Assessment of Evidence for COVID-19-Related Treatments: Updated 7/16/2020

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ANTIVIRAL AGENTS

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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 6/25/20*	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: 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 and critical 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 and 5 with severe COVID-19) received	**Optimal dosage and duration of treatment not known** [25] **Consider:** 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base [17] **Oral chloroquine phosphate dosage suggested in the EUA (now revoked):** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, suggested dosage was 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation. [25] **FDA now states that this dosage regimen is unlikely to have an antiviral effect in pts**	Efficacy and safety of chloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration

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		patients with viral infections [1-3, 13, 15-16] Known pharmacokinetics and toxicity profile based on use for other indications [13, 17]	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 trials and experience with 4-aminoquinoline antimalarials in the	**with COVID-19 based on a reassessment of in vitro EC_{50}/EC_{90} data and calculated lung concentrations;** it is unclear whether this dosage regimen would provide any beneficial immunomodulatory effects. [57] **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 dosage used in some clinical trials**: 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 recommends against use of chloroquine for the *treatment* of COVID-19, except in a clinical trial; the panel recommends against use of high-dose chloroquine (i.e., 600 mg twice daily for 10 days) for the treatment of COVID-19 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. The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure. [35] Because 4-aminoquinolines (chloroquine, hydroxychloroquine) are associated with QT prolongation, caution is advised if considering use of the drugs in pts with COVID-19 at risk for QT prolongation or receiving other drugs associated with arrhythmias; [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.)

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			management of COVID-19. Several clinical trials to evaluate chloroquine for the *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10] NCT04323527 NCT04328493 NCT04331600 NCT04428268 Several clinical trials to evaluate chloroquine for *prevention* of COVID-19 in the healthcare setting are registered at clinicaltrials.gov: [10] NCT04303507 NCT04333732 NCT04349371		NIH panel states that 4-aminoquinolines (chloroquine, hydroxychloroquine) should be used concomitantly with drugs that pose a moderate to high risk for QT_c prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, fluoroquinolones, macrolides [including azithromycin]) *only* if necessary. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving chloroquine (or hydroxychloroquine). [35] FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. [39] **Emergency use authorization (EUA) for chloroquine (now revoked):** Effective June 15, 2020, FDA has revoked the EUA for chloroquine and hydroxychloroquine [57] previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible. [24, 57] **Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met.** [57] Based on the totality of scientific evidence available, FDA concluded that it is unlikely that chloroquine and

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					hydroxychloroquine may be effective in treating COVID-19 and, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of chloroquine and hydroxychloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA. [57] (See Hydroxychloroquine in this Evidence Table.)
Favipiravir (Avigan®, Favilavir) ***Updated 7/16/20***	8:18.32 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [1–5] In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug [1, 5, 16] Licensed in Japan and China for treatment of influenza [2, 4, 6]	**Only very limited clinical trial data available** to date to evaluate use of favipiravir in the treatment of COVID-19 **Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir (Arbidol®; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe to critical COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe to critical disease compared with the group receiving umifenovir. [6] **In a small, open-label, nonrandomized study** in patients with non-severe COVID-19 in China (ChiCTR2000029600), favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily on days 2–14) (n=35) was associated with decreased median time to viral clearance (4 vs 11 days) and higher improvement rate on chest CT imaging on day 14 (91 vs 62%) compared with the control group receiving lopinavir/ritonavir (n=45); both groups also received aerosolized interferon α-1b. [15] **In a retrospective, observational, multicenter study** in 63 adults with COVID-19 in	A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days was used in several open-label COVID-19 studies in adults and adolescents ≥16 years of age in China [6, 15] Protocol in one ongoing trial (NCT04346628) specifies a favipiravir dosage of 1800 mg on day 1, then 800 mg twice daily on days 2–10 for treatment of mild or asymptomatic COVID-19 in adults [7] Protocol in one ongoing trial (NCT04464408) specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 800 mg twice daily for up to 7 days for treatment of mild COVID-19 in adults [7] Protocol in one ongoing trial (NCT04411433) specifies a favipiravir dosage of 1600 mg twice daily on day 1, then 1200 mg twice daily on days 2–5 or 1800 mg twice daily on day 1, then 1600 mg twice daily on days 2–5 for treatment of mild to moderate COVID-19 in adults [7] Protocol in one ongoing trial (NCT04425460) specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 600 mg three times daily for 2–14 days for treatment of moderate COVID-19 in adults [7] Protocols in two ongoing trials (NCT04392973, NCT04434248)	Not commercially available in the US Efficacy and safety of favipiravir for treatment of COVID-19 not established Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dosage and treatment duration Given the lack of pharmacokinetic and safety data for the high favipiravir dosages proposed for treatment of COVID-19, the drug should be used with caution at such dosages. [19, 20] 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]

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			Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and median maintenance doses of 17.9 mg/kg per day for a median total duration of 12 days), clinical improvement at day 7 was reported in 66.7% of patients (92.5% in patients *not* requiring oxygen supplementation, 47.2% in patients requiring oxygen supplementation) and clinical improvement at day 14 was reported in 85.7% of patients (100% in patients *not* requiring oxygen supplementation, 75% in patients requiring oxygen supplementation). Overall mortality at day 28 was 4.8%. Nearly all patients also received a chloroquine-based therapy and an HIV protease inhibitor. Multivariate analysis revealed that older age, higher baseline disease severity, and loading doses <45 mg/kg per day were negative predictors of early clinical improvement. [23] **US**: Randomized, controlled open-label proof-of-concept trial (NCT04358549) of favipiravir for the treatment of COVID-19 [7, 10] **US:** Randomized, double-blind, placebo-controlled trial (NCT04346628) to evaluate efficacy of favipiravir in pts with mild or asymptomatic 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.	specify a favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–14 or 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–14, respectively, for treatment of moderate or severe COVID-19 in adults [7] Protocol in one ongoing trial (NCT04358549) specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 for treatment of COVID-19 in adults [7] Protocol in one ongoing trial (NCT04373733; PIONEER) specifies a favipiravir dosage of 1800 mg twice daily on day 1, followed by 800 mg twice daily on days 2–10 for early treatment of suspected or confirmed COVID-19 in adults [7] Protocols in several ongoing trials (NCT04387760, NCT04445467, NCT04402203, NCT04310228, NCT04319900, NCT04333589, NCT04373733) specify a favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily for 6–13 days or 1800 mg twice daily on day 1, then 800 mg twice daily for 9–13 days for treatment of COVID-19 in adults [7] Protocol in one ongoing trial (NCT04448119) specifies a *prophylactic* favipiravir dosage of 1600 mg twice daily on day 1, then 800 mg twice daily on days 2–25 and a *treatment* favipiravir dosage of 2000 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 in older adults in long-term care homes experiencing COVID-19 outbreaks. The prophylactic regimen is considered pre-exposure prophylaxis, post-exposure prophylaxis, or pre-emptive therapy in this setting; those diagnosed with COVID-19 will be offered the treatment regimen [7]	

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				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 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 7/16/20***	8:18.08.08 HIV Protease Inhibitors	**Lopinavir (LPV):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells; [19] evidence of in vitro activity against SARS-CoV-1 and MERS-CoV; [1, 2, 9] some evidence of benefit in animal studies for treatment of MERS-CoV [2, 7, 9, 11]	**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (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	**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:** Efficacy for the treatment of COVID-19, with or without other antivirals, not established [22, 23] **Darunavir:** Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/cobicistat for treatment of COVID-19 and there are no published clinical studies that

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		Atazanavir (ATV): Some evidence that 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):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells [19]	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 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**	**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]	have evaluated efficacy and safety of DRV, DRV/cobicistat, or the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide for treatment of COVID-19. In addition, initial unpublished results from an open-label, controlled 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 [22] 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. The panel states that, based on the pharmacodynamics of HIV protease inhibitors, there are concerns whether drug concentrations achieved with oral doses of the drugs are adequate to inhibit SARS-CoV-2 protease. In addition, clinical trials to date using LPV/RTV have not demonstrated a clinical benefit in patients with COVID-19. [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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			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 (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:** Some clinical trials registered at clinicaltrials.gov listed below: [15]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			NCT04372628 (LPV/RTV vs hydroxychloroquine vs placebo) NCT04403100 (LPV/RTV vs hydroxychloroquine vs LPV/RTV plus hydroxychloroquine vs placebo in pts with mild disease) NCT04315948 (LPV/RTV plus interferon β-1a vs LPV/RTV vs remdesivir [each regimen given with standard care] vs standard care) NCT04425382 (LPV/RTV vs DRV/cobicistat) **Darunavir COVID-19 Clinical Trials:** A few trials registered at clinicaltrials.gov: [15] NCT04252274 (Open-label randomized trial to evaluate DRV/cobicistat) NTC04303299 (Open-label randomized trial includes treatment arms to evaluate DRV/RTV in conjunction with chloroquine or oseltamivir) NCT04425382 (DRV/cobicistat vs LPV/RTV)		
Hydroxychloroquine (Plaquenil®) ***Updated 7/16/20***	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] 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	Clinical **experience** in treating pts with COVID-19: 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 and critical disease. [35] **Hydroxychloroquine small pilot study conducted in China:** 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; [18] **both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV**. [30] Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up). [18] **Hydroxychloroquine randomized, parallel-group study in adults in China**	**Optimal dosage and duration of treatment not known** [26] **Oral hydroxychloroquine sulfate dosage suggested in the EUA (now revoked):** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, suggested dosage was 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation. [26] **FDA now states that this dosage regimen is unlikely to have an antiviral effect in pts with COVID-19 based on a reassessment of in vitro EC_{50}/EC_{90} data and calculated lung concentrations;** it is unclear whether this dosage regimen would provide any beneficial immunomodulatory effects. [57] **Oral hydroxychloroquine sulfate dosage used or being investigated in clinical trials:** 400 mg once or twice daily for 5-10 days [10, 18] **Oral hydroxychloroquine sulfate with azithromycin (NIAID trial A5395; NCT04358068):** 400 mg twice	Efficacy and safety of hydroxychloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] No data to date indicating that in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Data from randomized, controlled clinical trials needed to substantiate initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19, guide decisions regarding the most appropriate pts for treatment with such drugs, and identify optimal dose and treatment duration 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

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		dose-related toxicity profile than chloroquine,[13-16] but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs [13, 35]	**(ChiCTR2000029559):** 31 pts with COVID-19 and pneumonia received **hydroxychloroquine sulfate** (200 mg twice daily for 5 days) **and standard treatment (O_2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids)** and 31 other pts received **standard treatment alone** (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group). [31] **Note:** This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, [32] data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported. [31] **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	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]	NIH COVID-19 Treatment Guidelines Panel recommends against use of hydroxychloroquine for the *treatment* of COVID-19, except in a clinical trial. [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, because of the potential for toxicities. [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] The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure. [35] Because 4-aminoquinolines (hydroxychloroquine, chloroquine) and azithromycin are independently associated with QT prolongation and because concomitant use of the drugs may further increase the risk of QT prolongation, caution is advised if considering use of hydroxychloroquine (with or without azithromycin) in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. [35, 36, 38, 39, 41-44]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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		NIH panel states that 4-aminoquinolines (hydroxychloroquine, chloroquine) should be used concomitantly with drugs that pose a moderate to high risk for QT_c prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, fluoroquinolones, macrolides [including azithromycin]) *only* if necessary. In addition, because of the long half-lives of both hydroxychloroquine (up to 40 days) and azithromycin (up to 72 hours), caution is warranted even when these drugs are used sequentially. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving hydroxychloroquine (or chloroquine). [35] 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 (now revoked):** Effective June 15, 2020, FDA has revoked the EUA for hydroxychloroquine and chloroquine [57] previously issued on March 28, 2020 that permitted distribution of the drugs from the strategic national stockpile (SNS) for use in adults and adolescents weighing 50 kg or more

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			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 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		hospitalized with COVID-19 for whom a clinical trial was not available or participation not feasible. [24, 57] **Based on a review of new information and reevaluation of information available at the time the EUA was issued, FDA concluded that the original criteria for issuance of the EUA for these drugs are no longer met.** Based on the totality of scientific evidence available, FDA concluded that it is unlikely that hydroxychloroquine and chloroquine may be effective in treating COVID-19 and, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the known and potential benefits of hydroxychloroquine and chloroquine do not outweigh the known and potential risks associated with the use authorized by the EUA. [57] **The basis for the FDA decision to revoke the EUA for hydroxychloroquine and chloroquine is summarized below:** **1)** Suggested hydroxychloroquine and chloroquine dosage regimens as detailed in the EUA fact sheets for healthcare providers are unlikely to produce an antiviral effect. [57] **2)** Earlier observations of decreased viral shedding with hydroxychloroquine or chloroquine treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between hydroxychloroquine and standard of care alone. [57] **3)** Current US treatment guidelines do not recommend the use of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19 outside of a clinical trial and the NIH guidelines now recommend against such use outside of a clinical trial. [57] **4)** Recent data from a large, randomized, controlled trial showed no

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			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 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**		evidence of benefit in mortality or other outcomes such as hospital length of stay or need for mechanical ventilation for hydroxychloroquine treatment in hospitalized patients with COVID-19. [57] **Consult the FDA letter regarding the revocation of the EUA for hydroxychloroquine and chloroquine and the FDA memorandum explaining the basis for the revocation for additional information.** [57]

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			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):** 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		

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			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 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. **Retrospective, comparative cohort study evaluating clinical outcomes in COVID-19 pts treated with hydroxychloroquine vs hydroxychloroquine with azithromycin vs azithromycin alone:** Data for 2541 consecutive pts with laboratory-confirmed COVID-19 who were admitted to hospitals within the Henry Ford Health System in Michigan		

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			and received hydroxychloroquine and/or azithromycin or did not receive these drugs were analyzed. Median age of patients was 64 years; the majority had BMI of 30 or greater and many had various other comorbidities; 68% received corticosteroid treatment and 4.5% received tocilizumab; mSOFA scores were not available for 25% of pts and data were not available regarding duration of symptoms prior to hospitalization; and the median length of hospitalization was 6 days. The primary end point was inpatient mortality; median follow-up was 28.5 days. Results indicated that crude mortality rates were 18.1% in the entire group, 13.5% in the hydroxychloroquine group, 20.1% in the hydroxychloroquine with azithromycin group, 22.4% in the azithromycin group, and 26.4% in those not treated with hydroxychloroquine and/or azithromycin. The primary causes of mortality were respiratory failure (88%), cardiac arrest (4%), and cardiopulmonary arrest and multi-organ failure (8%). **Note: Only selected pts with minimal cardiac risk factors received hydroxychloroquine with azithromycin and all pts treated with hydroxychloroquine were monitored closely with telemetry and serial QTc evaluations.** **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		

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			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 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		

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			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 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]		

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			NCT04329923 NCT04332991 NCT04335552 NCT04345692 NCT04351620 NCT04353037 Multiple clinical trials to evaluate hydroxychloroquine for *prevention* of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed below): [10] NCT04318015 NCT04318444 NCT04328961 NCT04329923 NCT04331834 NCT04334148 NCT04341441 NCT04363450 NCT04353037 NCT04372017		
Neuraminidase inhibitors (e.g., oseltamivir) ***Updated 7/16/20***	8:18.28	Antivirals active against influenza viruses Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture [4] Oseltamivir did not inhibit the replication of SARS-CoV-2 in infected Vero E6 cells in vitro [6]	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] In a **retrospective case series** of 79 patients with COVID-19 who were negative for influenza A and B, early use of oseltamivir had no effect on COVID-19 and did not effectively slow the progression of the disease [6] 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] Some clinical trials for COVID-19 that include oseltamivir are listed below [5]: NCT04303299 NCT04261270 NCT04255017	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

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Remdesivir ***Updated 7/16/20***	8:18.32 Antiviral	Broad-spectrum antiviral (nucleotide analog prodrug) with activity against various viruses, including coronaviruses [24] In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells [1, 18] In Rhesus macaques infected with SARS-CoV-2, treatment with a 6-day regimen of IV remdesivir initiated 12 hours after virus inoculation was associated with some benefits (lower disease severity scores, fewer pulmonary infiltrates, lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control [19] In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected [1-8] Pharmacokinetic data available from evaluations for Ebola	**Randomized , double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al):** Pts were randomized 2:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10) or placebo initiated within 12 days of symptom onset. Primary outcome was time to clinical improvement within 28 days after randomization or hospital discharge, whichever came first. ITT population included 158 pts treated with remdesivir and 78 pts treated with placebo; 32% of pts also received interferon α-2b, 28% also received LPV/RTV, and 66% also received corticosteroids during hospitalization. **Median time to clinical improvement was not significantly different in remdesivir group (21 days) vs placebo group (23 days); 28-day mortality rate was similar in both groups (14 vs 13%).** When remdesivir was initiated within 10 days of symptom onset, median time to clinical improvement was numerically shorter (but not statistically significant) compared with placebo group (18 vs 23 days). Duration of invasive mechanical ventilation was numerically shorter (but not statistically significant) in remdesivir group; only a small percentage of pts (0.4%) were on invasive mechanical ventilation at time of enrollment. Remdesivir did not result in significant reduction in SARS-CoV-2 viral load in nasopharyngeal, oropharyngeal, and sputum samples. Remdesivir was discontinued in 18 pts (12%) because of adverse effects. **Note:** Enrollment was terminated before the pre-specified number of pts was attained (lack of available 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	**Optimal dosage and duration of treatment not known** [25, 26] **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 maintenance doses of 100 mg by IV infusion once daily from day 2. Optimal duration of treatment not known. For pts requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. For those **not** requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). [26] **Emergency use authorization (EUA) dosage recommended for children weighing 3.5 to less than 40 kg (using the lyophilized powder formulation only):** Loading dose of 5 mg/kg by IV infusion on day 1, followed by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2. Optimal duration of treatment not known. For pts requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. For those **not** requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). [26] **Phase 3 trial in adults and children ≥12 years of age with severe COVID-19 (NCT04292899; SIMPLE-Severe):** 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	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 FDA warns that concomitant use of remdesivir and chloroquine or hydroxychloroquine is not recommended; [26,33] there is in vitro evidence that chloroquine antagonizes intracellular metabolic activation and antiviral activity of remdesivir. [26] NIH COVID-19 Treatment Guidelines Panel recommends use of remdesivir for the treatment of **severe COVID-19** in hospitalized patients who have oxygen saturation (SpO_2) of 94% or lower on room air, require supplemental oxygen, or are on mechanical ventilation or ECMO. The panel recommends a 5-day remdesivir regimen in hospitalized patients with severe COVID-19 who are *not* intubated. The panel states that data are insufficient regarding optimal duration of remdesivir treatment for patients on mechanical ventilation or ECMO or for those without adequate improvement after a 5-day remdesivir regimen; the panel states that some experts extend the duration of remdesivir treatment up to 10 days in such patients. [20] NIH panel states that data are insufficient to recommend for or against use of remdesivir for the treatment of **mild or moderate COVID-19**. [20] **Emergency use authorization (EUA) for remdesivir:** FDA issued an EUA on May 1, 2020 that permits use of the drug for the treatment of COVID-19 *only* in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 who have severe disease (defined as oxygen saturation [SpO_2] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) and requires that the drug be

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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 improvement (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*	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 in adults and children ≥12 years of age with moderate COVID-19 (NCT04292730; SIMPLE-Moderate):** 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) [11] **Phase 3 NIAID adaptive study in adults (NCT04280705; ACTT-1):** 200 mg IV on day 1, then 100 mg IV daily for duration of hospitalization up to 10 days total [13]	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] 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
			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] **Comparative analysis of data from phase 3 SIMPLE-Severe trial and real-world retrospective cohort of patients:** The manufacturer announced results of an analysis that compared data for 312 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial with a retrospective cohort of 818 pts with similar baseline characteristics and disease severity who received standard of care treatment (without remdesivir) during the same time period. More than 90% of pts in both groups were enrolled at North American trial sites and the rest were enrolled at European or Asian trial sites. Clinical recovery (improvement in clinical status based on a 7-point ordinal scale) and mortality rate for these 2 groups were compared. By day 14, recovery was reported in 74.4% of pts treated with remdesivir and 59% of pts in the retrospective cohort treated with standard of care and the mortality rate was 7.6 and 12.5%, respectively. [34] **Subgroup analyses of data from Phase 3 SIMPLE-Severe trial:** The manufacturer announced results of subgroup analyses of 229 hospitalized pts with severe COVID-19 who received remdesivir in this randomized, open-label trial and were enrolled at US trial sites. Clinical improvement was defined as a 2-point or greater improvement on a 7-point ordinal scale. At day 14, the rate of clinical improvement was 84% in black pts (n=43), 76% in Hispanic white pts (n=17), 67% in Asian pts (n=18), 67% in non-Hispanic white pts (n=119), and 63% in pts who did not identify with any of these groups (n=32). An analysis of 397 pts who were enrolled globally indicated that black race, age less than 65 years, treatment outside of Italy, and requirement of only low-flow oxygen support or room air at baseline were factors significantly		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			associated with clinical improvement of at least 2 points on day 14. Another subgroup analysis was performed to evaluate outcomes in pts who received concomitant therapy with remdesivir and hydroxychloroquine vs those who received only remdesivir. At a median follow-up of 14 days, the rates and likelihood of recovery were lower in those treated with both drugs (57%) compared with those treated with remdesivir alone (69%). Although concomitant hydroxychloroquine was not associated with increased mortality at 14 days, the overall rate of adverse effects was higher and, after adjusting for baseline variables, the incidence of grade 3-4 adverse events was significantly higher in those treated with both drugs. [34] **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 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		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 (NCT04280705; NIAID Adaptive COVID-19 Treatment Trial 1 [ACTT-1]) in hospitalized adults with COVID-19:** 1063 pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10 or until hospital discharge or death) or placebo. [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]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 through treatment IND protocol sponsored by US Army Medical Research and Development Command [12] **Data from the manufacturer's compassionate use program (adults):** 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,		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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. **Data from the manufacturer's compassionate use program (pediatric pts):** The manufacturer announced that preliminary data are available for 77 pediatric pts treated with remdesivir in the compassionate use program. Analysis of day-28 data indicated that 73% of these pediatric pts were discharged from the hospital, 12% remained hospitalized but on ambient air, and 4% had died. There were 39 critically ill pediatric pts who required invasive mechanical ventilation at baseline and 80% of these pts recovered; there were 38 pediatric pts who did not require invasive ventilation and 87% of these pts recovered. No new safety signals were identified for remdesivir in this population. [34] **Data from the manufacturer's compassionate use program (pregnant and postpartum women):** The manufacturer announced that preliminary data are available for 86 pregnant and postpartum women treated with remdesivir in the compassionate use program. Analysis of data for these pts (median age 33 years) indicated that 96% of the pregnant women and 89% of the postpartum women achieved improvement in oxygen support levels. Those with more severe illness at baseline achieved similarly high rates of clinical recovery (93 or 89% in those who were pregnant or postpartum, respectively). Pregnant women not on invasive oxygen support at baseline had the shortest median time to recovery (5 days), and both pregnant and		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			postpartum women on invasive ventilation at baseline had similar median times to recovery (13 days). No new safety signals were identified for remdesivir in this population; the most common adverse events were due to underlying disease and most laboratory abnormalities were grades 1–2. [34] **Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib (NCT04401579; ACTT2):** This iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) is evaluating possible benefits of using baricitinib (a Janus kinase [JAK] inhibitor) in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection and evidence of lung involvement (abnormal chest x-rays, SpO_2 of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO). Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization up to 10 days total) with either oral baricitinib (4 mg once daily for the duration of hospitalization up to 14 days total) or placebo. [29, 31] **Randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with tocilizumab (NCT04409262; REMDACTA):** This trial will evaluate possible benefits of using tocilizumab (an interleukin-6 [IL-6] inhibitor) in conjunction with remdesivir in hospitalized patients 12 years of age or older with severe COVID-19 pneumonia. Pts will be randomized to receive remdesivir (IV loading dose on day 1, then once-daily IV maintenance doses on days 2-10) with either tocilizumab (single IV infusion on day 1) or placebo. [32]		
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	**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	**Dosage recommended for treatment of COVID-19 in China:** Adults, 200 mg orally 3 times daily for no more than 10 days [5, 7]	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
		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]	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 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	**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]	

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 (Kineret®) *Updated 7/2/20*	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] Anakinra has been used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis. IL-1 levels are elevated in patients with these conditions. Case reports and series describe a favorable response to anakinra in these syndromes, including survival benefit in sepsis and reversing cytokine storm in adults with MAS after tocilizumab failure. [7]	Currently no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19 [7] Encouraging preliminary results reported in China with another disease-modifying antirheumatic drug, tocilizumab [5, 6] **France:** A cohort study (Ana-COVID) included a prospective cohort of 52 adults with severe COVID-19 treated with anakinra plus standard of care and a historical comparison group of 44 patients who received standard and supportive care at Groupe Hospitalier Paris Saint-Joseph. Inclusion criteria included severe COVID-19-associated bilateral pneumonia on chest x-ray or lung CT scan, laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and an oxygen saturation of ≤93% under oxygen ≥6 L/min or deterioration (saturation ≤93% under oxygen 3 L/min with loss of 3% oxygen saturation in ambient air over previous 24 hours). Anakinra was given subcutaneously in a dosage of 100 mg twice daily on days 1–3, then 100 mg once daily from day 4–10. The primary outcome measure was a composite of either ICU admission for invasive mechanical ventilation or death. Admission to the ICU or death occurred in 13 (25%) of anakinra-treated patients and in 32 (73%) of patients in the historical comparison group. [9] **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:** Retrospective cohort study (part of NCT04318366) with high- or low-dose anakinra in adults with COVID-19, moderate to severe acute respiratory distress syndrome (ARDS), and hyperinflammation (defined as elevated serum C-reactive protein [CRP] and/or ferritin levels) managed with non-invasive ventilation outside of the ICU at a	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 Europe are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge [3] In a French case series and a French cohort study, anakinra was given subcutaneously in a dosage of 100 mg twice daily (i.e., every 12 hours) on days 1–3, then 100 mg once daily from day 4–10 [8, 9] A retrospective cohort study in Italy compared high-dose anakinra by IV infusion (5 mg/kg twice daily) and low-dose anakinra (100 mg twice daily) given subcutaneously [10] (Note: Anakinra is approved only for subcutaneous administration in the U.S.) [1, 7]	NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of anakinra in the treatment of COVID-19 [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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Milan hospital. Patients received standard therapy (hydroxychloroquine and lopinavir/ ritonavir) and either high-dose anakinra (5 mg/kg twice daily by IV infusion for a median of 9 days followed by daily low-dose subcutaneous administration [100 mg twice daily] for 3 additional days to prevent relapse) or low-dose anakinra (100 mg twice daily subcutaneously) and were compared with a historical cohort of patients who did not receive anakinra. At 21 days, high-dose anakinra was associated with reduced CRP levels and progressive improvement in respiratory function in 21 of 29 (72%) of patients; 5 patients (17%) were placed on mechanical ventilation and 3 patients (10%) died. High-dose IV anakinra appeared to be relatively well tolerated. Anakinra was discontinued in the low-dose subcutaneous anakinra group after 7 days because of a lack of improvement in CRP levels and clinical status. In the standard treatment alone group (retrospective cohort), 8 out of 16 patients (50%) showed respiratory improvement at 21 days; 1 patient (6%) was placed on mechanical ventilation and 7 patients (44%) died. [10] **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] Numerous other clinical trials evaluating anakinra in the treatment of COVID-19 are planned or under way, mainly in Europe [3]		
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	**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]	Current data not specific to COVID-19; additional study needed [6]

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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Azithromycin *Updated 6/25/20*	8:12.12 Macrolides	Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) [1, 3-5] No data to date on in vitro activity against coronaviruses, including SARS-CoV-2 Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated [2, 6, 8, 9, 11-14, 17] Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza) [10, 13] Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the management of certain respiratory conditions (e.g., bronchiectasis, bronchiolitis, cystic fibrosis, COPD exacerbations, ARDS) [6, 8, 17]	**Adjunctive therapy in certain respiratory viral infections:** Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza). [10, 12, 13] However, in a retrospective cohort study in critically ill pts with laboratory-confirmed MERS, there was no statistically significant difference in 90-day mortality rates or clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not. [12] **Adjunctive therapy in certain respiratory conditions:** Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS). [8] In a retrospective cohort study in pts with moderate or severe ARDS, a statistically significant improvement in 90-day survival was reported in those who received adjunctive azithromycin. [8] **Clinical experience in pts with COVID-19:** Has been used for antibacterial coverage in hospitalized pts with COVID-19 [15] **Use in conjunction with hydroxychloroquine in pts with COVID-19:** Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), [7] open-label uncontrolled study in France (11 pts), [18] 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	**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, because of the potential for toxicities. [21] (See Hydroxychloroquine in this Evidence Table.) 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 azithromycin and 4- aminoquinolines (hydroxychloroquine, chloroquine) are independently associated with QT prolongation, caution is advised if considering use of azithromycin with one of these drugs in pts with COVID-19, especially in outpatients who may not receive close monitoring and in those at risk for QT prolongation or receiving other drugs associated with arrhythmias. [20-22, 25-28] NIH panel states that macrolides (including azithromycin) should be used concomitantly with hydroxychloroquine (or chloroquine) *only* if necessary. In addition, because of the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the drugs are used sequentially. The panel states that use of doxycycline (instead of azithromycin) should be considered for empiric therapy of atypical pneumonia in COVID-19 pts receiving

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 is evaluating 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] NCT04329832 NCT04332107 NCT04334382 NCT04335552 NCT04358081 NCT04370782		hydroxychloroquine (or chloroquine). [21] 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.)
Baricitinib (Olumiant®) *Updated 7/2/20*	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 [11] 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 second phase of **NIAID's Adaptive COVID-19 Treatment Trial (ACTT 2; NCT04401579)**. [3, 12, 15, 17] Inclusion criteria: Laboratory- confirmed COVID-19 infection and evidence of lung involvement (abnormal chest X-rays, SpO_2 of 94% or lower on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO). [12, 17] Patients randomized to	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) NIH COVID-19 Treatment Guidelines Panel recommends dosage adjustment if baricitinib is administered concurrently with a strong OAT3 inhibitor [11]	Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and many other drugs; [4, 14] however, dosage adjustment recommended when used with strong OAT3 inhibitors [11] Not recommended in patients with severe hepatic or renal impairment [11] 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
			receive treatment with remdesivir with or without baricitinib.[12] Remdesivir administered as one 200-mg IV dose on day 1 followed by 100 mg IV daily for the duration of hospitalization (up to 10-day treatment course). Baricitinib administered as a 4-mg oral dose administered once daily for the duration of hospitalization (up to 14-day treatment course). [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] **A randomized, double-blind, placebo-controlled, phase 3 trial (COV-BARRIER; NCT04421027) sponsored by the manufacturer** (Lilly) is currently under way to evaluate the efficacy and safety of baricitinib in hospitalized adults with COVID-19 who have at least one elevated marker of inflammation but do not require mechanical ventilation upon study entry. Targeted enrollment is 400 patients; study will be conducted in the U.S., Europe, and Latin America. Patients in the baricitinib treatment arm will receive an oral dosage of 4 mg daily for up to 14 days or until hospital discharge in addition to their background therapy. [15, 16] 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]		
Colchicine *Updated 7/2/20*	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 hyper-inflammatory state of	Limited anecdotal experience and clinical trial data reported to date in COVID-19 [4, 16, 17] **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]	Dosage in NCT04326790 (GRECCO-19): Colchicine loading dosage: 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin); maintenance dosage: 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing <60 kg) until hospital discharge or maximum of 21 days [17] Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days [1]	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
		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]	**Uncontrolled case series:** 9 patients in community setting with COVID-19 received colchicine (1 mg orally every 12 hours on day 1, then 1 mg daily until third day of temperature <37.5°C); colchicine was initiated at a median of 8 days (range: 6-13 days) after symptom onset and after 3-5 days of spiking fever despite acetaminophen or antibiotic treatment. Defervescence occurred within 72 hours in all patients. One patient was hospitalized because of persistent dyspnea and discharged after 4 days of oxygen therapy. Basis for diagnosis of COVID-19 not stated. [16] **Open-label, randomized, 16-hospital clinical trial (NCT04326790, GRECCO-19) in hospitalized adults with RT-PCR-confirmed COVID-19:** 55 patients received colchicine plus standard treatment and 50 received standard treatment alone; colchicine was administered orally as a loading dose of 1.5 mg followed in 1 hour by 0.5 mg (reduced to a single 1-mg dose in those receiving azithromycin) followed by a maintenance dosage of 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing <60 kg) until hospital discharge or for a maximum of 21 days. Most patients also received chloroquine or hydroxychloroquine (98%) and azithromycin (92%). **Clinical deterioration (2-grade increase on a 7-grade ordinal scale) was observed in a greater proportion of control patients than colchicine-treated patients** (7 patients [14%] vs 1 patient [1.8%]); cumulative 10-day event-free survival was higher with colchicine than with control (97 vs 83%). Baseline score on the 7-grade scale was 3 or 4 in 97% of study patients. No difference observed between the groups in baseline or peak high-sensitivity cardiac troponin or peak C-reactive protein concentration. Small number of clinical events limited the statistical robustness of the results. [17] **Phase 3, randomized, double-blind, placebo-controlled study** (NCT04322682; COLCORONA) initiated in adults ≥40 years of age with COVID-19 and at least one high-risk criterion to evaluate effect of colchicine on mortality, hospitalization rate, and need	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]	

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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: NCT04322565, NCT04328480, NCT04350320, NCT04355143, NCT04392141, NCT04375202, NCT04360980, NCT04367168, NCT04403243, NCT04363437, NCT04416334, NCT04324463 [2,3]		
Corticosteroids (general) *Updated 7/2/20*	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 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 widespread implementation of lung protection strategies. [5, 8, 9, 14, 17] In a recent multicenter, unblinded, randomized controlled study (DEXA-ARDS), the effects of dexamethasone in conjunction	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] However, lower dosages of dexamethasone (i.e., 6 mg once daily for 10 days) were used in the RECOVERY trial. [32, 33] The NIH COVID-19 Treatment Guidelines Panel recommends an IV or oral dexamethasone dosage of 6 mg daily for up to 10 days in COVID-19 patients requiring mechanical ventilation and in patients who require supplemental oxygen but who are not mechanically ventilated. [24] 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] **Critically ill patients:** The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 randomized controlled open-label trial (NCT04325061; DEXA-COVID19) has been initiated to specifically evaluate the use of IV dexamethasone at the same dosage of 20 mg once daily on days 1-5, followed by 10 mg once daily on days 6-10 in patients with ARDS due to COVID-19. [21] A large open-label, randomized controlled adaptive trial (NCT04381936; RECOVERY) was conducted to evaluate the effect of potential treatments (including low-dose dexamethasone) on all-cause mortality in hospitalized patients with COVID-19. The study enrolled 11,320 patients with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the dexamethasone treatment arm, 2104 patients were randomized to receive dexamethasone (6 mg once daily orally or IV for up to 10 days) plus standard care and 4321 patients were randomized to receive standard care alone. Preliminary data analysis indicates that overall 28-day mortality was reduced in patients receiving dexamethasone compared with those receiving standard care (21.6 vs 24.6%) with the greatest benefit observed in patients requiring mechanical ventilation at enrollment. In a subgroup analysis based on level of respiratory support, dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation and by 20% in those receiving supplemental oxygen without mechanical ventilation; however, there was no evidence of benefit in patients who did not require respiratory support. Dexamethasone was associated with a reduction in 28-day mortality among those patients with COVID-19 symptoms for >7 days compared with those having more recent		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] Based on preliminary findings from the RECOVERY trial, the NIH COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone (6 mg daily for up to 10 days) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. The panel recommends against the use of dexamethasone in COVID-19 patients who do not require supplemental oxygen. The guideline panel states that it is not known at this time whether other corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone) will have a similar benefit as dexamethasone. [24] IDSA suggests the use of corticosteroids over no corticosteroid therapy in hospitalized patients with severe COVID-19 (i.e., defined as patients with SpO_2 ≤94% on room air and those who require supplemental oxygen, mechanical ventilation, or ECMO). These experts suggest the use of dexamethasone 6 mg orally or IV daily for 10 days or until hospital discharge, whichever comes first, or substitution of equivalent daily dosages of another corticosteroid (e.g., methylprednisolone 32 mg, prednisone 40 mg) if dexamethasone is unavailable. However, IDSA suggests against using corticosteroids in hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen. [25]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			symptom onset. Dexamethasone treatment also was associated with a shorter duration of hospitalization and a greater probability of discharge within 28 days with the greatest effect observed among patients receiving invasive mechanical ventilation at baseline. [32, 33] **Confirmation of these preliminary results is pending until completion of full data analysis and publication of the final report. Note:** Data regarding potential adverse effects, efficacy in combination with other treatments (e.g., remdesivir), and efficacy in other patient populations (e.g., pediatric patients and pregnant women) not available to date. [24] Other clinical trials have been initiated in various countries to evaluate use of IV corticosteroids (e.g., dexamethasone, hydrocortisone), oral corticosteroids (e.g., prednisone), or inhaled corticosteroids (e.g., budesonide, 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 NCT04395105 (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]		**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 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

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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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]
Inhaled prostacyclins (e.g., epoprostenol, iloprost) ***Updated 7/16/20***	48:48 Vasodilating Agents	Selective pulmonary vasodilators; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19[1-9] Inhaled prostacyclins are used to improve oxygenation in patients with ARDS who develop refractory hypoxemia[1-3, 6, 8, 9] **Inhaled** epoprostenol has been suggested as an alternative to inhaled nitric oxide due to its similar	There are currently no published studies specifically evaluating use of inhaled prostacyclins in COVID-19 patients[10] In patients with ARDS, inhaled prostacyclins have been shown to substantially reduce mean pulmonary artery pressure and improve oxygenation; however, data demonstrating clinical benefit (e.g., mortality reduction) are lacking[3, 6-9] A phase 2, open-label study (ILOCOVID; NCT04445246) evaluating use of inhaled iloprost in adults with suspected or confirmed COVID-19 has been initiated[13] A phase 2, open-label study (VPCOVID; NCT04452669) evaluating inhaled	Various dosages of inhaled epoprostenol have been used in patients with ARDS: Dosages up to 50 ng/kg per minute (titrated to response) have been used in clinical studies.[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] Dosage of inhaled iloprost in the phase 2, open-label study (NCT04445246) that has been initiated in patients with suspected or	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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		efficacy, lower potential for systemic adverse effects, lower cost, and ease of delivery [1, 2, 9] Experience with inhaled iloprost is more limited, but the drug is thought to have a similar theoretical benefit as epoprostenol in patients with ARDS [1, 2, 9]	epoprostenol delivered via a dedicated delivery system (VentaProst) in patients with COVID-19 requiring mechanical ventilation has been initiated [13]	confirmed COVID-19 is 20 mcg every 8 hours for 5 days (delivered by nebulization) [13]	is observed, the patient should be tapered off treatment [10, 12]
Interferons *Updated 7/2/20*	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 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,	**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) NCT04324463 (IFN beta) NCT04343768 (IFN beta-1a, IFN beta-1b) NCT04385095 (SNG001 [inhaled IFN beta-1a]) 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 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	**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] **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):	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
		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]	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] Open-label, randomized study in Iran in hospitalized adults with severe suspected or RT-PCR-confirmed COVID-19: **IFN beta-1a** (12 million units sub-Q 3 times weekly for 2 weeks) plus standard care (7- to 10-day regimen of hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir) (n = 42) was compared with standard care (control; n = 39). Time to clinical response (primary outcome; defined as hospital discharge or 2-score improvement in a 6-category ordinal scale) did not differ significantly between the IFN beta-1a group and the control group (9.7 vs 8.3 days); durations of hospital stay, ICU stay, and mechanical ventilation also did not differ between the groups. Discharge rate on day 14 (67% vs 44%) was higher and 28-day overall mortality rate (19 vs 44%) was significantly lower with IFN beta-1a compared with control; early initiation of IFN beta-1a (<10 days after symptom onset), but not late initiation of the drug (≥10 days after symptom onset), was associated with reduced mortality. **NOTE:** Total of 92 patients were randomized; results are based on the 42 IFN beta-1a-treated patients and 39 control patients who completed the study. Percentage of patients with RT-PCR-confirmed disease not reported to date. Patients were recruited from general, intermediate, and ICU wards; 45% of the IFN beta-1a-treated patients and 59% of the control patients were admitted to ICU; 36 and 44%, respectively, required invasive mechanical ventilation. Mean time from symptom onset to treatment initiation was 11.7 days for the IFN beta-1a group and 9.3 days for the control group. [20] **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	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
			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]		
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	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
			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]		
Nitric oxide (inhaled) ***Updated 7/2/20***	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 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	There are currently no published studies specifically evaluating use of inhaled nitric oxide 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, NCT04421508, NCT04397692, NCT04398290, NCT04338828, NCT04305457, NCT04306393, NCT04312243 [3]	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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]			
Ruxolitinib (Jakafi®) ***Updated 7/2/20***	10:00 Antineoplastic Agents	Janus kinase (JAK) 1 and 2 inhibitor; [7] may potentially combat cytokine release syndrome (CRS) in severely ill patients [4, 5] Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19 [5, 7]	Limited published clinical trial evidence regarding efficacy and safety in patients with COVID-19 **Single-hospital retrospective chart review:** Based on the hospital's COVID-19 treatment algorithm, patients with severe COVID-19 were prospectively stratified using a newly developed clinical inflammation score (CIS; maximum score = 16); those identified as being at high risk for systemic inflammation (CIS ≥10, without sepsis) were evaluated for ruxolitinib treatment; 14 patients received ruxolitinib (median cumulative dose: 135 mg [52.5-285 mg], median treatment duration: 9 days [5-17 days]) initiated at a median of 15.5 days (5-24 days) after symptom onset. A decrease in CIS of ≥25% from baseline to day 7 was observed in 12 of 14 patients. At baseline, 10 required noninvasive ventilation, 3 required supplemental oxygen, and 1 required invasive ventilation. [14] **Prospective, randomized, single-blind, placebo-controlled study in adults with severe COVID-19:** Patients received ruxolitinib (5 mg orally twice daily) plus standard care (n = 22) or placebo (ascorbic acid 100 mg orally twice daily) plus standard care (n = 21); **no significant difference observed between ruxolitinib and placebo in time to clinical improvement** (defined as hospital discharge or a 2-point improvement on a 7-category ordinal scale) **although median time to improvement was numerically shorter with ruxolitinib (12 vs 15 days).** Chest CT improvement observed at day 14 in greater proportion of ruxolitinib-treated vs placebo-treated patients (90 vs 62%). By day 28, 3 patients had died (all 3 in placebo group). NOTE: Median time from symptom onset to randomization was 20 days; similar proportions of patients in	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 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			both treatment groups received systemic corticosteroids and antivirals. Study excluded critically ill and ventilator-dependent patients. Interpretation is limited by small sample size. [13] **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] **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 patients ≥12 years of age 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] NCT04338958 NCT04348695 NCT04403243 NCT04414098		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Sarilumab (Kevzara®) *Updated 6/18/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Sarilumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients [1, 2, 5, 7]	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 large, U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled, adaptively designed study (NCT04315298) evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently under way. [3, 4, 9, 10] Patients in this study were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an Independent Data Monitoring Committee recommended discontinuing the 200-mg arm and restricting future enrollment only to critically ill patients (i.e., those requiring mechanical ventilation, high-flow oxygenation, or ICU treatment). Of the first 457 patients enrolled, 28% had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab rapidly lowered C-reactive protein (CRP) levels, meeting the primary end point. Baseline IL-6 levels were elevated in all treatment arms; higher levels were observed in critical patients compared with severe patients. At the time of data analysis, of the 226 critical patients, 32% in the sarilumab 400-mg group had died or were on a ventilator, compared with 46% in the 200-mg group and 55% in the placebo group. Comparing mortality alone, 23% of those in the sarilumab 400-mg group died compared with 36% in the 200-mg group and 27% in the placebo group. In contrast to the positive outcomes among critical patients, negative trends for most outcomes were observed in severe patients. [9] A second manufacturer-sponsored phase 3 clinical trial is under way in countries outside the U.S. (Italy, Spain, Germany, France, Canada, Russia, Israel, and Japan). Approximately 400 patients hospitalized with COVID-19 are expected to be enrolled; initial results expected in the third quarter of 2020. [9]	**Large US-based controlled study (NCT04315298):** Dosage of 400 mg IV as a single dose or multiple doses (based on protocol criteria); the lower-dose (200-mg) treatment arm was discontinued following a preliminary analysis of study results [9, 10] (see Trials or Clinical Experience) Note: IV formulation not commercially available in the U.S., but is being studied in the above-mentioned clinical trial. The sub-Q formulation is not FDA-labeled to treat cytokine release syndrome (CRS) in the U.S. [7]	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] No new safety findings observed with use in COVID-19 patients [9]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Italian case series (Benucci et al.) describes 8 patients hospitalized with COVID-19 pneumonia at one hospital in Florence treated with sarilumab (initial 400-mg IV dose followed by 200-mg IV doses after 48 and 96 hours) in addition to standard therapy (hydroxychloroquine, azithromycin, darunavir, cobicistat, enoxaparin). Treatment was started within 24 hours of hospitalization. Sarilumab was used in these patients because of a lack of tocilizumab at this institution. Seven of the patients demonstrated an improvement in oxygenation and lung echo score and were discharged within 14 days; the remaining patient died in 13 days. [8] **Multiple clinical trials to evaluate sarilumab for treatment of COVID-19** are registered at clinicaltrials.gov [10] **For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)** [6]		
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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
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]
Tocilizumab (Actemra®) *Updated 6/25/20*	92:36 Disease-modifying Antirheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients [1-3, 6, 9,10, 14]	Case reports and observational and open studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world [1, 3, 5, 10, 12, 15, 17] 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]	Tocilizumab is typically given IV to treat cytokine release syndrome (CRS) and in patients with COVID-19; however, the drug has been given subcutaneously in some patients [9, 17] The subcutaneous formulation of tocilizumab is *not* intended for IV use [9] IV infusion: **China** recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg [2] **US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA):** Will evaluate an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose may be given if symptoms worsen or show no improvement [8]	**In China**, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels [2] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of tocilizumab in the treatment of COVID-19 [9] The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study [14]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			A single-center, retrospective observational study of 20 kidney transplant recipients in Italy with COVID-19 hospitalized for pneumonia included 6 patients who received tocilizumab. Half of the patients experienced reduced oxygen requirements and 2 (33%) showed improved radiologic findings following administration; 2 (33%) of the 6 tocilizumab-treated patients died. [12] **Italy:** A prospective, open, single-arm, multicenter study evaluated use of tocilizumab in 63 hospitalized adults with severe COVID-19. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg) based on drug availability; a second dose given within 24 hours was administered to 52 of the 63 patients. Following tocilizumab administration, fevers resolved in all but one patient within 24 hours and C-reactive protein (CRP), ferritin, and D-dimer levels declined from baseline to day 14. The PaO_2/FiO_2 ratio improved between admission and Day 7. Overall mortality was 11%. Tocilizumab appeared to be well tolerated. [17] 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] **France:** An open-label, phase 2, randomized clinical trial (CORIMUNO-TOCI, NCT04331808) is under way at Assistance Publique – Hôpitaux de Paris hospitals in Paris. Interim results from this study have been released in a press release (non-peer-reviewed). Sixty-five out of 129 adults with moderate to severe COVID-19 pneumonia not requiring intensive care upon admission were randomized to receive tocilizumab 8 mg/kg (1–2 doses) along with standard of care, and 64 patients were randomized to receive standard of		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			care alone. A significantly lower proportion of the patients in the tocilizumab arm attained the primary outcome of need for ventilation or death at day 14. Results of this study will be submitted for publication in a peer-reviewed journal [15, 16] **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 6/18/20*	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.[1-3, 9] **Large, observational study analyzed a cohort of pts tested for COVID-19 to evaluate the relationship between previous treatment with 5 common classes of antihypertensive agents (including ACE inhibitors, ARBs) and the likelihood of a positive or negative test result for COVID-19 as well as the likelihood of severe COVID-19 illness among pts who tested positive:** Study included data obtained from a large health network in New York City for 12,594 pts who were tested for COVID-19 from Mar 1 to Apr 15, 2020. Among these pts, 4357 (34.6%) had a history of hypertension. Of these patients, 2573 (59.1%) tested positive for COVID-19. Among the 2573 pts with hypertension and positive results for COVID-19, 634 pts (24.6%) had severe disease (i.e., indicated by ICU admission, mechanical ventilation, or death). Results of COVID-19 testing were stratified in propensity-score-matched patients with hypertension according to previous treatment with selected antihypertensive agents. Propensity-score matching was based on age, sex, race, BMI, medical history, various comorbidities, and other classes of medications. The authors stated that no substantial increase was observed in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive in association with any single antihypertensive class (including ACE inhibitors, ARBs).[13] **Large, population-based case-control study was conducted to evaluate the association between the use of RAAS blockers (including ACE inhibitors, ARBs) and the risk of COVID-19:** Study included data obtained from a regional healthcare database in the Lombardy region of Italy for 6272 case pts with confirmed severe COVID-19 acute respiratory syndrome		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]

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			from Feb 21 to Mar 11, 2020 who were matched to 30,759 controls based on sex, age, and place of residence. Information about use of selected drugs and clinical profiles was obtained from regional healthcare databases. Use of ACE inhibitors or ARBs was more frequent in patients with COVID-19 than among controls because of their higher prevalence of cardiovascular disease. Percentage of patients receiving ACE inhibitors was 23.9% for case pts and 21.4% for controls. Percentage of patients receiving ARBs was 22.2% and 19.2% for case and control pts, respectively. The authors concluded that there was no evidence that treatment with ACE inhibitors or ARBs significantly affected the risk of COVID-19 or altered the course of infection or resulted in more severe disease. [14] **Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to evaluate the relationship between cardiovascular disease and preexisting treatment with ACE inhibitors or ARBs with COVID-19 (Mehra et al; now retracted):** Original publication included multinational data for 8910 pts hospitalized with COVID-19 between Dec 20, 2019 and Mar 15, 2020 that were obtained from a global healthcare data collaborative. The authors concluded that those data confirmed previous observations suggesting that underlying cardiovascular disease is independently associated with an increased risk of death in hospitalized pts with COVID-19. They also stated that they were not able to confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital mortality. [10] **Note: This published study has now been retracted by the publisher at the request of the original authors. Concerns were raised with respect to the veracity of the data and analyses that were the basis of the authors' conclusions.** [11,12] Clinical trial underway: Initiation of losartan in adults with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA)		

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			respiratory score. (NCT04312009) [7] Other clinical trials have been initiated in various countries to evaluate the effect of continuing or discontinuing treatment with ACE inhibitors or ARBs on clinical outcomes in patients with COVID-19, including the following trials registered at clinicaltrials.gov: [7] NCT04329195 NCT04330300 NCT04331574 NCT04338009 NCT04351581 NCT04353596 NCT04357535		
Anticoagulants *Updated 7/2/20*	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] Most common pattern of coagulopathy in hospitalized COVID-19 patients is characterized by elevated D-dimer levels, high fibrinogen levels, minimal prolongation of aPTT and/or PT, and mild thrombocytopenia; microvascular and macrovascular thrombosis also have been reported. [1-6, 9, 11, 13, 16, 26, 27, 29] In addition, high rates of VTE have been observed 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]	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, including the following: NCT04373707, NCT04372589, NCT04345848, NCT04412304, NCT04416048, NCT04444700, NCT04401293, NCT04393805 [12]	See Comments column for available dosage-related information.	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] WHO recommends pharmacologic prophylaxis (e.g., LMWH) according to local and international standards for prevention of VTE in adults and adolescents hospitalized with COVID-19 unless contraindicated [25] The International Society for Thrombosis and Haemostasis and American Society of Hematology recommend that all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, severe thrombocytopenia, fibrinogen <0.5 g/L). [4, 5]

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		Anticoagulant therapy therapy is given to reduce the risk of thrombotic complications and improve clinical outcomes. [2, 4, 5, 14, 25, 27]			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, 30, 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 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

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					(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. [15, 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 7/2/20*		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 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	**Study with retrospectively matched control in US (Liu et al):** Preliminary (non-peer-reviewed) data from a study of 39 hospitalized adults with severe to life-threatening COVID-19 who received ABO-compatible COVID-19 convalescent plasma (2 units [total volume approximately 500 mL] infused IV over 1-2 hours), obtained from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 or greater, suggest that stable or improved supplemental oxygen requirements by post-transfusion day 14 were more likely in these convalescent plasma recipients than in the matched control group not treated with convalescent plasma (odds ratio: 0.86); this effect appeared to be confounded by use of therapeutic anticoagulants, but not by other types of drugs (i.e., azithromycin, broad-spectrum antibiotics, hydroxychloroquine, corticosteroids, antivirals, interleukin-1 [IL-1] and IL-6 inhibitors) or duration of symptoms before admission. Overall, survival was improved in patients in the convalescent plasma group compared to the control group; after adjusting for covariates, data suggest a significant improvement in		Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. [11, 25] The NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend for or against the use of convalescent plasma in patients with COVID-19. [25] The Surviving Sepsis Campaign COVID-19 subcommittee suggests that convalescent plasma not be used routinely in critically ill adults with COVID-19 because efficacy and safety not established and uncertainty surrounding optimal preparation of convalescent plasma. [30] 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

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		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]	survival in non-intubated patients (hazard ratio: 0.19) receiving convalescent plasma, but not in the small cohort of intubated patients (hazard ratio: 1.24). No significant transfusion-related morbidity or mortality was observed in patients receiving convalescent plasma. [32] **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 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		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] Analysis of key safety indicators in 5000 adults who participated in a US FDA Expanded Access Program (NCT04338360) suggests that IV transfusion of COVID-19 convalescent plasma is safe in hospitalized patients with COVID-19; [31] however, potential risks associated with COVID-19 convalescent plasma therapy (e.g., inadvertent transmission of other infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], antibody-dependent enhancement of infection) and steps to mitigate such risks not fully determined and require further evaluation. [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]

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			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] **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		**There are no convalescent blood products currently licensed by the FDA.** [25] **COVID-19 convalescent plasma is regulated as an investigational product.** [11] **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]

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			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 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] **Expanded access IND protocol (Joyner et al):** Analysis of key safety indicators in 5000 adults hospitalized with laboratory-confirmed SARS-CoV-2 infection who had, or were considered at high risk of progression to, severe or life-threatening COVID-19 who participated in a US FDA Expanded Access Program (NCT04338360) suggests that IV transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. [31] Patients received ABO-compatible COVID-19 convalescent plasma (200 – 500 mL) IV according to institutional transfusion guidelines; no minimum titer of neutralizing antibody was specified for the		**Patient eligibility**: For healthcare providers seeking an eIND for the treatment of patients with severe or life-threatening disease, consideration should be given to following the patient eligibility criteria used in the National Expanded Access Treatment Protocol https://www.uscovidplasma.org. [11] According to the protocol, **severe** disease is defined as one or more of the following: shortness of breath, respiratory frequency 30/minute or greater, blood oxygen saturation 93% or lower, PaO_2/FiO_2 ratio less than 300, lung infiltrates greater than 50% within 24-48 hours, and **life-threatening disease** is defined as one or more of the following: respiratory failure, septic shock, multiple organ dysfunction or failure. [11]

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			convalescent plasma. [31] Within the first 4 hours after transfusion, 36 serious adverse events (i.e., transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], severe allergic transfusion reaction) were reported (incidence of <1% of all transfusions with a mortality rate of 0.3%); however, only 2/36 serious adverse events were judged by the treating clinician as definitely related to convalescent plasma transfusion. [31] **Open-label, prospective study (non-peer-reviewed) (Madariaga et al):** The relationship between clinical and serologic parameters in a group of COVID-19 convalescent plasma donors and antibody responses in recipients of convalescent plasma was evaluated. SARS-CoV-2 anti-receptor binding domain (anti-RBD) and anti-spike antibody titers ranged from 0 to 1:3892 and 0 to 1:3289, respectively, in 103 convalescent plasma donors; mean duration of COVID-19 symptoms in the plasma donors was 11.9 days and mean interval between symptom onset and convalescent plasma donation was 45.1 days; predictors of higher antibody titers in the donors included advanced age, fever, absence of myalgia, fatigue, ABO blood type, and previous hospitalization. In this study, 10 hospitalized adults with severe or life-threatening COVID-19 received 1 or 2 units (approximately 300 mL per unit administered IV over 4 hours) of ABO-compatible COVID-19 convalescent plasma (units had SARS-CoV-2 anti-RBD antibody titers of 1:73 to 1:3892 and anti-spike antibody titers of 1:69 to 1:2921) within 21 days after symptom onset and 80% of these patients had a significant increase in SARS-CoV-2 anti-spike and anti-RBD antibody titer by post-transfusion day 3 and were discharged after clinical improvement; antibody titers in the convalescent plasma recipients were independent of donor antibody titer. SARS-CoV-2 antibody titers in the convalescent plasma recipients continued to increase for up to 14 days in 4 recipients; however, 2 severely ill patients receiving extracorporeal membrane oxygenation (ECMO) who received convalescent		

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			plasma on day 20-21 of illness and had SARS-CoV-2 anti-spike antibody titers of up to 1:13,833 on day 0 had a decrease in antibody titer after receiving convalescent plasma. No convalescent plasma recipients experienced toxicity associated with the transfusion or clinical deterioration or worsening of disease status immediately related to plasma transfusion. Convalescent plasma transfusion was safe in high-risk individuals in this study (i.e., immunosuppressed, end-stage renal disease). [33] **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) NCT04389710 (Expanded Access) NCT04420988 (Expanded Access) NCT04343261 (US) NCT04372368 (US) NCT04343755 (US) NCT04344535 (US) NCT04364737 (US) NCT04344015 (US) NCT04376034 (US) NCT04359810 (US) NCT04362176 (US) NCT04411602 (US) NCT04388527 (US) NCT04397757 (US) NCT04412486 (US) NCT04392232 (US) NCT04360486 (US ARMY) NCT04347681 NCT04346446		

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			NCT04345523 NCT04342182 NCT04352751 NCT04375098 NCT04357106 NCT04327349 NCT04292340		
Famotidine *Updated 7/2/20*	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	Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19 Randomized, double-blind, placebo-controlled, comparative trial (NCT04370262) is evaluating high-dose IV famotidine plus standard care vs placebo plus standard care in **hospitalized adults with moderate to severe COVID-19;** targeted enrollment is at least 942 patients [5] Retrospective cohort study of 10 **outpatients self-medicating with high-dose famotidine** following onset of symptoms consistent with COVID-19: No hospitalizations reported; all patients reported symptomatic improvement within 1-2 days, with continued improvement over 14-day period. Patients were symptomatic for 2-26 days before initiating famotidine. Total of 7 patients had PCR-confirmed COVID-19, 2 had serologic confirmation of antibodies against SARS-CoV-2, and 1 had clinical diagnosis only. Famotidine dosage of 80 mg 3 times daily was reported by 6 patients (range: 20-80 mg 3 times daily); median reported duration of use was 11 days (range: 5–21 days); high-dose famotidine generally was well tolerated. Data were collected by telephone interviews and written questionnaires. Patients retrospectively provided symptom scores on a 4-point ordinal scale. Potential exists for placebo effect, recall bias, and enrollment bias; symptomatic improvement also could reflect treatment-independent convalescence [8]	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

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		(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 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) ***Updated 7/16/20***	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 from randomized controlled trials are lacking on the use of statins in patients with COVID-19. **Retrospective cohort study** in 13,981 patients in China hospitalized with COVID-19: Statin use during hospitalization was associated with lower risk of mortality. The 28-day all-cause mortality was 22% lower in patients who received statins during hospitalization compared with patients who did not receive statins. Among propensity-score-matched patients (861 patients in the statin group vs. 3444 matched patients in the no-statin group), the risk of 28-day all-cause mortality was 42% lower in patients who received statins during hospitalization compared with those who did not receive statins. In addition, lower incidence of invasive mechanical ventilation was observed in the statin-treated patients. The authors note that patients in the statin group were older and had a higher prevalence of comorbidities and more severe symptoms at baseline; matched non-statin patients therefore had more severe baseline symptoms and comorbidities than unmatched		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]

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			patients, which could account for the increased mortality in the non-statin group after propensity score matching. [11] **Retrospective cohort study** in 154 nursing home residents in Belgium with clinically suspected COVID-19 and/or positive PCR test for SARS-CoV-2: Statin use was associated with absence of symptoms (i.e., asymptomatic infection) in this cohort; 45% of the 31 patients receiving statin therapy remained asymptomatic compared with 22% of the 123 patients not receiving statins [10] 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 evaluating statin use in COVID-19:** Multiple trials registered at clinicaltrials.gov (some listed below): [9] NCT04333407 NCT04343001 NCT04348695 NCT04426084 NCT04407273		
Immune Globulin *Updated 6/18/20*	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 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	**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] **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]	IGIV dosage of 0.3-0.5 g/kg daily for 3-5 days has been used or is being investigated in patients with COVID-19 [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 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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. [18]	**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 SARS-CoV-2 immune globulin in patients with COVID-19, including the following trials: [12] NCT04264858 NCT04350580 NCT04381858 NCT04261426 NCT04411667		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] The Surviving Sepsis Campaign COVID-19 subcommittee suggests that IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, currently available IGIV preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury). [13]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Ivermectin ***Updated 7/16/20***	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 from randomized, controlled clinical trials regarding efficacy or safety in the treatment of COVID-19 **Pilot observational study comparing efficacy of add-on ivermectin in pts with mild to moderate COVID-19 (not peer reviewed):** A total of 16 pts received a single dose of oral ivermectin (0.2 mg/kg) given on the day of hospital admission in addition to initiation of treatment with hydroxychloroquine and azithromycin, and results were compared with 71 pts who received hydroxychloroquine and azithromycin alone (matched controls). The primary outcome was percentage of pts cured (defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR tests from nasopharyngeal swabs at least 24 hours apart) within 23 days. The investigators reported that all 16 pts who received ivermectin were cured compared with 97% of pts who did not receive ivermectin and the mean duration of hospitalization was shorter in the ivermectin group (7.6 days) than in the control group (13.2 days). Note: These results need to be validated in a larger prospective trial. [11] **Retrospective observational evaluation of COVID-19 pts treated with ivermectin (not peer reviewed):** Outcome data for 173 pts with confirmed COVID-19 who received at least one dose of oral ivermectin (0.2 mg/kg) at any time during hospitalization, at the discretion of the treating physician, in addition to usual care were compared with outcome data for 107 pts who received usual care. The primary outcome measure was all-cause in-hospital mortality. The investigators reported that overall mortality was lower in the ivermectin group (15%) than in the group not treated with ivermectin (25.2%); there was no difference in duration of hospitalization between the groups (median of 7 days for both groups). Note: The effect of ivermectin on viral load was not evaluated and the impact of confounding factors in these patients (e.g., time from diagnosis to initiation of treatment, differences in drugs used for		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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			standard care and variances in clinical benefits of such drugs) is not known. [12] Several clinical trials evaluating ivermectin for the treatment of COVID-19 are registered at clinicaltrials.gov [10]		
Nebulized drugs ***Updated 7/16/20***		**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, 4, 5]	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, 4] In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose or dry powder inhalers in patients who are awake and who can perform specific breathing techniques because of the risk of the virus becoming airborne when treating patients infected with COVID-19. [2, 5] There is a lack of published information and guidance on the optimal administration of aerosolized drugs in the treatment of patients with COVID-19. The safe and effective delivery of aerosol therapy to such patients may require modifications in dosage, frequency, and delivery techniques. [5] WHO states there is insufficient evidence to classify nebulizer therapy as an aerosol-generating procedure associated with COVID-19 transmission and that further study is needed. [6]
Niclosamide ***Updated 7/16/20***	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]	Protocol in one ongoing trial (NCT04372082) specifies a niclosamide dosage of 2 g on day 1, then 500 mg twice daily for 10 days for treatment of COVID-19 in adults [3] Protocol in one ongoing trial (NCT04399356) specifies a niclosamide dosage of 2 g once daily for 7	Not commercially available in the US No data to date support use in treatment of COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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] Randomized, double-blind placebo-controlled trial (NCT04436458) to evaluate niclosamide in adults with moderate COVID -19 with GI signs and symptoms [3]	days for treatment of mild to moderate COVID-19 in adults [3] Protocol in one ongoing trial (NCT04436458) specifies a 3-times daily niclosamide regimen (dose unspecified) for 14 days for treatment of moderate COVID-19 in adults with GI signs and symptoms [3]	
Nitazoxanide ***Updated 7/16/20***	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] Some in vitro evidence of potential synergism between nitazoxanide and remdesivir and between nitazoxanide and umifenovir against SARS-CoV-2; additional data needed [10]	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 trials initiated to evaluate nitazoxanide for treatment of hospitalized pts with noncritical COVID-19 (NCT04423861) and pts with moderate COVID-19 (NCT04348409) [8] **Two randomized, double-blind, placebo-controlled clinical trials** have been initiated by the manufacturer (Romark) to	**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 two clinical trials (NCT04423861, NCT04441398) specify a nitazoxanide dosage of 600 mg three times daily for 7 days for treatment of non-severe COVID-19 in adults; [8] protocol in one trial (NCT04348409) specifies a nitazoxanide dosage of 600 mg twice daily for 7 days for treatment of moderate COVID-19 in adults [8] Protocol in one ongoing trial (NCT04406246) specifies a nitazoxanide dosage of 500 mg every 6 hours for 2 days, then every 12 hours for 4 days for treatment of potential COVID-19 in symptomatic healthcare workers not requiring hospitalization [8] Protocol in one ongoing trial (NCT04463264) specifies a nitazoxanide dosage of 1 g every 8 hours for 14 days for treatment of mild COVID -19 in adults [8] Protocol in one ongoing trial (NCT04459286) specifies a nitazoxanide dosage of 1 g twice daily for	Current data not specific to COVID-19; additional study needed [1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			evaluate efficacy and safety for postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers (NCT04359680) or elderly residents of long-term care facilities (NCT04343248) [8] **Multiple other clinical trials planned or initiated** to evaluate nitazoxanide in combination with other drugs (e.g., hydroxychloroquine, ivermectin) or alone for treatment of COVID-19 [8]	treatment of moderate to severe COVID-19 in adults [8] Protocol in two ongoing trials sponsored by the manufacturer (NCT04343248, NCT04359680) evaluating postexposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks in adults; [8] another study (NCT04435314) specifies a dosage of 600 mg 3 times daily for 7 days for postexposure prophylaxis in adults [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]	
Nonsteroidal Anti-inflammatory Agents (NSAIAs) *Updated 6/18/20*	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." WHO states that there is no evidence of severe adverse events or effects on acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIAs. [9]

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

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