-19 patients [3]	The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign recommend against the routine use of inhaled nitric oxide in mechanically ventilated COVID-19 patients with ARDS; however, a trial of inhaled pulmonary vasodilator as rescue therapy may be considered in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment [10, 12]
Ruxolitinib (Jakafi®) *Updated 6/3/20*	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	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) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.) [1, 10]	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] **Phase 3 study (NCT04377620):** Ruxolitinib 5 or 15 mg twice daily (approximately every 12 hours) [12]	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] **Severe reactions** requiring drug discontinuance observed in 2 COVID-19 patients following initiation of ruxolitinib: purpuric lesions with thrombocytopenia

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		management of hyperinflammation resulting from viral infections such as COVID-19 [5, 7]	**Phase 3, randomized, double-blind, placebo-controlled clinical trial (**NCT04377620; RUXCOVID-DEVENT) is evaluating ruxolitinib plus standard of care vs placebo plus standard of care in adults with COVID-19-associated acute respiratory distress syndrome (ARDS) who require mechanical ventilation (sponsored by Incyte) [12] **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 clinical trials also registered, including: [3] NCT04331665 NCT04338958 NCT04348071 NCT04348695 NCT04403243		and deep-tissue infection in one patient, and progressive decrease in hemoglobin and erythrodermic rash over the whole body surface area in the second patient; these cases differed in the timing of ruxolitinib initiation and the severity of COVID-19 illness [11]
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] 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]	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
Siltuximab (Sylvant®) *Added 5/13/20*	10:00 Antineoplastic agents	Recombinant chimeric monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients [1-5]	**Italy:** Early (non-peer-reviewed) findings from an observational case-control study of the first 21 patients with COVID-19 and pneumonia/acute respiratory distress syndrome (ARDS) who participated in a compassionate use program (SISCO study; NCT04322188) in one hospital and were followed for up to 7 days showed reduced and normalized C-reactive protein (CRP) levels (a marker of systemic inflammation) by day 5 in all 16 siltuximab-treated patients with sufficient available data. An interim analysis revealed that the condition of 33% of the siltuximab-treated patients improved and no clinically relevant change in condition was reported in 43% of patients while 24% of patients worsened, including one patient who died and another with a cerebrovascular event. This cohort study with patients treated with standard therapy is ongoing. [4, 6] Other clinical trials evaluating siltuximab in the treatment of COVID-19 currently are recruiting in **Belgium** (NCT04330638) [7] and **Spain** (NCT04329650) [8]	In the SISCO study in Italy, patients received an initial dose of siltuximab 11 mg/kg by IV infusion over 1 hour; a second dose could be administered at the physician's discretion (5 of the first 21 patients received a second dose after 2-3 days) [4] Other clinical studies under way are evaluating a single siltuximab dose of 11 mg/kg by IV infusion [7, 8]	Efficacy and safety of siltuximab in the treatment of COVID-19 not established; additional study needed
Sirolimus (Rapamune®) *Updated 5/28/20*	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] Limited experience in patients with H1N1 pneumonia suggests possible benefit; in one study, treatment with sirolimus 2 mg daily in conjunction with corticosteroids for 14 days was associated with improved patient outcomes (e.g., shortened duration of mechanical ventilation, improved hypoxia and multiorgan function) [3]	Clinical trials evaluating sirolimus for the treatment of COVID-19 are planned or underway including the following trials: [4] NCT04341675 NCT04374903 NCT04371640	Dosage being investigated in a randomized, double-blind, placebo-controlled trial (NCT04341675): 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
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] 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]	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
			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 ***Updated 6/11/20***	20:12.04 Anticoagulants	Patients with COVID-19, particularly those with severe disease, may develop a hypercoagulable state, which has been associated with poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-6, 14, 16, 28, 29] Observed coagulation abnormalities include prothrombotic disseminated intravascular coagulation (DIC), elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. [1-6, 9, 11, 13, 16, 26, 27]	Limited data from a retrospective study in China showed reduced mortality in COVID-19 patients with severe sepsis-induced coagulopathy or markedly elevated D-dimer levels (>6 x ULN) who received prophylactic anticoagulation (low molecular weight heparin [LMWH] or unfractionated heparin [UFH]).[4, 19] Observational data derived from a large US cohort of hospitalized patients with COVID-19 suggest possible benefit of therapeutic-dose anticoagulation; however, the study had important limitations (e.g., indications for anticoagulation initiation and details on patient characteristics not reported). [28, 31] Several clinical trials have been initiated or currently underway to evaluate anticoagulant strategies in patients with COVID-19,		Additional study is needed to understand the anticoagulant needs of COVID-19 patients. [9, 11, 27-29] VTE risk should be assessed in all patients on an individual basis. [4, 5, 10, 17, 18, 27, 28, 32] Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy. [4, 5, 9, 25, 27, 28, 30, 32] The NIH COVID-19 Treatment Guidelines Panel recommends VTE prophylaxis according to the usual standard of care in all hospitalized adults with COVID-19 unless contraindicated. [28] The International Society for Thrombosis and Haemostasis, American College of Cardiology, and American Society of Hematology recommend that all hospitalized COVID-19 patients receive

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		High rates of VTE have been reported in critically ill patients with COVID-19. [7, 8, 11, 15, 18, 28, 36] Pathogenesis of COVID-19-related coagulopathy not completely known, but may be related to an uncontrolled immunothrombotic response to viral infection.[16, 17, 27-29, 32] Anticoagulant therapy may reduce the risk of thrombotic complications and improve clinical outcomes. [2, 4, 5, 14, 25, 27]	including the following: NCT04373707, NCT04372589, NCT04345848, NCT04412304, NCT04416048 [12]		prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, severe thrombocytopenia, fibrinogen <0.5 g/L). [4, 5, 30] WHO recommends pharmacologic prophylaxis with LMWH (preferred) or UFH (5000 units sub-Q twice daily) in adults and adolescents with COVID-19 who do not have contraindications. [25] LMWH or UFH may be preferred over oral anticoagulants in critically ill hospitalized patients with COVID-19 because of their shorter half-lives, ability to be administered parenterally, and fewer drug-drug interactions.[28] Patient-specific factors (e.g., renal function) and practical concerns (e.g., need for frequent monitoring, convenience of administration, risk of medical staff exposure) may influence choice of anticoagulant. [14, 15, 20, 27, 32] Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, some clinicians have used (or suggested the use of) higher prophylactic doses or even therapeutic doses of anticoagulants to prevent thromboembolic complications in such patients; however, prospective studies are needed to evaluate these approaches. [8, 11, 14-17, 20-24, 26-28, 30, 31, 32, 34, 36] Pending additional data, use of higher-intensity nonstandard VTE prophylaxis or therapeutic-dose anticoagulation should ideally be done in the context of a clinical trial. [28, 30] Based on expert opinion, the Anticoagulation Forum suggests increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, heparin 7500 units sub-Q 3 times daily, or low-intensity heparin infusion) for critically ill patients (e.g., in the ICU) with confirmed or suspected COVID-19. [32] NIH and other experts state that the current data are insufficient to

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					recommend for or against the use of therapeutic anticoagulation in COVID-19 patients in the absence of confirmed or suspected thrombosis. [4, 28, 30] The efficacy of intermediate or full-dose therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is currently being evaluated. [4, 12] Patients who are already on anticoagulant therapy for an existing condition (e.g., VTE, atrial fibrillation) should continue to receive such treatment unless significant bleeding occurs or other contraindications are present. [4, 28] Extended VTE prophylaxis after hospital discharge is not routinely recommended in patients with COVID-19, but may be considered based on the same protocols and risk-benefit analysis as for patients without COVID-19. [27, 28, 30, 32] Although a relationship between markedly elevated D-dimer levels and mortality has been shown, whether this can be applied to predicting or managing VTE risk is not known. [5, 6, 7, 30, 32, 33] Bleeding appears to be infrequent in COVID-19 patients. [5, 30] 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, 32]
COVID-19 Convalescent Plasma *Updated 6/11/20*		Plasma obtained from patients who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2 may provide short-term *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, 25] Convalescent plasma therapy has been used in the	**Uncontrolled pilot study in China (Duan et al):** 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 radiologic improvement in pulmonary lesions. Titers of neutralizing antibody increased in 5 patients after the		Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. [11, 25] The NIH COVID-19 Treatment Guideline Panel states that there are insufficient data to recommend for or against the use of convalescent plasma in patients with COVID-19. [25] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		treatment of other viral diseases with various degrees of success. [16, 20, 22, 24, 25] In patients with SARS-CoV-1 infection, use of convalescent plasma was reported to shorten the duration of hospitalization 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]	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 (Shen et al):** 5 critically ill adults with rapidly progressing severe COVID-19 and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation who had high viral loads despite antiviral treatment received 2 transfusions of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody end point dilution titers of 80-480 depending on the donor); patients continued to receive antiviral treatments (e.g., LPV/RTV, favipiravir, umifenovir [Arbidol®], darunavir, interferon 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 (Zeng et al)**: 6 critically ill adults with COVID-19 were treated with convalescent plasma at a median of 21.5 days after first detection of viral shedding. Although viral clearance was observed in all patients following transfusion, death occurred in 5 of 6 patients. [16] **Uncontrolled descriptive study in China (Ye et al):** 6 adults with COVID-19 received convalescent plasma at a relatively late stage of the disease (most patients received 2 or 3 plasma transfusions); various laboratory, radiologic, and clinical improvements were reported. [18]		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 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, 25] **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] **There are no convalescent blood products currently licensed by the FDA.** [25] **COVID-19 convalescent plasma is regulated as an investigational product.** [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Uncontrolled case series in US (Salazar et al): 25 adults with severe and/or life-threatening COVID-19 disease received convalescent plasma in addition to multiple other treatments (e.g., antivirals, anti-inflammatory agents). [26] The median time from symptom onset to plasma transfusion was 10 days and 24/25 patients received a single transfusion. [26] Convalescent plasma was well tolerated and no transfusion-related adverse events were reported. At day 7 post-transfusion, 9 patients (36%) had clinical improvement (defined as at least a 1-point improvement based on a 6-point ordinal scale); by day 14 post-transfusion, 19 patients (76%) had clinical improvement or were discharged. The contribution of convalescent plasma to clinical improvement in these patients is unclear since there was no control group and patients also received other treatments. [26] **Cochrane review:** A systematic review of 8 published studies evaluating convalescent plasma in adults with COVID-19 (total of 32 study participants) found very low confidence in the efficacy and safety of this treatment approach based on the current evidence. There was a high risk of bias within and across the studies (all were uncontrolled, nonrandomized, and included a small number of participants) and great variability in terms of dose and timing of convalescent plasma administration, donor and recipient characteristics, and outcomes evaluated. [27] **Open-label, randomized, controlled study in China (Li et al):** Results of this study in 103 adults with severe or life-threatening COVID-19 found no significant difference in time to clinical improvement within 28 days, mortality, or time to hospital discharge in patients treated with convalescent plasma (containing a high titer of antibody to SARS-CoV-2) plus standard of care compared with standard of care alone. [28] Convalescent plasma therapy was well tolerated by the majority of patients; 2 cases of transfusion-associated adverse events were reported. [28] There was a signal of possible benefit in the subgroup of		**FDA states that there are 3 available pathways for administering or studying the 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 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			patients with severe COVID-19 disease.[28, 29] However, the study had several limitations that preclude any definite conclusions, including the possibility of being underpowered as the result of early termination because of the lack of available patients.[28, 29] In addition, most patients received convalescent plasma treatment at least 14 days after symptom onset and it is unclear whether earlier treatment would have resulted in greater benefit.[28, 29] **Although there is some evidence suggesting possible benefits of convalescent plasma in patients with COVID-19, available data to date are largely from case reports or series; confirmation from additional randomized controlled studies is required.**[1, 20-23, 27-29] **Multiple clinical trials have been initiated globally** 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 trials 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		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
Famotidine *Updated 6/3/20*	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:** 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] Retrospective matched cohort study of COVID-19 patients hospitalized, but not requiring intubation within the first 48 hrs, at a single New York medical center indicated that the risk for the composite outcome of death or intubation was reduced (mainly due to difference in mortality) in patients who received famotidine within 24 hours of hospital admission (n = 84) vs those who did not receive the drug (n = 1536); overall, 21% of patients met the composite outcome (8.8% were intubated and 15% died); the finding appeared to be specific to the H_2 antagonist and to COVID-19, as the investigators reported	Currently no known published prospective 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		observing no protective effect with proton-pump inhibitors or in non-COVID-19 patients. Home use of famotidine was documented on admission in 15% of patients who received the drug in hospital vs 1% of those who did not; 28% of all famotidine doses were IV; 47% of doses were 20 mg, 35% were 40 mg, and 17% were 10 mg; the median duration of use was 5.8 days, and the total median dose was 136 mg (63-233 mg) [7]			
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]
Immune Globulin ***Updated 6/11/20***	80:04 Immune Globulin	Commercially available immune globulin (IGIV, IVIG, γ-globulin) is derived from pooled plasma and contains many antibodies normally present in adult human blood; used for replacement therapy in patients with primary [8]	**SARS Experience:** IGIV has been used in the treatment of SARS. [4-7, 15] Benefits were unclear because of patient comorbidities, differences in stage of illness, and effect of other treatments; [5] IGIV may have contributed to hypercoagulable state and thrombotic complications in some patients. [6, 7]	IGIV dosage of 0.3-0.5 g/kg daily for 5 days has been used in patients with COVID-19 [8, 12]	Role of commercially available immune globulin (IGIV, IVIG, γ-globulin) and investigational SARS-CoV-2 immune globulin in the treatment of COVID-19 unclear. [16] The Surviving Sepsis Campaign COVID-19 subcommittee suggests that IGIV not be used routinely in critically ill adults

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		humoral immunodeficiency who are unable to produce sufficient IgG antibodies and also used to provide *passive* immunity to certain viral infections in other individuals. [1] Investigational SARS-CoV-2 immune globulin is a concentrated immune globulin preparation containing specific antibody derived from the plasma of individuals who have recovered from COVID-19.[16] Immune globulin preparations containing antibodies specific to SARS-CoV-2 may theoretically help suppress the virus and modulate the immune response to COVID-19 infection. [2, 16] Commercially available preparations of immune globulin (IGIV, IVIG, γ-globulin) may contain antibodies against some previously circulating coronaviruses. [2, 3, 13, 18] Antibodies that cross-react with SARS-CoV-1, MERS-CoV, and SARS-CoV-2 antigens have been detected in some currently available IGIV products; [18] however, further evaluation is necessary to assess potential in vivo activity of such anti-SARS-CoV-2 antibodies using functional tests such as neutralization assays. [1]	**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 patients also received antivirals and 1 patient also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration. [8] **COVID-19 clinical experience in China:** IGIV has been used as an adjunct in the treatment of COVID-19 and has been mentioned in Chinese guidelines as a possible treatment option for severe and critically ill children with COVID-19. [9-11, 14] **Multicenter retrospective study in China:** Among a cohort of 325 patients with severe or critical COVID-19 disease, no difference in 28-day or 60-day mortality was observed between patients who were treated with IGIV and those who were not treated with IGIV. However, patients who received IGIV were older and more likely to have coronary heart disease and critical status at study entry; patients also received numerous other treatments which limit interpretation of these findings. [16, 19] **Retrospective study in China:** 58 cases of severe or critical COVID-19 illness in ICU patients were reviewed. [17] Patients received IGIV in addition to other treatments (e.g., antiviral and anti-inflammatory agents). A statistically significant difference in 28-day mortality was observed between patients who received IGIV within 48 hours of admission compared with those who received IGIV after 48 hours (23 vs 57%). Treatment with IGIV within 48 hours also was associated with reduced duration of hospitalization and reduced ICU length of stay and need for mechanical ventilation. [17] **Efficacy data not available from controlled clinical studies to date.** **Several clinical studies have been initiated** to evaluate efficacy and safety of IGIV or		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] The NIH COVID-19 Treatment Guidelines Panel recommends against the use of commercially available IGIV (i.e., non-SARS-CoV-2-specific IGIV) for the treatment of COVID-19 except in the context of a clinical trial and states that current IGIV preparations are not likely to contain SARS-CoV-2 antibodies. [16] This does not preclude the use of IGIV when it is otherwise indicated for the treatment of complications arising during the course of COVID-19 disease. [16] NIH states that there are insufficient data to recommend for or against the use of investigational SARS-CoV-2 immune globulin for the treatment of COVID-19. [16]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			SARS-CoV-2 immune globulin in patients with COVID-19, including the following trials: [12] NCT04264858 NCT04350580 NCT04381858 NCT04261426		
Ivermectin *Updated 5/15/20*	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, 9] pharmacokinetic modeling predicts that plasma concentrations attained with dosages up to 10 times higher than usual dosage also are substantially lower than concentrations associated with in vitro inhibition of the virus [9] 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]
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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Niclosamide *Updated 5/28/20*	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] Randomized, double-blind placebo-controlled trial in Boston, (NCT04399356) to evaluate niclosamide in adults with mild to moderate COVID-19 [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] Protocol in one ongoing trial (NCT04399356) for treatment of mild to moderate COVID-19 specifies a dosage of 2 g once daily for 7 days [3]	Not commercially available in the US No data to date support use in treatment of COVID-19
Nitazoxanide *Updated 5/28/20*	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] Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice [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 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]	**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] 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] Results of a physiologically based pharmacokinetic model predict that nitazoxanide dosages of 1200 mg 4 times daily, 1600 mg 3 times daily, and 2900 mg twice daily in the fasted state and 700 mg 4 times daily, 900 mg 3 times daily, and 1400 mg twice daily in the fed state are capable of maintaining plasma and lung tizoxanide (major metabolite of nitazoxanide) exposures exceeding the EC_{90} for SARS-CoV-2 [9]	Current data not specific to COVID-19; additional study needed [1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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]		
Nonsteroidal Anti-inflammatory Agents (NSAIAs) *Updated 5/21/20*	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:** In vitro antiviral activity in SARS-CoV-2 pseudovirus-infected Vero E6 cells; [7] also has in vitro activity against **other** coronaviruses: SARS-CoV-1 (in Vero E6 and human pulmonary epithelial [A549] cells) and canine coronavirus; also has in vivo activity against canine coronavirus in dogs [6, 7] (interferes with viral RNA synthesis) [6, 8]	**Ibuprofen:** None; anecdotal [1] **Indomethacin:** In vitro studies and animal models only; [6, 7] currently no published studies evaluating use specifically in COVID-19 patients		**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 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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] 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] **Indomethacin**: Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy in the treatment of COVID-19
Tissue Plasminogen Activator (t-PA; alteplase) *Updated 6/3/20*	20:12.20 Thrombolytic agents	A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which has been shown to contribute to poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-3, 5-9, 14, 16, 18, 19] Coagulation abnormalities observed include	Results of a small phase 1 study suggested possible benefit of plasminogen activators in 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] In a case series of 5 COVID-19 patients who had severe hypoxemia, declining	Two dosage regimens of t-PA (alteplase) are being evaluated in the open-label systemic fibrinolytic therapy trial (NCT04357730): 50 mg (administered as a 10-mg IV bolus followed by IV infusion of the remaining 40 mg over a total time of 2 hours) and 100 mg (administered as a 10-mg IV bolus dose followed by IV administration of the remaining 90 mg over a total time of 2 hours); a heparin infusion will be initiated	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] Several institutions (Beth Israel Deaconess, University of Colorado Anschultz Medical Campus, Denver Health) are currently testing this approach under

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		prothrombotic disseminated intravascular coagulation (DIC), venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. [1, 2, 5-10, 13, 14, 16] A consistent finding in patients with ARDS (regardless of the cause) is fibrin deposition and microthrombi formation in the alveoli and pulmonary vasculature. [1, 11, 14] Dysregulation of the clotting system in ARDS is a result of both enhanced activation of coagulation and suppression of fibrinolysis. [12, 19] Thrombolytic therapy may restore microvascular patency and limit progression of ARDS in patients with COVID-19 [1, 14, 19]	respiratory status, and increasing oxygen requirements, administration of t-PA (alteplase) at an initial IV bolus dose of 25 mg over 2 hours followed by a continuous IV infusion of 25 mg over the next 22 hours appeared to improve oxygen requirements in all patients and prevent progression to mechanical ventilation in 3 of the patients; however, multiple confounding factors limit interpretation of these findings. [20] An open-label, randomized trial (NCT04357730) is being conducted to evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure [12] An open-label, nonrandomized pilot study (NCT04356833) is being conducted to evaluate an inhaled formulation of t-PA (via nebulization) in patients with ARDS due to COVID-19; [12] the inhaled formulation of t-PA is investigational at this time [15]	immediately following completion of the alteplase infusion [12] Other dosage regimens have been evaluated in patients 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; however, the optimum dose, route of administration, and duration of treatment remain to be determined. [1, 9, 14, 20]	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 NIH COVID-19 Treatment Guidelines Panel states that current data are insufficient to recommend for or against the use of thrombolytic agents in hospitalized COVID-19 patients outside the setting of a clinical trial; patients who develop catheter thrombosis or other indications for thrombolytic therapy should be treated according to the usual standard of care in patients without COVID-19. [17] 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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