AHFS Clinical Drug Information™ Assessment of Evidence for COVID-19-Related Treatments: Updated 05/13/2021

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Selected entries were updated 05/13/2021; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by **.

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ANTIVIRAL AGENTS

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Baloxavir *Updated 1/14/21*	8:18.92 Antiviral	Antiviral active against influenza viruses Conflicting data regarding possible in vitro antiviral activity against SARS-CoV-2 [1, 4]	**Only very limited data available** regarding use of baloxavir for treatment of COVID-19 Exploratory, open-label, randomized controlled study at a single center in China (ChiCTR2000029544): 29 adults hospitalized with COVID-19 receiving antiviral treatment with lopinavir/ritonavir, darunavir/cobicistat, or umifenovir (Arbidol®), in combination with inhaled interferon-α, were randomized to treatment with baloxavir marboxil (80 mg orally on day 1 and on day 4, and 80 mg orally on day 7 as needed) (n=10), favipiravir (1600 or 2200 mg orally on day 1, followed by 600 mg three times daily for up to 14 days) (n=9), or control (standard antiviral treatment) (n=10). Results did not indicate a benefit of adding baloxavir to the treatment regimen. 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. [1] There are no clinical trials registered at clinicaltrials.gov to evaluate baloxavir for treatment of COVID-19.	A baloxavir marboxil dosage of 80 mg on day 1 and on day 4, and another dose of 80 mg on day 7 (as needed; not to exceed 3 total doses) was used in one open-label COVID-19 study in adults in China. [1]	Although investigated as a potential treatment during the early stages of the COVID-19 pandemic, [1, 6, 7] in vitro antiviral activity against SARS-CoV-2 was not confirmed and there are no data to support the use of baloxavir in the treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel states that treatment of influenza is the same in all pts regardless of SARS-CoV-2 coinfection. [3] (See Neuraminidase Inhibitors in this Evidence Table.) Significant drug interactions not expected with baloxavir and remdesivir. [3] CDC states that baloxavir may be used for the treatment of suspected or confirmed uncomplicated influenza in *outpatients*; the drug is not recommended for use in pregnant or nursing women, as monotherapy in severely immunosuppressed pts, or for the treatment of severe influenza. [5]
Chloroquine Phosphate *Updated 2/25/21*	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 **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 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	**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, 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 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]	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 various published randomized, controlled clinical trials and retrospective, cohort studies have not substantiated initial reports of efficacy of 4-aminoquinoline antimalarials for treatment of COVID-19. (See Hydroxychloroquine in this Evidence Table.) NIH COVID-19 Treatment Guidelines Panel **recommends against** use of

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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]	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;** NCT04323527**):** Efficacy and safety of two different chloroquine dosages were evaluated for adjunctive therapy in hospitalized adults with severe COVID-19. According to the initial study protocol, pts were randomized 1:1 to receive high-dose chloroquine (600 mg twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. Analysis of data available for the first 81 enrolled pts indicated that, by day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QT_c >500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). **Note:** The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data at the time of the interim analysis were insufficient to evaluate efficacy. [37] See Hydroxychloroquine in this Evidence Table for additional information on clinical trials and experience with 4-aminoquinoline antimalarials in the management of COVID-19. Several clinical trials evaluating chloroquine for *treatment* or *prevention* of COVID-19 are registered at clinicaltrials.gov. [10]	**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]	chloroquine (with or without azithromycin) for the *treatment* of COVID-19 in hospitalized pts and **recommends against** use of chloroquine (with or without azithromycin) for the *treatment* of COVID-19 in nonhospitalized patients, except in a clinical trial. The panel also **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 against** use of chloroquine (with or without azithromycin) for the *treatment* of COVID-19 in hospitalized pts. [38] NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of any drugs, including chloroquine, for preexposure prophylaxis (**PrEP**) for *prevention* of SARS-CoV-2 infection, except in a clinical trial. The NIH Panel **recommends against** the use of hydroxychloroquine for postexposure prophylaxis (**PEP**) for *prevention* of SARS-CoV-2 infection (see Hydroxychloroquine in this Evidence Table) and also **recommends against** the use of other drugs for PEP, except in a clinical trial. The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before or after an exposure. [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.) NIH panel states that 4-aminoquinolines (chloroquine, hydroxychloroquine)

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					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 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

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					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®, Avifavir®, Favilavir) *Updated 3/11/21*	8:18.32 Antiviral	Nucleoside analog prodrug; RNA polymerase Inhibitor [2, 11, 14] 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]	Some data regarding use of favipiravir for the treatment of COVID-19 are available from open-label, randomized or nonrandomized studies and prospective or retrospective observational studies performed in various countries. **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] **Open-label, prospective, randomized, multicenter study** in 60 hospitalized adults with moderate COVID-19 pneumonia in Russia (NCT04434248): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg twice daily on days 2–14 or 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–14) was associated with higher rate of viral clearance at 10 days (92.5 vs 80%) compared with the control group receiving the standard of care. Favipiravir also was associated with decreased median time to normalization of body temperature (2 vs 4 days) and higher improvement rate on chest CT imaging on day 15 (90 vs 80%) compared with the control group. Data are based on interim results of the pilot stage of the study. [24]	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 other countries [6, 15, 24] Protocols in many registered trials generally specify a favipiravir dosage of 1600 or 1800 mg twice daily on day 1, then a total daily dosage of 1200–2000 mg in 2, 3, or 4 divided doses for 4–13 days for treatment of COVID-19 in adults [7] Protocol in one 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 preemptive therapy in this setting; those diagnosed with COVID-19 will be offered the treatment regimen [7] Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2, [1, 5, 13] it has been suggested that high favipiravir dosages, like those used in the treatment of Ebola virus disease, should be considered for the treatment of COVID-19. [11, 19, 20] One such favipiravir regimen used in the treatment of Ebola virus disease includes a loading dosage of 6000 mg (doses of 2400 mg, 2400 mg, and 1200 mg given 8 hours apart on day 1), then a maintenance dosage of 1200 mg every 12 hours on days 2–10. [12, 13]	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] There is conflicting evidence as to whether favipiravir is associated with QT prolongation. [21, 41] 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] Based on a pharmacokinetic interaction, if favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g. [17, 18] Note that favipiravir-induced fever has been described in several COVID-19 pts receiving the drug. [36, 40]

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			Open-label, prospective, randomized, multicenter study in patients hospitalized with asymptomatic or mild COVID-19 in Japan (jRCTs041190120): Early treatment (beginning on day of hospital admission) with favipiravir (two 1800-mg doses given orally at least 4 hours apart on day 1, then 800 mg orally twice daily for a total of up to 19 doses over 10 days) (n=36) was not associated with significant improvement in viral clearance compared with late treatment with favipiravir (same regimen beginning day 6 after admission) (n=33). Viral clearance occurred by day 6 in 66.7 and 56.1% of patients in the early and late treatment groups, respectively. Viral clearance was assessed by RT-PCR of nasopharyngeal specimens. Most common adverse effect was transient hyperuricemia (84.1% of patients). [29] In an **open-label, randomized controlled trial** in Oman in 89 adults (≤75 years of age) hospitalized with moderate to severe COVID-19 pneumonia (NCT04385095), pts received favipiravir (1600 mg on day 1, then 600 mg twice daily for a maximum of 10 days) in combination with inhaled interferon β-1b (n=44) or standard of care (which included hydroxychloroquine) (n=45). At interim analysis, there were no differences between the groups in improvement in inflammatory markers or other clinical outcomes (e.g., hospital length of stay, hospital discharge, 14-day mortality); however, the study lacked sufficient power to detect such differences. [43] **In an **open-label, randomized controlled trial** in India in 150 adults with asymptomatic, mild, or moderate COVID-19, pts received favipiravir (1800 mg twice daily on day 1, then 800 mg twice daily for up to 14 days total) plus standard care (n=75) or standard care alone (n=75). The median time to cessation of oral viral shedding of SARS-CoV-2 (primary end point) was 5 days in the favipiravir group compared with 7 days in the control group; this was numerically lower but not statistically significant. The median time to clinical cure among pts who were symptomatic at baseline was significantly faster in the favipiravir group (3 days) compared with the control group	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] Another pharmacokinetic simulation model suggested that, despite rapid clearance of the parent drug from plasma, a favipiravir dosage of 1600 mg twice daily on day 1 followed by maintenance doses of 800 or 1200 mg twice daily may be sufficient to provide therapeutic intracellular concentrations of the favipiravir metabolite across the dosing interval, owing to its long intracellular half life. [46] **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] While its molecular weight, protein binding rate, and volume of distribution suggest that favipiravir would be eliminated by dialysis, data from a COVID-19 pt treated with favipiravir (1800 mg twice daily on day 1, then 800 mg twice daily) who was undergoing hemodialysis (2 or 3 times weekly) indicated that blood concentrations of the drug were similar to those reported in nondialysis pts. [35]	

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			(5 days). The authors noted that the lack of statistical significance of the primary end point may be attributable to limitations of the RT-PCR assay. [47] In a **randomized multicenter trial** in Egypt in 96 adults with mild or moderate COVID-19, pts received favipiravir (1600 mg twice daily on day 1, then 600 mg twice daily on days 2–10) (n=48) or chloroquine (600 mg twice daily for 10 days) (n=48) in addition to standard care. Pts in the favipiravir group had a lower, though not statistically significant, mean duration of hospital stay compared with pts in the chloroquine group (13.3 versus 15.9 days). No pts in the favipiravir group required mechanical ventilation compared with 4 pts in the chloroquine group. [48] **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 prospective, observational, single-center study** in 174 adults in Turkey with probable or confirmed COVID-19 (20.1% with mild disease, 61.5% with moderate disease, 18.4% with severe pneumonia) admitted to the hospital within a median of 3 days after symptom onset, 32 pts received a regimen that included favipiravir. Most pts who received favipiravir (93.8%) received the drug either in combination with, or as sequential therapy to, hydroxychloroquine with or without azithromycin. In pts who received a favipiravir-containing regimen, the median time to defervescence and to clinical improvement on therapy was 3 and 6 days, respectively. Critically ill pts with sepsis and/or ARDS at the time of admission were excluded. [31] **In a small, observational study** in Turkey in 107 critically ill adults with COVID-19	Data from 4 critically ill pts with COVID-19 who received favipiravir 1600 mg twice daily on day 1, then 600 mg twice daily on days 2–7 (a dosage considered to be "low dose") indicate that the drug was well-tolerated in these pts. [39]	

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			pneumonia, 65 pts received favipiravir (1600 mg twice daily on day 1, then 600 mg daily for 4 days) and 42 pts received lopinavir/ritonavir. While length of hospital stay in the favipiravir group was decreased (6.6 vs 9 days), mortality in the favipiravir group was increased (66.2 vs 54.8%). [42] **In an open-label, prospective, nonrandomized, observational, single-center sequential cohort study** in Hungary, 150 hospitalized adults with moderate to severe COVID-19 received treatment with favipiravir (n=75) or other antivirals (n=75). Disease progression, 14-day all cause mortality, requirement for mechanical ventilation, and PCR negativity rate were unaffected in pts receiving favipiravir (1600 mg twice daily on day 1, then 600 mg twice daily for a total course of at least 10 days) compared with those receiving other antivirals (i.e., chloroquine/hydroxychloroquine, oseltamivir, or LPV/RTV). [44] **In a prospective, single-center study** in 13 pts requiring mechanical ventilation for severe COVID-19 in Japan, pts received favipiravir (3600 mg orally on day 1, then 1600 mg orally on days 2–14), along with methylprednisolone, and low molecular weight heparin (LMWH) or unfractionated heparin. Improvements in PaO_2/FiO_2 (P/F ratio), interleukin-6 concentration, and prepsepsin concentration suggested that favipiravir may have some effect on inflammatory mediators, but could not completely control inflammatory mediators or respiratory status. [32] **In a retrospective, observational, multicenter study** in 63 adults with COVID-19 in Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and median maintenance doses of 17.9 mg/kg per day for a median total duration of 12 days), clinical improvement at day 7 was reported in 66.7% of patients (92.5% in patients *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		

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			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] In a **retrospective cohort study** of 26 pts with COVID-19 who received various antiviral regimens in Japan, 3 pts ≥74 years of age received treatment that included favipiravir; 2 of these pts demonstrated improvement and 1 pt died. [38] In a **meta-analysis** of 13 studies assessing the efficacy and safety of favipiravir in the treatment of COVID-19, clinical deterioration was less likely with favipiravir than with other antiviral agents, although the difference was not statistically significant, and those treated with favipiravir had substantial clinical and radiological improvements compared with those treated with standard of care. Viral clearance, requirement for oxygen or noninvasive ventilation, and adverse effects were similar between the favipiravir and standard of care treatment groups. [33] **Multiple clinical trials initiated** in pts with COVID-19 in the US, China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents.		
HIV Protease Inhibitors *Updated 2/25/21*	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] **Atazanavir (ATV):** Some evidence that ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6	**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (Cao et al)** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, **time to clinical improvement was not shorter with LPV/RTV compared with standard care** (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for up to 14 days with or without other antivirals (e.g., interferon, umifenovir) has been used. [3, 6, 15, 16, 24] **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	**LPV/RTV:** Efficacy for the treatment of COVID-19, with or without other antivirals, not established. [22, 23] Results of several large, randomized trials evaluating LPV/RTV in pts with COVID-19 have not revealed evidence of clinical benefit. [22, 23, 27, 29] **Darunavir:** Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/c for treatment of COVID-19. Results of an open-label, controlled study in China indicated that a 5-day regimen of DRV/c was not effective for treatment of

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		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), [19, 28] Ritonavir (RTV), [19] Saquinavir (SQV), [19] and Tipranavir (TPV) [19]:** Some evidence of in vitro activity against SARS-CoV-2 in Vero cells **LPV/RTV:** Some evidence of clinical benefit when used in conjunction with ribavirin and/or interferon in pts with SARS or MERS. [1, 8-11]	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 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	orally twice daily with interferon β-1b (0.25 mg/mL sub-Q on alternate days) for 14 days [1, 4, 8]	COVID-19 [21, 26] and there are no published clinical studies that have evaluated efficacy and safety of DRV/RTV or the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide for treatment of COVID-19. [21] **Atazanavir, Nelfinavir, Saquinavir, Tipranavir:** No clinical trial data 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 in hospitalized and nonhospitalized patients. The panel states that, based on the pharmacodynamics of LPV/RTV, there are concerns whether it is possible to achieve drug concentrations that can inhibit SARS-CoV-2 proteases. In addition, results of large randomized clinical trials evaluating LPV/RTV in hospitalized COVID-19 patients did not demonstrate efficacy and data are lacking regarding use in nonhospitalized COVID-19 patients. [22] IDSA **recommends against** use of LPV/RTV for the treatment of COVID-19 in hospitalized pts. [23]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 in randomized, controlled, open-label, platform trial (NCT04381936; RECOVERY):** This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the LPV/RTV arm (now terminated), 1616 pts were randomized to receive LPV/RTV (LPV 400 mg/RTV 100 mg every 12 hours for 10 days or until discharge, whichever came first) plus standard of care and 3424 pts were randomized to standard of care alone. At the time of study enrollment, 26% of pts did not require oxygen support, 70% required oxygen support, and only 4% were on mechanical ventilation. The primary outcome was all-cause mortality at day 28. **Results of this study indicated that LPV/RTV is not an effective treatment for COVID-19 in hospitalized pts.** Mortality rate at 28 days was 23% in those treated with LPV/RTV plus standard of care vs 22% in those treated		

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			with standard of care alone. In addition, LPV/RTV did not reduce the time to hospital discharge (median length of stay was 11 days in both groups) and, in those not requiring mechanical ventilation at baseline, LPV/RTV did not decrease the risk of progression to mechanical ventilation (10% in the LPV/RTV group vs 9% in standard of care alone group). Results were consistent across all prespecified pt subgroups (age, sex, ethnicity, level of respiratory support, time since symptom onset, and predicted 28-day mortality risk at time of randomization). [27] **Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY):** The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. [29, 30] From March 22 to July 4, 2020, 1411 pts were randomized to receive LPV/RTV (two tablets containing LPV 200 mg/RTV 50 mg orally twice daily for 14 days) with local standard of care and 1380 pts were randomized to LPV/RTV control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (1399 pts in LPV/RTV group and 1372 pts in standard of care group) indicated that **LPV/RTV did not reduce in-hospital mortality** (either overall or in any subgroup defined by age or ventilation status at study entry) **and did not reduce the need for initiation of ventilation or the duration of hospitalization**. The log-rank death rate ratio for LPV/RTV in the ITT population was 1.00; 148/1399 pts treated with LPV/RTV (9.7%) and 146/1372 pts treated with standard of care (10.3%) died. Ventilation was initiated after randomization in 126 pts receiving LPV/RTV and 121 pts receiving standard of care. [29]		

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			Darunavir and cobicistat (DRV/c) randomized, open-label trial in China (Chen et al; NCT04252274): A total of 30 adults with mild, laboratory-confirmed COVID-19 were randomized 1:1 to receive DRV/c (fixed combination darunavir 800 mg/cobicistat 150 mg once daily for 5 days) or no DRV/c (control group); all pts received interferon alfa-2b and standard of care. The primary end point was viral clearance rate at day 7 (defined as RT-PCR negative for SARS-CoV-2 in at least 2 consecutive oropharyngeal swabs collected at least 1-2 days apart). At day 7, viral clearance rate in the intention-to-treat (ITT) population was 47% in those treated with DRV/c and 60% in the control group. In the per-protocol (PP) population, viral clearance rate at day 7 was 50% in those treated with DRV/c and 60% in the control group. The median time from randomization to negative RT-PCR result was 8 and 7 days, respectively. **This study indicated that a 5-day regimen of DRV/c in pts with mild COVID-19 did not provide clinical benefits compared with use of standard care alone.** [26] Several clinical trials evaluating LPV/RTV for treatment of COVID-19 are registered at clinicaltrials.gov. [15]		

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Hydroxychloroquine (Plaquenil®) *Updated 2/25/21*	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 dose-related toxicity profile than chloroquine, [13-16] but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs [13, 35]	**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 (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	**Oral hydroxychloroquine sulfate dosage suggested in the EUA (now revoked):** For treatment of hospitalized adults and adolescents weighing 50 kg or more, suggested dosage was 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation. [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 or 400 mg twice daily on day 1 then 200 mg twice daily on days 2-5 [10, 18, 66] **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]	Efficacy and safety of hydroxychloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 35, 38, 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 various published randomized, controlled clinical trials and retrospective, cohort studies have not substantiated initial reports of efficacy of 4-aminoquinoline antimalarials (with or without azithromycin) for the treatment of COVID-19; [35, 38, 40, 45, 46, 53, 59, 60, 61, 64, 66] a few studies reported benefits when hydroxychloroquine was used in pts with COVID-19. [35, 38, 58] There has been concern about limitations related to trial design of some studies evaluating efficacy of hydroxychloroquine (e.g., lack of blinding and/or randomization, retrospective and/or observational nature, insufficient statistical power, inconsistency regarding concomitant therapy), and there are some ongoing studies. [10, 35, 38] NIH COVID-19 Treatment Guidelines Panel **recommends against** use of hydroxychloroquine (with or without azithromycin) for the *treatment* of COVID-19 in hospitalized pts and **recommends against** use of hydroxychloroquine (with or without azithromycin) for the *treatment* of COVID-19 in nonhospitalized pts, except in a clinical trial. [35] IDSA **recommends against** use of hydroxychloroquine (with or without azithromycin) for the *treatment* of COVID-19 in hospitalized pts. [38] NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of any drugs, including hydroxychloroquine, for preexposure prophylaxis (**PrEP**) for *prevention* of SARS-CoV-2 infection, except in a clinical trial. [35] The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given before an exposure. [35]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			(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 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]		NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of hydroxychloroquine for postexposure prophylaxis (**PEP**) for *prevention* of SARS-CoV-2 infection and also **recommends against** the use of other drugs for PEP, except in a clinical trial. [35] The panel states that, to date, no agent is known to be effective for preventing SARS-CoV-2 infection when given after an exposure. In addition, results of several randomized, controlled trials evaluating hydroxychloroquine for PEP (see Trials or Clinical Experience) indicated the drug was not effective and increased the risk of adverse events compared with placebo. [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] 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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.		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 for treatment or prevention of COVID-19 outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to 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 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

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			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 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		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 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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			(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 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**		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 **hospitalized** pts (735 received hydroxychloroquine with azithromycin, 271 received hydroxychloroquine alone, 211 received azithromycin alone, 221 received neither drug) and assessed in-hospital mortality (primary outcome). Overall, in-hospital mortality was 20.3%; in-hospital mortality was 25.7, 19.9, 10, or 12.7% in those treated with hydroxychloroquine with azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug, respectively. [45] **Geleris et al** analyzed data for 1376 **hospitalized** pts (811 received hydroxychloroquine [486 of these also received azithromycin] and 565 did not receive hydroxychloroquine [127 of these received azithromycin]) and assessed the primary end point of time from study baseline to intubation or death. Overall, 346 pts (25.1%) progressed to a primary end point of intubation and/or death and the composite end point of intubation or death was not affected by hydroxychloroquine treatment (intubation or death reported in 32.3% of pts treated with hydroxychloroquine and 14.9% of pts not treated with the drug). [46] **Large, randomized, controlled, open-label, platform trial evaluating efficacy of various treatments in hospitalized pts with COVID-19 (NCT04381936; RECOVERY):** This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. The protocol-specified primary outcome is all-cause mortality at day 28; secondary outcomes include duration of hospitalization and composite of initiation of invasive mechanical ventilation (including ECMO) or death among those not receiving invasive mechanical ventilation at time of randomization. In the hydroxychloroquine sulfate arm (now terminated), 1561 adults were randomized to		

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			receive 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 or until hospital discharge, whichever came first) plus standard of care and 3155 were randomized to standard of care alone. **Data analyses for this intention-to-treat (ITT) population indicated that hydroxychloroquine did not reduce mortality and did not provide other benefits in pts hospitalized with COVID-19.** The 28-day mortality rate was 27% in those treated with hydroxychloroquine plus standard care vs 25% in those treated with standard care alone (death rate ratio 1.09); results were consistent across all subgroups defined at the time of randomization (age, sex, race, time since illness onset, level of respiratory support, predicted 28-day risk of death). In addition, pts in the hydroxychloroquine group had a longer duration of hospitalization than those in the standard care alone group (median time to discharge 16 vs 13 days) and a lower probability of discharge alive within 28 days. Among those not receiving invasive mechanical ventilation at baseline, the number of pts who progressed to invasive mechanical ventilation or death was higher in the hydroxychloroquine group than the standard care alone group (risk ratio 1.14).[53] **Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY):** The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. [64, 65] From March 22 to June 19, 2020, 954 pts were randomized to receive hydroxychloroquine sulfate (two 800-mg doses given 6 hours apart followed by a 400-mg dose given 12 hours after the initial dose on day 1, then 400 mg twice daily for 10 days) with local standard of care and		

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			909 pts were randomized to hydroxychloroquine control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (947 pts in hydroxychloroquine group and 906 pts in standard of care only group) indicated that **hydroxychloroquine did not reduce in-hospital mortality** (either overall or in any subgroup defined by age or ventilation status at study entry) **and did not reduce the need for initiation of ventilation or the duration of hospitalization**. The log-rank death rate ratio for hydroxychloroquine in the ITT population was 1.19; 104/947 pts treated with hydroxychloroquine (10.2%) and 84/906 pts treated with standard of care (8.9%) died. Ventilation was initiated after randomization in 75 pts receiving hydroxychloroquine and 66 pts receiving standard of care. [64] **Multicenter, randomized, blinded, placebo-controlled trial evaluating hydroxychloroquine in adults hospitalized with COVID-19 (Self et al):** A total of 479 adults with laboratory-confirmed SARS-CoV-2 infection were randomized 1:1 to receive hydroxychloroquine sulfate (400 mg twice daily on day 1, then 200 mg twice daily on days 2-5) or placebo. Baseline characteristics were similar between both groups; median age was 57 years and median duration of symptoms prior to randomization was 5 days. The primary outcome was clinical status at 14 days after randomization and clinical status was assessed using a 7-category ordinal scale (COVID outcomes scale); secondary outcomes included all-cause all-location mortality at 14 and 28 days after randomization, time to recovery, composite of death or need for ECMO, and support-free days through 28 days (e.g., no need for hospitalization, oxygen, intensive care, ventilator, vasopressors). At day 14, there was no difference in clinical status between the hydroxychloroquine group (242 pts) and placebo group (237 pts); median score (interquartile range) on the COVID outcomes scale was 6 (4-7) in both groups (score of 6 was defined as not hospitalized and unable to perform normal activities). There also was no difference in		

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			clinical status at day 14 between the hydroxychloroquine and placebo groups in any of the prespecified subgroups (e.g., based on age, sex, race/ethnicity, baseline illness severity, duration of symptoms). In addition, there were no differences in any of the secondary outcomes between the treatment groups. Data for pts with confirmed vital status at day 28 indicated that 10.4% of those in the hydroxychloroquine group and 10.6% of those in the placebo group had died. [66] **Retrospective, comparative cohort study evaluating clinical outcomes in hospitalized COVID-19 pts treated with hydroxychloroquine vs hydroxychloroquine with azithromycin vs azithromycin alone (Arshad et al):** Data for 2541 consecutive pts with laboratory-confirmed COVID-19 who were admitted to hospitals within the Henry Ford Health System in Michigan and received hydroxychloroquine and/or azithromycin or did not receive these drugs were analyzed. Median age of patients was 64 years; the majority had BMI of 30 or greater and many had various other comorbidities; 68% received corticosteroid treatment and 4.5% received tocilizumab; mSOFA scores were not available for 25% of pts and data were not available regarding duration of symptoms prior to hospitalization; and the median length of 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.** [58]		

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			Open-label, randomized study in hospitalized pts with mild to moderate COVID-19 (Cavalcanti et al; Brazil; NCT04322123): Adults hospitalized with COVID-19 were randomized 1:1:1 to receive standard care (control group), hydroxychloroquine (400 mg twice daily for 7 days) with standard care, or hydroxychloroquine (same dosage) plus azithromycin (500 mg once daily for 7 days) with standard care. Pts *not* requiring supplemental oxygen or only requiring supplemental oxygen at a rate of 4 L/min or less at baseline were enrolled; pts with a history of severe ventricular tachycardia or with QT_c of 480 msec or greater at baseline were excluded. The median time from onset of symptoms to randomization was 7 days. The primary outcome was clinical status at day 15 evaluated using a 7-point ordinal scale. Data for the 504 pts in the modified intention-to-treat population with laboratory-confirmed COVID-19 (173 pts in the control group, 159 pts in the hydroxychloroquine group, 172 pts in the hydroxychloroquine and azithromycin group) indicated **there was no significant difference in clinical status at day 15 in those treated with hydroxychloroquine with or without azithromycin compared with the control group.** There also were no significant differences in secondary outcomes (e.g., need for mechanical ventilation, duration of hospitalization, in-hospital death) among the groups. [61] **Open-label, randomized study in outpatients with mild COVID-19 (Mitja et al; Spain):** Total of 293 adults with laboratory-confirmed COVID-19 who did not require hospitalization and had mild symptoms (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, influenza-like illness) for less than 5 days before study enrollment were randomized 1:1 to receive hydroxychloroquine (800 mg on day 1, then 400 mg once daily for 6 days) or usual care only. The primary outcome was reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment initiation. Median age of pts was 41.6 years, 53% reported chronic health conditions, and 87% were healthcare workers. The median time from symptom onset		

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			to randomization was 3 days, and the mean viral load at baseline was 7.9 log_{10} copies/mL. **Results indicated that a 7-day hydroxychloroquine regimen did not provide any clinical benefits compared with usual care alone in these outpatients with mild COVID-19.** There was no significant reduction in viral load at day 3 or 7 in those treated with hydroxychloroquine vs those treated with usual care only and there was no decrease in median time to resolution of COVID-19 symptoms (10 and 12 days, respectively) and no decrease in risk of hospitalization (7 and 6%, respectively). [59] **Double-blind, randomized, placebo-controlled study in outpatients with confirmed or probable early COVID-19 (Skipper et al; US and Canada; NCT04308668):** A total of 423 symptomatic adults with laboratory-confirmed COVID-19 or with symptoms compatible with COVID-19 and a high-risk exposure to a contact with laboratory-confirmed COVID-19 were randomized 1:1 to receive hydroxychloroquine (initial dose of 800 mg, 600 mg given 6-8 hours later, then 600 mg once daily for the next 4 days) or placebo. Enrolled pts had been symptomatic for no more than 4 days and did not require hospitalization at the time of enrollment. The primary efficacy end point specified in the initial study protocol was subsequently changed to overall symptom severity over 14 days; symptoms and severity were self-reported by the pts at days 3, 5, 10, and 14 using a survey with a 10-point visual analog scale. Median age of pts was 40 years, 68% reported no chronic medical conditions, 57% were healthcare workers, 25% had been exposed to COVID-19 through household contacts, and 56% of pts had enrolled within 1 day of symptom onset. **Results indicated that a 5-day hydroxychloroquine regimen did not provide any substantial improvement in symptom severity in these outpatients with confirmed or probable COVID-19.** At day 5, 54% of pts in the hydroxychloroquine group and 56% in the placebo group reported symptoms. At day 14, 24% of those treated with hydroxychloroquine had ongoing symptoms compared with 30% of those treated with placebo.		

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			Overall, the decrease in prevalence of symptoms and the reduction in symptom severity score over 14 days were not significantly different between the two groups (symptom severity in the 10-point scale decreased 2.6 points in those treated with hydroxychloroquine and 2.3 points in those treated with placebo). In addition, there was no difference between the groups in the incidence of hospitalization or death. [60] **Large, multinational, retrospective study analyzed outcome data for hospitalized pts with confirmed COVID-19 to assess the effects of hydroxychloroquine or chloroquine used with or without a macrolide (Mehra et al; now retracted):** Original publication included data obtained worldwide for 96,032 pts hospitalized with COVID-19 between Dec 20, 2019 and Apr 14, 2020, including 14,888 pts who received chloroquine or hydroxychloroquine with or without a macrolide (azithromycin or clarithromycin) initiated within 48 hours of diagnosis (treatment group) and 81,144 pts who did not receive these drugs (control group). Based on those data, in-hospital mortality rate in the control group was 9.3% compared with 18% in those treated with hydroxychloroquine alone (n=3016), 23.8% in those treated with hydroxychloroquine and a macrolide (n=6221), 16.4% in those treated with chloroquine alone (n=1868), and 22.2% in those treated with chloroquine and a macrolide (n=3783). [50] **Note: This published study has now been retracted by the publisher at the request of 3 of the original authors. [52] Concerns were raised with respect to the veracity of the data and analyses conducted by a global healthcare data collaborative.** [51, 52] **Hydroxychloroquine for postexposure prophylaxis of COVID-19 randomized, placebo-controlled trial in the US and Canada (NCT04308668):** Asymptomatic adults with occupational or household exposure to an individual with COVID-19 were 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		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			hours after first dose on day 1, then 600 mg once daily for 4 additional days) or placebo (folate tablets). A total of 821 asymptomatic adults were enrolled within 4 days after COVID-19 exposure (414 randomized to hydroxychloroquine and 407 randomized to placebo); 66% were healthcare workers. Overall, 88% of participants reported high-risk exposures (occurred at a distance of <6 feet for >10 minutes while not wearing a face mask or eye shield) and the others reported moderate-risk exposures (occurred at a distance of <6 feet for >10 minutes while wearing a face mask but no eye shield). **Note: Participants were recruited primarily through social media outreach and traditional media platforms and were enrolled using an internet-based survey. The exposure event and subsequent onset of new symptoms and illness compatible with COVID-19 after enrollment were self-reported using email surveys on days 1, 5, 10, and 14 and at 4-6 weeks.** Results of these surveys and information obtained using additional forms of follow-up indicated that confirmed or probable COVID-19 (based on self-reported symptoms or PCR testing) developed in 13% of participants overall (107/821) and did not differ significantly between those who received hydroxychloroquine prophylaxis (11.8%) and those who received placebo (14.3%). [55] **Note: The various limitations of the trial design should be considered when interpreting the results.** Exposure to someone with confirmed COVID-19, time from the exposure event to initiation of prophylaxis, and all outcome data (including possible COVID-19 symptoms and PCR test results) were self-reported by study participants. COVID-19 was confirmed with PCR testing in only a small percentage (<3%) of participants who self-reported COVID-19 symptoms. Survey results indicated that full adherence to the 5-day prophylaxis regimen was reported by only 75% of patients randomized to hydroxychloroquine and 83% of those randomized to placebo. In addition, a total of 52 participants did not complete any surveys after study enrollment. [55, 56]		

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			Double-blind, placebo-controlled, randomized trial in the US to evaluate hydroxychloroquine for preexposure prophylaxis (PrEP) for prevention of COVID-19 (Abella et al; NCT04329923): Healthcare personnel working ≥20 hours per week in hospital-based units (nurses, physicians, certified nursing assistants, emergency technicians, respiratory therapists) who had no known history of SARS-CoV-2 infection and no symptoms suggestive of COVID-19 within 2 weeks prior to trial enrollment were randomized 1:1 to receive hydroxychloroquine (600 mg daily) or placebo for preexposure prophylaxis of COVID-19. Nasopharyngeal swab tests for SARS-CoV-2 and serologic tests for anti-nucleocapside IgG, anti-spike protein receptor-binding domain (RBD) IgM, and anti-RBD IgG were performed at the time of randomization (baseline) and at 4 and 8 weeks; participants also were surveyed weekly for adherence and adverse events. The primary outcome was rate of conversion to SARS-CoV-2 -positive status based on nasopharyngeal swab testing at 8 weeks. A total of 125 participants were evaluable for the primary outcome (64 in the hydroxychloroquine arm and 61 in the placebo arm); 22 of the evaluable participants (17.6%) discontinued study treatment early. Results indicate that **preexposure prophylaxis with hydroxychloroquine did not provide clinical benefits in hospital-based healthcare personnel**. The rate of COVID-19 positivity was similar in the hydroxychloroquine group (6.3%) and placebo group (6.6%); cases of infection occurred throughout the 8-week study period. All 8 individuals who became infected (4 in each group) were either asymptomatic or had mild disease with full recovery; none required hospitalization. After reviewing data at the time of a second planned interim analysis, the data safety and monitoring board recommended that the trial be terminated early. Grade 3 or 4 adverse events were not reported in any participants; the incidence of adverse events was significantly higher in the hydroxychloroquine group than the placebo group (45 vs 26%). **Note:** Limitations of this trial include the possibility that it was insufficiently powered because of low		

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			enrollment, data are not available to quantify the frequency of participant exposures to the virus or specific timing of such exposures, and most participants were young and healthy. [62] **Efficacy of hydroxychloroquine for preexposure prophylaxis (PrEP) for prevention of COVID-19 was also evaluated in another double-blind, placebo-controlled, randomized trial in the US and Canada (Rajasingham et al; NCT04328467):** This study enrolled 1483 healthcare personnel ≥18 years of age at high risk because of ongoing exposure to patients with SARS-CoV-2 (i.e., personnel working in emergency departments, intensive care units, or COVID-19 hospital wards; those performing aerosol-generating procedures; first responders) and randomized them to PrEP with hydroxychloroquine (two 400-mg doses given 6-8 hours apart, then 400 mg once or twice weekly for 12 weeks) or similar regimens of placebo (folic acid). The primary outcome was laboratory-confirmed COVID-19 or COVID-19-compatible illness. **Results indicated that a once- or twice-weekly regimen of hydroxychloroquine did not reduce laboratory-confirmed COVID-19 or COVID-19-compatible illness in healthcare personnel at high risk of infection.** Overall, COVID-19 (laboratory-confirmed or symptomatic compatible illness) occurred in 39 (7.9%) of those in the placebo group compared with 29 (5.9%) of those in the once-weekly hydroxychloroquine group and 29 (5.9%) of those in the twice-weekly hydroxychloroquine group. This corresponded to an incidence of 0.38 events/person-year with placebo compared with 0.27 events/person-year with once-weekly and 0.28 events/person-year with twice-weekly hydroxychloroquine. [67] **Double-blind, placebo-controlled, randomized trial in the US to evaluate hydroxychloroquine for postexposure prophylaxis (PEP) for prevention of COVID-19 following contact with an infected individual (Barnabas et al; NCT04328961):** Trial participants were adults with known exposure to an individual with SARS-CoV-2		

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			infection (household or healthcare-associated exposure) within the prior 96 hours. Households were randomly assigned in a 1:1 ratio to receive PEP with hydroxychloroquine (400 mg daily for 3 days, then 200 mg daily for 11 days) or ascorbic acid as placebo equivalent (500 mg daily for 3 days, then 250 mg daily for 11 days); all eligible participants in the same household were randomly assigned to the same group to prevent unblinding between study participants. The primary end point was laboratory-confirmed SARS-CoV-2 infection through day 14. **Results indicated that a 14-day hydroxychloroquine regimen was not effective for PEP in household contacts of individuals with COVID-19.** A total of 689 participants were included in the modified intention-to-treat (mITT) primary analysis. A total of 98 SARS-CoV-2 infections were detected in the first 14 days of follow-up among participants who were negative at baseline. Overall, there were 53 SARS-CoV-2 acquisition events in the hydroxychloroquine group and 45 events the control group. [68] **Efficacy of hydroxychloroquine for postexposure prophylaxis (PEP) for prevention of COVID-19 following contact with an infected individual was also evaluated in another double-blind, placebo-controlled, randomized trial in the US and Canada (Boulware et al; NCT04308668):** Trial participants were adults with household or occupational exposure to an individual with laboratory-confirmed COVID-19 at a distance of <6 feet for >10 minutes while not wearing a face mask or eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Within 4 days of exposure, participants were randomly assigned to receive PEP with hydroxychloroquine (800-mg dose, then 600 mg 6-8 hours later, then 600 mg daily for 4 days) or placebo (folic acid). The primary outcome was laboratory-confirmed SARS-CoV-2 infection or COVID-19-related symptoms through day 14. **Results indicated that hydroxychloroquine was not effective for PEP in high- or moderate-risk household or occupational contacts of an individual**		

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			with confirmed COVID-19. A total of 821 participants (87.6% with high-risk exposures) were included in the efficacy analysis. COVID-19 (either PCR-confirmed or symptomatically compatible) developed in 107 participants (13%) during the 14 days of follow-up. The incidence of new illness compatible with COVID-19 was 11.8% in the hydroxychloroquine group and 14.3% in the placebo group. [69] **Retrospective cohort study in the US to evaluate possible SARS-CoV-2 preventive benefits of hydroxychloroquine therapy used in pts with rheumatic conditions (Gentry et al):** Possible benefit of long-term hydroxychloroquine therapy used for management of rheumatic conditions for prevention of SARS-CoV-2 infection in such pts was investigated retrospectively using data obtained from the US Veterans Affairs Medical Centers (VAMCs) database. Adults in the database with ICD-10 diagnostic code entries for rheumatoid arthritis, systemic lupus erythematosus, and associated rheumatologic conditions were identified and each such pt receiving hydroxychloroquine was matched to 2 such pts not receiving hydroxychloroquine (controls). The primary end point was the proportion of pts with PCR-confirmed SARS-CoV-2 infection between March 1 and June 30, 2020 among those receiving long-term hydroxychloroquine therapy versus the propensity-matched patients not receiving hydroxychloroquine. Data analyses indicated that **long-term hydroxychloroquine therapy in patients receiving the drug for rheumatic conditions was not associated with a preventive effect against SARS-CoV-2 infection**. The incidence of SARS-CoV-2 infection was similar in pts receiving hydroxychloroquine (0.3%; 31 of 10,703 pts) and those not receiving the drug (0.4%; 78 of 21,406 pts). In those who developed active SARS-CoV-2 infection, there were no significant differences in secondary outcomes between the hydroxychloroquine group and control group. [63] Various clinical trials evaluating hydroxychloroquine for *treatment* or *prevention* of COVID-19 are registered at clinicaltrials.gov. [10]		

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Neuraminidase inhibitors (e.g., oseltamivir) *Updated 1/14/21*	8:18.28	Antivirals active against influenza viruses Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV-1 in in vitro cell culture [4] Oseltamivir did not demonstrate in vitro antiviral activity against SARS-CoV-2 in Vero E6 cells [6, 9] Data are not available on in vitro antiviral activity of peramivir or zanamivir against SARS-CoV-2 [8]	Oseltamivir has been included as a component of various antiviral regimens used for the treatment of COVID-19.[1, 5, 6, 7] While oseltamivir is noted to have been widely used for confirmed or suspected COVID-19 cases in hospitals in China in the early stages of the pandemic, there has been no evidence that oseltamivir is effective in the treatment of COVID-19. [2] In a **retrospective case series** of 99 adults with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of pts received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died. [1] In a **retrospective case series** of 79 adults with COVID-19 who were negative for influenza A and B, early use of oseltamivir had no effect on COVID-19 and did not effectively slow the progression of the disease. [6] In a **retrospective cohort study** of 1190 adults with COVID-19 at a single center in Wuhan from 12/29/19 to 2/28/20, 61.6% of pts received antiviral therapy (e.g., oseltamivir, ganciclovir, lopinavir/ritonavir, interferon, umifenovir). A survival analysis indicated that administration of oseltamivir appeared to have reduced the risk of death in pts with severe disease and seemed to have been associated with less deterioration (i.e., progression from nonsevere to severe disease or severe disease to death). [7] **Note:** Limitations of this study include missing laboratory data because of retrospective data extraction, lack of information on possible mixed viral infections, and inability to analyze possible reasons for mortality benefit. Oseltamivir may be included in some COVID-19 clinical trials registered at clinicaltrials.gov. [5]	Dosage of oseltamivir in the case series of 99 COVID-19 patients was 75 mg orally every 12 hours. [1] Dosages of oseltamivir from registered COVID-19 trials have included 75 mg orally twice daily or 300 mg (or 4-6 mg/kg) orally daily. [5]	Although oseltamivir was suggested as a potential treatment and included in various antiviral regimens used during the early stages of the COVID-19 pandemic, [1, 5, 6, 7, 11] the drug does not appear to have in vitro activity against SARS-CoV-2 and there are no data to support the use of oseltamivir or other neuraminidase inhibitors in the treatment of COVID-19. NIH COVID-19 Treatment Guidelines Panel states that, when SARS-CoV-2 and influenza are cocirculating, testing for both viruses is recommended in all hospitalized pts with acute respiratory illness and also recommended in outpatients with acute respiratory illness if results will change clinical management of the pt. Testing is the only way to distinguish between influenza and SARS-CoV-2 and identify coinfection. Treatment of influenza is the same in all pts regardless of SARS-CoV-2 coinfection. If SARS-CoV-2 and influenza are cocirculating, the panel recommends that *hospitalized* pts suspected of having one or both viral infections should receive oseltamivir for empiric influenza treatment as soon as possible without waiting for influenza testing results; empiric influenza treatment can be de-escalated based on results of testing and intubation status. Significant drug interactions not expected with oseltamivir and remdesivir. [8] CDC states that, when SARS-CoV-2 and influenza are cocirculating, priority groups for influenza antiviral treatment include pts who are hospitalized with respiratory illness; outpatients with severe, complicated, or progressive respiratory illness; and outpatients at higher risk for influenza complications presenting with any symptoms of acute respiratory illness (with or without fever). CDC recommends oseltamivir for treatment of *hospitalized* pts with suspected or confirmed influenza and states that oseltamivir, zanamivir, or peramivir may be used for the treatment of influenza in *outpatients*, taking into account the severity and progression of illness and the presence of complications [10]

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Remdesivir (Veklury®) *Updated 4/30/21*	8:18.32 Antiviral	Nucleotide analog prodrug; RNA polymerase inhibitor [46] Broad-spectrum antiviral with activity against various viruses, including coronaviruses [24] In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells; [1, 18] antiviral activity against SARS-CoV-2 in human airway epithelial (HAE) cells [46] 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 studies in healthy adults [46]	**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 **severe COVID-19** not receiving mechanical ventilation at study entry; [10] protocol was	**Remdesivir dosage for FDA-labeled indication for treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing at least 40 kg (lyophilized powder formulation or solution concentrate formulation):** Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts **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). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.[46] **Emergency use authorization (EUA) remdesivir dosage for treatment of COVID-19 in pediatric patients weighing 3.5 to <40 kg (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. For pts **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). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days. [26] **Emergency use authorization (EUA) remdesivir dosage for treatment of COVID-19 in pediatric patients <12 years of age weighing ≥40 kg (lyophilized powder formulation only):** Loading dose of 200 mg by IV infusion on day 1, followed by maintenance doses of 100 mg by IV infusion once daily from day 2. For pts **not** requiring invasive mechanical	The only direct-acting antiviral (DAA) currently approved by FDA for treatment of COVID-19 in certain populations. **Received FDA approval on October 22, 2020 for treatment of COVID-19 in adults and pediatric patients ≥12 years of age weighing at least 40 kg** who are hospitalized or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. [46] FDA states that such alternative care sites may include temporary facilities intended to provide additional hospital surge capacity/capabilities for communities overwhelmed by patients with COVID-19 and at-home care provided by hospitals that have received CMS waiver approval as part of CMS's Acute Hospital Care at Home (AHCaH) program. The drug may be used for the FDA-labeled indication to treat patients admitted directly to an alternative care site and, if clinically indicated, to complete the course of treatment in patients transferred to an alternative care site. [48] **Available under an emergency use authorization (EUA) for treatment of suspected or laboratory-confirmed COVID-19 in pediatric patients weighing 3.5 to <40 kg and pediatric patients <12 years of age weighing at least 3.5 kg** who are hospitalized or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. [39] **Emergency use authorization (EUA) for remdesivir:** The original EUA issued by FDA on May 1, 2020 permitted use of remdesivir for treatment of COVID-19 in hospitalized adults and children with suspected or laboratory-confirmed COVID-19 and severe disease (defined as oxygen saturation [SpO_2] ≤94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO); [25] on August 28, 2020, FDA broadened the EUA to allow use of the drug in hospitalized patients irrespective of disease severity. [38] In response

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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* 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	ventilation and/or ECMO, recommended total treatment duration is 5 days; if pt does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total treatment duration of 10 days). For those requiring invasive mechanical ventilation and/or ECMO, recommended total treatment duration is 10 days.[26] **NIH COVID-19 Treatment Guidelines Panel-recommended duration of remdesivir treatment:** The NIH panel recommends that hospitalized pts who require supplemental oxygen but do not require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, should receive remdesivir for a duration of 5 days or until hospital discharge, whichever comes first. If such pts progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO during such treatment, the panel recommends that the remdesivir course be completed. The panel states that there are insufficient data on the optimal duration of remdesivir treatment for pts who have not shown clinical improvement after a 5-day regimen; some experts would extend the total duration of remdesivir treatment to up to 10 days in these patients. [20]	to FDA approval of remdesivir for use in adults and pediatric patients ≥12 years of age weighing at least 40 kg, the **EUA was reissued on October 22, 2020 to allow continued authorization of the drug (lyophilized powder formulation only) for emergency use in pediatric patients weighing 3.5 to <40 kg and pediatric patients <12 years of age weighing at least 3.5 kg with suspected or laboratory-confirmed COVID-19.** [39] **The EUA for remdesivir requires** that the drug be administered by a healthcare provider in an inpatient hospital setting (or alternative care site capable of providing acute care comparable to general inpatient hospital care) via IV infusion at dosages recommended in the EUA. [26, 39] The EUA also requires that healthcare facilities and healthcare providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). [26, 39] Although distribution of remdesivir under the EUA was previously directed by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state health departments, [25, 38] the EUA now designates the manufacturer (Gilead) and its authorized distributor(s) as the parties responsible for distribution of the drug. [39] For additional information about the remdesivir EUA, consult the EUA letter of authorization, [39] EUA fact sheet for healthcare providers, [26] and EUA fact sheet for parents and caregivers. [27] Healthcare providers should contact Gilead's sole US distributor (AmerisourceBergen at 800-746-6273) to purchase remdesivir for age-appropriate use under the FDA-approved indication (lyophilized powder formulation or solution concentrate formulation) or the EUA (lyophilized powder formulation only). [47] **Concerns regarding variations in remdesivir packaging:** The manufacturer is alerting healthcare providers that

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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		there are variations in remdesivir packaging and labeling (e.g., use of the tradename Veklury®, expiration dates) depending on whether the drug was originally manufactured for use under the EUA or for commercial use. [49] FDA states that, if patient safety can be assured, they do not intend to object to remdesivir supplies that have labels specifying "for use under Emergency Use Authorization" being distributed for appropriate use under the FDA-labeled indication during the first six months after the drug received this approval. [48] Questions related to carton or vial labeling or expiration dates should be directed to Gilead at 866-633-4474 or www.askgileadmedical.com. [49] **The NIH COVID-19 Treatment Guidelines Panel issued the following recommendations for use of remdesivir (with or without dexamethasone) for the management of COVID-19 based on disease severity:** **1) Hospitalized with moderate COVID-19 not requiring supplemental oxygen:** The panel states that data are insufficient to recommend either for or against routine use of remdesivir. For pts at high risk of disease progression, use of remdesivir may be appropriate. [20] **2) Hospitalized requiring supplemental oxygen but not requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO:** The panel recommends remdesivir (e.g., for pts requiring minimal supplemental oxygen) **or** remdesivir *plus* dexamethasone (e.g., for pts requiring increasing amounts of supplemental oxygen) **or** dexamethasone alone (e.g., when combination therapy with remdesivir is unavailable or cannot be used). In rare circumstances when corticosteroids cannot be used, the panel states that remdesivir *plus* baricitinib can be used instead of remdesivir *plus* dexamethasone (see Baricitinib in this Evidence Table). The panel **recommends against** use of remdesivir *plus* dexamethasone *plus* baricitinib, except in a clinical trial. [20]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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 compared with standard care alone in adults with **moderate COVID-19** (i.e., hospitalized with evidence of pulmonary infiltrates and SpO_2 >94% on room air); protocol was subsequently modified to change the primary end point to clinical status on day 11 based on a 7-point ordinal scale, include pts 12 years of age or older, and add an extension phase to include additional pts. [11, 30] Data for the initial group of adults who received a 5-day regimen of remdesivir with standard care (n=191), 10-day regimen of the drug with standard care (n=193), or standard care alone (n=200) have been published. At day 11, 70, 65, or 61% of pts in the 5-day, 10-day, or standard of care alone group, respectively, had clinical improvement based on at least a 2-point improvement from baseline on a 7-point ordinal scale. Pts in the 5-day remdesivir group had statistically significant higher odds of a better clinical status distribution on the 7-point scale on day 11 than those receiving standard care (odds ratio: 1.65) but the difference was of uncertain clinical importance; the difference in clinical status distribution between pts in the 10-day remdesivir group and the standard care group was not statistically significant. At day 11, 4 deaths were reported in		**3) Hospitalized requiring high-flow oxygen or noninvasive ventilation:** The panel recommends dexamethasone alone **or** dexamethasone *plus* remdesivir. The panel **recommends against** use of remdesivir alone. In rare circumstances when corticosteroids cannot be used, the panel states that baricitinib *plus* remdesivir can be used (see Baricitinib in this Evidence Table). The panel **recommends against** use of remdesivir *plus* dexamethasone *plus* baricitinib, except in a clinical trial. [20] **4) Hospitalized requiring invasive mechanical ventilation or ECMO:** The panel recommends dexamethasone. Dexamethasone *plus* remdesivir may be considered for pts who were recently intubated. The panel **recommends against** use of remdesivir alone. [20] **5) Not hospitalized, mild to moderate disease:** The panel states that data are insufficient to recommend either for or against any specific antiviral or antibody therapy. The panel states that dexamethasone should **not** be used. [20] (See Corticosteroids [Systemic] in this Evidence Table.) Although safety and efficacy of combined use of remdesivir with dexamethasone or other corticosteroids have not been specifically studied in clinical trials to date, the NIH panel states that there are theoretical reasons that such combined therapy may be beneficial in some pts with severe COVID-19. Concomitant use of remdesivir with dexamethasone is expected to result in minimal or no reduction in remdesivir exposure. [20] **IDSA issued the following recommendations for use of remdesivir in hospitalized pts:** 1) **Hospitalized with SpO_2 >94% on room air without need for supplemental oxygen:** IDSA **suggests against** routine use of remdesivir. Additional study needed to assess benefits and harms of remdesivir in pts with moderate COVID-19. [52]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			the standard care alone group compared with none in the 5-day group and 2 in the 10-day group. There were no significant differences between the 5- or 10-day remdesivir groups and standard care group for any of the exploratory end points at day 11 (time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, time to discontinuation of oxygen support). At day 14, the clinical status of pts in the 5-day and 10-day remdesivir groups was significantly different than that of the standard care group. **Note:** Effect of remdesivir on SARS-CoV-2 viral load was not assessed. Limitations of this study include the open-label design and use of an ordinal scale to evaluate outcomes that was not ideal for detecting differences in pts with moderate COVID-19. [30] **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:** 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. All pts received supportive care according to the standard of care for the trial site hospital. The primary outcome was time to recovery, defined as the first day within 28 days after enrollment when clinical status met criteria for category 1, 2, or 3 on an 8-category ordinal scale (i.e., discharged from hospital with or without limitations on activities or requirement for home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). A total of 1062 pts were randomized with 541 assigned to remdesivir and 521 assigned to placebo (intention-to-treat population). 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. A total of 957 pts (90.1%) had severe disease (i.e., required mechanical ventilation, required supplemental oxygen, had SpO_2 ≤94% on		2) **Hospitalized with severe COVID-19 (i.e., SpO_2 ≤94% on room air and requiring supplemental oxygen, mechanical ventilation, or ECMO):** IDSA suggests use of remdesivir over no antiviral treatment. Based on available data, these experts recommend remdesivir be prioritized for those with severe, but not critical, COVID-19. IDSA also suggests use of dexamethasone in pts with severe, but noncritical, COVID-19 and recommends use of dexamethasone in critically ill pts (see Corticosteroids [Systemic] in this Evidence Table). If corticosteroids cannot be used with remdesivir, these experts suggest use of baricitinib with remdesivir rather than remdesivir alone (see Baricitinib in this Evidence Table). IDSA states that a 10-day remdesivir regimen may be desirable in those on mechanical ventilation, but a 5-day regimen is suggested in those on supplemental oxygen but not on mechanical ventilation. [52] **Pregnant women:** The NIH panel states that remdesivir should not be withheld from pregnant women if it is otherwise indicated. [20] The manufacturer states that available data from published case reports and compassionate use of remdesivir are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. [46] Concomitant use of remdesivir and chloroquine or hydroxychloroquine is **not recommended**; [20, 26, 33, 46] FDA warns that there is in vitro evidence that chloroquine antagonizes intracellular metabolic activation and antiviral activity of remdesivir. [26] Remdesivir clinical drug interaction studies have not been performed to date. In vitro studies indicate remdesivir is a substrate for cytochrome P-450 (CYP) isoenzyme 3A4, organic anion transporting polypeptide (OATP) 1B1, and P-glycoprotein (P-gp), and is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion transporter (MATE) 1.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			room air, or had tachypnea with respiratory rate ≥24 breaths/minute) at study enrollment, and the median time from symptom onset to randomization was 9 days (range: 6-12 days). Final trial data indicated **shorter median time to recovery in the remdesivir group (10 days) vs the placebo group (15 days); recovery rate ratio 1.29.** Those who received remdesivir were more likely to have clinical improvement at day 15 than those who received placebo (odds ratio 1.5). Kaplan-Meier estimates of mortality by day 15 were 6.7% in the remdesivir group vs 11.9% in the placebo group (hazard ratio 0.55); by day 29, mortality was 11.4 and 15.2%, respectively (hazard ratio 0.73). Posthoc analysis of efficacy based on disease severity at enrollment suggested that benefits of remdesivir were most apparent in hospitalized pts receiving low-flow oxygen (recovery rate ratio 1.45); the recovery rate ratio in the subgroup of pts on mechanical ventilation or ECMO at enrollment was 0.98. [42] There was no observed benefit of remdesivir compared with placebo in the subgroup with mild to moderate disease (defined as SpO_2 >94% on room air or a respiratory rate <24 beats/minute without supplemental oxygen) at enrollment; however, the number of pts in this subgroup was relatively small. Although there was no observed difference in time to recovery in subgroups requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO at enrollment, the trial was not powered to detect differences in outcomes within subgroups and there is uncertainty about the effects of remdesivir on the course of COVID-19 in patients who are mechanically ventilated or on ECMO. [20] **Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (NCT04315948; SOLIDARITY):** The protocol-specified primary outcome was in-hospital mortality; protocol-specified secondary outcomes were initiation of ventilation and		The clinical relevance of these in vitro assessments has not been established. [46]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			duration of hospitalization. [44, 53] From March 22 to October 4, 2020, 2750 pts were randomized to receive remdesivir (200 mg on day 1, then 100 mg on days 2-10) with local standard of care and 2725 pts were randomized to remdesivir control (i.e., local standard of care only). Clinical characteristics at baseline were well balanced between groups. Data analysis for the intention-to-treat (ITT) population (2743 pts in remdesivir group and 2708 pts in standard of care group) indicated that **remdesivir did not reduce in-hospital mortality** (either overall or in any subgroup defined by age or ventilation status at study entry) **and did not reduce the need for initiation of ventilation or the duration of hospitalization**. The log-rank death rate ratio for remdesivir in the ITT population was 0.95; 301/2743 pts treated with remdesivir (12.5%) and 303/2708 pts treated with standard of care (12.7%) died. Ventilation was initiated after randomization in 295 pts in the remdesivir group and 284 pts in the standard of care group. [44] **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, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug		

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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			the most common adverse events were due to underlying disease and most laboratory abnormalities were grades 1–2. [34] **Phase 2/3 single-arm, open-label trial in pediatric patients (NCT04431453; CARAVAN):** The manufacturer (Gilead) initiated a trial to evaluate safety, tolerability, pharmacokinetics, and efficacy of remdesivir in pediatric pts (birth to <18 years of age) with laboratory-confirmed COVID-19. [35] **Phase 3 adaptive, randomized, double-blind trial compared a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib in hospitalized adults (NCT04401579; ACTT-2):** Pts were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for a total treatment duration of 10 days or until hospital discharge) with either baricitinib (4 mg once daily orally or through a nasogastric tube for 14 days or until hospital discharge) or 14-day regimen of oral placebo. The primary end point was time to recovery through day 29 (defined as discharged without limitations on activities, discharged with limitations on activities and/or requiring home oxygen, or still hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). Data for the 1033 pts in the intention-to-treat (ITT) population (515 in the remdesivir and baricitinib group and 518 in the remdesivir alone group) indicate that those who received the combined regimen were more likely to have better clinical outcomes than those who received remdesivir alone. [29, 51] Based on results of this trial and other data, FDA issued an emergency use authorization (EUA) for baricitinib to permit use of the drug in combination with remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric pts ≥2 years of age. [51] (See Baricitinib in this Evidence Table.) **Phase 3 adaptive, randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with interferon beta-1a**		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			(NCT04492475; ACTT-3): This iteration of NIAID's Adaptive COVID-19 Treatment Trial (ACTT) is evaluating possible benefits of using interferon beta-1a in conjunction with remdesivir in hospitalized adults with laboratory-confirmed SARS-CoV-2 infection. [36, 37] Inclusion criteria include evidence of lung involvement (radiographic infiltrates, SpO_2 of 94% or lower on room air, or requiring supplemental oxygen or mechanical ventilation); exclusion criteria include need for ECMO, prior treatment with ≥3 doses of remdesivir, treatment with any interferon preparation within the previous 2 weeks, prior treatment with convalescent plasma or IGIV or various other drugs used for management of COVID-19. Pts will be randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for the duration of hospitalization up to 10 days total) with either sub-Q interferon beta-1a (44 mcg once daily on days 1, 3, 5, and 7 during hospitalization for a total of 4 doses) or placebo. [36, 37] **Randomized, double-blind trial to compare a regimen of remdesivir alone vs a regimen of remdesivir with tocilizumab (NCT04409262; REMDACTA):** This trial is evaluating possible benefits of using tocilizumab (an interleukin-6 [IL-6] inhibitor) in conjunction with remdesivir in hospitalized patients 12 years of age or older with severe COVID-19 pneumonia. Pts will be randomized to receive remdesivir (IV loading dose on day 1, then once-daily IV maintenance doses on days 2-10) with either tocilizumab (single IV infusion on day 1) or placebo. [32] **Phase 3 randomized, double-blind, placebo-controlled, adaptive trial sponsored by NIAID to evaluate safety, tolerability, and efficacy of a regimen of remdesivir vs a regimen of remdesivir with investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hyperimmune globulin intravenous [hIGIV]) in hospitalized adults (NCT04546581; ITAC):** Pts with documented COVID-19 and duration of symptoms ≤12 days will be randomized to receive remdesivir (200 mg IV on day 1, then 100		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			mg IV once daily during hospitalization for up to 10 days total) with either placebo or investigational anti-SARS-CoV-2 hIGIV (single IV dose of 400 mg/kg). [45, 50] (See Immune Globulin in this Evidence Table.) **Phase 3 randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of remdesivir for treatment of COVID-19 in outpatients (NCT 04501952):** Manufacturer (Gilead) initiated a study to evaluate a 3-day regimen of IV remdesivir in adults and pediatric pts ≥12 years of age with early-stage COVID-19 to determine efficacy in an outpatient setting for reducing the rate of hospitalization or death. [41]		
SARS-CoV-2-Specific Monoclonal Antibodies *Updated 4/29/21*	8:18.24 Monoclonal Antibodies	Monoclonal antibodies (mAbs) used in the treatment or prevention of infectious diseases are engineered versions of antibodies naturally produced by the immune system in response to invading viruses or other pathogens. [1, 6, 21, 30, 31] mAbs that are specific for certain infectious agents or their toxins (e.g., respiratory syncytial virus, *Bacillus anthracis*, *Clostridioides difficile*) have been used for the treatment or prevention of infections caused by these agents. [1] Animal studies evaluating neutralizing mAbs specific for other coronaviruses (SARS-CoV-1, MERS-CoV) have demonstrated benefits in such models. [1, 2, 4, 5, 6, 30] SARS-CoV-2-specific mAbs are designed to directly target the virus and may act as neutralizing antibodies (nAbs). Most SARS-CoV-2-specific mAbs being investigated target epitopes on the spike protein (S protein) of the virus	Clinical trials have been initiated to evaluate several different SARS-CoV-2-specific mAbs, including the following: **Casirivimab and Imdevimab (REGN10933 and REGN10987; REGN-COV2):** Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of casirivimab and imdevimab for **treatment** of COVID-19 in **hospitalized** adults **(NCT04426695)**. [22] Initial study protocol included 4 different cohorts of pts (i.e., on low-flow oxygen, not requiring oxygen, on high-flow oxygen without mechanical ventilation, on mechanical ventilation) to be randomized to receive casirivimab and imdevimab (administered together) or placebo. [22] The manufacturer announced that further enrollment of hospitalized pts requiring high-flow oxygen or mechanical ventilation was terminated following a recommendation from the independent data monitoring committee (IDMC) based on a potential safety signal and unfavorable risk/benefit profile in such pts. Enrollment of hospitalized pts not requiring oxygen or on low-flow oxygen is continuing as recommended by the IDMC. [37] The manufacturer announced preliminary data analyses (not peer reviewed) for pts hospitalized with laboratory-confirmed COVID-19 who were on low-flow oxygen (defined as maintaining O_2 saturation of >93% via nasal cannula, simple facemask,	Because mAbs generally have long half-lives, it is likely that only a single dose of the SARS-CoV-2-specific mAbs may be required. [1] **Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016):** **Emergency use authorization (EUA) dosage and administration of bamlanivimab and etesevimab for treatment of mild to moderate COVID-19** in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing **who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization:** Single dose of 700 mg of bamlanivimab and 1.4 g of etesevimab administered together after dilution as a single IV infusion; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. [65] **Casirivimab and Imdevimab (REGN10933 and REGN10987):** **Emergency use authorization (EUA) dosage and administration of casirivimab and imdevimab for treatment of mild to moderate COVID-19** in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct	SARS-CoV-2-specific mAbs are not commercially available. Safety and efficacy of investigational SARS-CoV-2-specific mAbs for the *treatment* or *prevention* of COVID-19 have not been established. Although results of controlled clinical trials are needed to provide additional information on safety and efficacy of mAbs that specifically target SARS-CoV-2, preliminary data suggest that **outpatients** may benefit from receiving a SARS-CoV-2-specific mAb early in the course of the infection [57] and it has been suggested that such mAbs may offer some advantages over other immunotherapies used for the treatment of COVID-19 (e.g., COVID-19 convalescent plasma, IGIV) in terms of specificity and safety. [2, 3, 30, 31] **Bamlanivimab (LY-CoV555):** **Effective April 16, 2021, FDA revoked the EUA for use of bamlanivimab alone (monotherapy) for the treatment of mild to moderate COVID-19.** [81] Because of a sustained increase in SARS-CoV-2 viral variants in the US that are resistant to bamlanivimab *alone* and because testing technologies are not available to enable healthcare providers to test individual COVID-19 patients for SARS-CoV-2 viral variants prior to initiation of mAb treatment, there is an increased

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		and block the receptor-binding domain (RBD) of the S protein from interacting with human angiotensin-converting enzyme 2 (ACE2), thereby preventing the virus from entering cells and inhibiting viral replication. [1-6, 25, 27, 30] SARS-CoV-2-specific mAbs potentially could limit or modify SARS-CoV-2 infection and may be effective for both treatment and prevention since such mAbs could provide immediate and longer-term (weeks or months) protection against the virus. [1-3, 30] Various mAbs specific for SARS-CoV-2 are being investigated for the treatment and prevention of COVID-19, including the following: **Casirivimab and Imdevimab (REGN10933 and REGN10987; REGN-COV2):** Combination of two different recombinant neutralizing IgG_1 mAbs (casirivimab and imdevimab) that bind to non-overlapping epitopes on the S protein RBD of SARS-CoV-2 and block the virus from binding to the human ACE2 receptor; [21, 25, 27, 29, 49] preclinical studies demonstrated neutralizing activity in vitro and protective effects against SARS-CoV-2 infection and viral replication in animal models. [27, 28] **Bamlanivimab (LY-CoV555; LY3819253):** Recombinant neutralizing IgG_1 mAb that specifically binds to an epitope on the S protein of SARS-CoV-2	or similar device) and were randomized to receive 2.4 g of casirivimab and imdevimab (1.2 g of each mAb; low dose), 8 g of casirivimab and imdevimab (4 g of each mAb; high dose), or placebo in addition to standard of care (67% received remdesivir and 74% received systemic corticosteroids). Results of the preliminary analysis (i.e., futility analysis) indicated that the mAb regimen had sufficient efficacy to warrant continuing the trial. Data for the 217 pts seronegative for endogenous antibodies against SARS-CoV-2 at baseline indicated that casirivimab and imdevimab treatment reduced the time-weighted average daily viral load through day 7 by -0.54 log_{10} copies/mL and through day 11 by -0.63 log_{10} copies/mL (nominal p = 0.002 for combined doses). Data for the 270 pts seropositive at baseline indicated that clinical and virologic benefit of the mAb treatment was limited in these pts (time-weighted average viral load through day 7 reduced by -0.20 log_{10} copies/mL for combined doses). Efficacy of the low- and high-dose regimens of casirivimab and imdevimab was similar. [60] Randomized, placebo-controlled, phase 1/phase 2/phase 3 trial sponsored by the manufacturer (Regeneron) to evaluate safety, tolerability, and efficacy of a single IV dose of casirivimab and imdevimab (administered together) for **treatment** of COVID-19 in **outpatients (NCT04425629)**. [23] Results of a preplanned interim analysis that included the first 275 outpatients enrolled in the **phase 1/phase 2 portion** of this trial have been published. Enrolled pts were randomized 1:1:1 to receive a single IV infusion of 2.4 g of casirivimab and imdevimab (1.2 g of each mAb; low dose) or 8 g of casirivimab and imdevimab (4 g of each mAb; high dose), or placebo in addition to usual standard of care. All pts had SARS-CoV-2 infection confirmed by testing ≤72 hour prior to randomization and had symptom onset ≤7 days prior to randomization. Results of this interim analysis indicated that casirivimab and imdevimab reduced viral load and there was a positive trend in reduction of medical visits; benefits were greatest in those who had not mounted their own effective immune response. [58]	SARS-CoV-2 viral testing **who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization:** Single dose of 1.2 g of casirivimab and 1.2 g of imdevimab **administered together after dilution as a single IV infusion**; administer in an outpatient setting as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. [65] **Concerns about medication errors and variations in packaging:** The manufacturer is alerting healthcare providers that **casirivimab and imdevimab are packaged individually in separate cartons and vials, but must be combined and administered together after dilution as a single IV infusion only.** Beginning in February 2021, casirivimab and imdevimab are being shipped in "dose packs" with the tradename **REGEN-COV®**; although there are 4 different dose pack presentations, each contains a sufficient number of cartons and vials of the drugs to prepare a single treatment dose. Although some cartons and vials of the drugs may be labeled "for intravenous infusion or subcutaneous injection", [52] the drugs **must be administered together by IV infusion only as specified in the EUA**. [49, 52] Casirivimab and imdevimab may each be supplied as two different vial sizes (1332 mg/11.1 mL or 300 mg/2.5 mL); [49, 52] instructions for preparing the casirivimab and imdevimab solution for IV infusion (e.g., number of vials) specified in the EUA fact sheet for healthcare providers must be followed to ensure the correct dose. [49] Some cartons and vials of casirivimab and imdevimab may be labeled REGN10933 and REGN10987, respectively. [49, 52]	risk of treatment failure if bamlanivimab is administered *alone.* Therefore, based on the totality of scientific evidence available, FDA concluded that the known and potential benefits of bamlanivimab *alone* no longer outweigh the known and potential risks of monotherapy with the drug. **Note: The EUA for use of bamlanivimab in a combined regimen with etesevimab remains unchanged. Healthcare facilities that have existing supplies of bamlanivimab alone, distributed prior to revocation of the EUA for use of the drug as monotherapy, should contact the authorized US distributor (AmerisourceBergen) to obtain etesevimab to pair with their existing supplies of bamlanivimab to enable use under the EUA for bamlanivimab and etesevimab.** [81, 82] **Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016):** **FDA issued an Emergency Use Authorization (EUA) for bamlanivimab and etesevimab on February 9, 2021 that permits** combined use of the drugs for the **treatment** of **mild to moderate COVID-19** in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing **who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization**. FDA states that, based on a review of data from an ongoing randomized, double-blind, placebo-controlled phase 2/3 trial in outpatients with mild to moderate COVID-19 (BLAZE-1; NCT04427501), it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization and, when used under the conditions of the EUA, the known and potential benefits of bamlanivimab and etesevimab administered together for treatment

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		overlapping the ACE2 binding site; [12, 13, 43] preclinical studies demonstrated neutralizing activity against SARS-CoV-2 in Vero E6 cells and protective effects against SARS-CoV-2 infection and viral replication in an animal model. [13] **Etesevimab (LY-CoV016; LY3832479; JS016):** Recombinant, fully human neutralizing mAb that specifically binds to a region on the S protein of SARS-CoV-2 complementary to the binding site of bamlanivimab; has high affinity for and effectively blocks the virus from binding to ACE2 host cell surface receptors; prophylactic and therapeutic effects against SARS-CoV-2 infection demonstrated in an animal model. [32] **VIR-7831 (GSK4182136)**: mAb that specifically targets the S protein of SARS-CoV-2; preclinical studies demonstrated affinity for and highly potent neutralizing activity against the virus; [15] engineered for enhanced lung bioavailability and extended half-life. [34] **AZD7442:** Contains two mAbs (AZD8895 and AZD1061) that specifically target SARS-CoV-2 at two non-overlapping sites; [20, 30] has an extended half-life and reduced Fc receptor binding. [20] **COVID-GUARD (STI-1499) and COVI-AMG (STI-2020):** Both of these mAbs specifically target the S protein of SARS-CoV-2; preclinical	Key end points included the time-weighted average change in viral load from baseline through 7 and percentage of pts with at least one COVID-19-related medically attended visit through day 29. At least one medically attended visit was reported in 6 or 3% of pts in the placebo or mAb group, respectively; among those who were antibody-negative at baseline, 15% in the placebo group and 6% in the mAb group reported such visits. [58] The manufacturer subsequently announced results for an additional 524 outpatients enrolled in **the phase 1/phase 2 portion** of this trial (not peer reviewed) and stated that analysis of data for these pts confirmed that a combined regimen of casirivimab and imdevimab significantly reduces viral load, is associated with reduced COVID-19-related medical visits, and is most beneficial in pts who are at risk for poor outcomes due to higher viral load and/or no detectable antibodies at baseline; data also indicated there were no significant differences in virologic or clinical efficacy between the high- and low-dose casirivimab and imdevimab regimens. [36] Based on phase 1/phase 2 results, the **phase 3 protocol** of this placebo-controlled trial in outpatients was amended to compare a dosage regimen of 1.2 g of casirivimab and imdevimab or 2.4 g of casirivimab and imdevimab with placebo. The manufacturer has announced preliminary results of the **phase 3 portion** (not peer reviewed) indicating that the combined regimen met the primary end point and all secondary end points. Compared with placebo, a single IV infusion of the combined regimen reduced the risk of hospitalization or death by 70% (1.2 g of casirivimab and imdevimab) or 71% (2.4 g of casirivimab and imdevimab). [76] Randomized, controlled, open-label, phase 3 trial with a casirivimab and imdevimab arm is evaluating the combined use of these mAbs (single IV infusion containing 4 g each of casirivimab and imdevimab) with standard of care vs standard of care alone for **treatment** in **hospitalized** COVID-19 pts ≥12 years of age **(NCT04381936; RECOVERY)**. [26, 38]		of COVID-19 in such pts outweigh the known and potential risks. [64] **Casirivimab and Imdevimab (REGN10933 and REGN10987):** **FDA issued an Emergency Use Authorization (EUA) for casirivimab and imdevimab on November 21, 2020 that permits** combined use of these drugs for the **treatment** of **mild to moderate COVID-19** in adults and pediatric pts ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing **who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization**. FDA states that, based on a review of phase 1/2 data from an ongoing randomized, double-blind, placebo-controlled, phase 1/2/3 trial of casirivimab and imdevimab in outpatients with mild to moderate COVID-19 (NCT04425629), it is reasonable to believe that casirivimab and imdevimab administered together may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization and, when used under the conditions of the EUA, the known and potential benefits of casirivimab and imdevimab for treatment of COVID-19 in such pts outweigh the known and potential risks. [48, 49] **The EUAs for currently available SARS-CoV-2-specific mAbs define pts at high risk for progressing to severe COVID-19 and/or hospitalization** as those who meet at least one of the following criteria: BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressive treatment; ≥65 years of age; ≥55 years of age with cardiovascular disease or hypertension or COPD or other chronic respiratory disease; 12-17 years of age with BMI ≥85th percentile for their age and gender based on CDC growth charts, sickle cell

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		studies demonstrated that both have neutralizing activity against SARS-CoV-2 in Vero E6 cells and protective effects against the virus in an animal model; STI-2020 is an affinity-matured version of STI-1499 and has greater in vitro potency than STI-1499. [17, 18] Note that various recombinant humanized monoclonal antibodies that target key immunologic and inflammatory mediators (e.g., complement, granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-6 [IL-6]) but do **not** target the SARS-CoV-2 virus are being investigated for the treatment of COVID-19. [7, 8] (See Sarilumab, Siltuximab, and Tocilizumab in this Evidence Table.)	Randomized, double-blind, placebo-controlled, phase 3 trial sponsored by the manufacturer (Regeneron) is evaluating safety, tolerability, and efficacy of a single sub-Q dose of casirivimab and imdevimab for **prevention** of SARS-CoV-2 infection in healthy, **asymptomatic, household contacts** of individuals infected with SARS-CoV-2 **(NCT04452318)**. Initial study protocol only included adults; protocol was modified to include adults and adolescents ≥12 years of age weighing ≥40 kg. [24] The manufacturer announced preliminary results of this study (not peer reviewed) indicating that a single dose of 1.2 g of casirivimab and imdevimab administered sub-Q to uninfected household contacts reduced the risk of symptomatic SARS-CoV-2 infection by 72% during the first week and by 81% through day 29 compared with placebo. [77] **Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016):** Randomized, placebo-controlled, double-blind, sponsor-unblinded, single ascending dose, phase 1 study sponsored by the manufacturer (Eli Lilly) evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of an IV dose of **bamlanivimab** in **hospitalized** adults with COVID-19. Study completed; results not yet published **(NCT04411628)**. [9] Randomized, placebo-controlled, phase 1 study sponsored by the manufacturer (Eli Lilly) evaluated safety, tolerability, pharmacokinetics, and immunogenicity of an IV dose of **etesevimab**) in *healthy* adults. Study completed; results not yet published **(NCT04441931)**. [33] Randomized, double-blind, placebo-controlled phase 2/3 study is evaluating efficacy and safety of **bamlanivimab used alone or with etesevimab** for early **treatment** of COVID-19 in adults and adolescents ≥12 years of age who are **outpatients** with mild to moderate disease **(NCT04427501; BLAZE-1)**. [10] Results of a preplanned interim analysis of the 3 bamlanivimab monotherapy arms (single IV dose of 700 mg, 2.8 g, or 7 g) of the phase 2		disease, congenital or acquired heart disease, neurodevelopmental disorder such as cerebral palsy, medical-related technological dependence such as tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19, or asthma or reactive airway or other chronic respiratory disease that requires daily medication for control. [43, 49, 65] **The EUAs for currently available SARS-CoV-2-specific mAbs state that these drugs are not authorized for use in pts who are hospitalized due to COVID-19**, require oxygen therapy due to COVID-19, or are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and require an increase in baseline oxygen flow rate due to COVID-19. [48, 49, 64, 65] Benefits have not been observed when used in hospitalized pts; SARS-CoV-2-specific mAbs may be associated with worse clinical outcomes when administered to hospitalized COVID-19 pts requiring high flow oxygen or mechanical ventilation. [49, 65] **If a patient is hospitalized for reasons other than COVID-19** (e.g., an elective orthopedic procedure) and reports mild to moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, FDA states that treatment with a SARS-CoV-2-specific mAb available under an EUA may be appropriate if the patient is also at high risk for progressing to severe COVID-19 and/or hospitalization for COVID-19 and terms and conditions of the EUA are met. [56, 67, 69] **The EUAs for currently available SARS-CoV-2-specific mAbs require** that the dosage of these drugs recommended in their respective EUAs be administered via IV infusion by a healthcare provider in an **outpatient setting** where there is immediate access to medications to treat a severe infusion reaction such as anaphylaxis and ability to activate the emergency medical system (EMS) as necessary. The EUAs also require that healthcare facilities and healthcare providers administering bamlanivimab,

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			portion of this ongoing study have been published. At the time of the interim analysis, data were available for 452 outpatients ≥18 years of age with mild or moderate COVID-19 (309 pts randomized to bamlanivimab and 143 randomized to placebo). Based on the primary outcome (change in SARS-CoV-2 viral load from baseline to day 11 assessed by RT-PCR of nasopharyngeal swabs), only the 2.8-g dose group had lower viral load than the placebo group; decreased viral load at day 11 did not appear to be a clinically meaningful end point since viral load was substantially reduced from baseline for the majority of pts, including those in the placebo group. [39] A final analysis of data for 309 adults randomized to the 3 bamlanivimab monotherapy arms, 112 adults randomized to the bamlanivimab and etesevimab combination arm (single IV infusion containing 2.8 g of each mAb), and 156 adults randomized to placebo have now been published. **There was a statistically significant difference in change in SARS-CoV-2 viral load from baseline to day 11 in the bamlanivimab and etesevimab group compared with placebo; however, the change in viral load in each of the 3 bamlanivimab monotherapy dosage groups was not significantly different compared with placebo.** At day 29, the proportion of pts with hospitalizations or emergency department visits related to COVID-19 was 1-2% in the bamlanivimab monotherapy groups, 0.9% in the bamlanivimab and etesevimab group, and 5.8% in the placebo group. [61] Randomized, double-blind, placebo-controlled phase 2 study evaluating various mAb regimens for **treatment** of mild to moderate COVID-19 in **outpatients** (NCT04634409; BLAZE-4): Certain treatment arms evaluated **bamlanivimab with etesevimab**. Pts were randomized to receive a single IV infusion of bamlanivimab 700 mg and etesevimab 1.4 g (158 patients), bamlanivimab 2.8 g and etesevimab 2.8 g (101 patients), bamlanivimab 700 mg alone (103 patients), or placebo (153 patients). The primary end point was the proportion of pts with SARS-CoV-2 viral load by cycle threshold (CT) greater than 5.27 on		bamlanivimab and etesevimab, or casirivimab and imdevimab comply with **certain mandatory record keeping and reporting requirements** (including adverse event reporting to FDA MedWatch). [48, 49, 64, 65] **The EUAs for the SARS-CoV-2-specific mAbs were each reissued to require that manufacturers establish a process for monitoring genomic databases for emergence of global viral variants of SARS-CoV-2 and, if requested by FDA, assess activity of the drugs against any global SARS-CoV-2 variants of interest.** [48, 64] The EUA fact sheets for healthcare providers for each currently available mAb includes information on specific variants and resistance. [49, 65] Information on SARS-CoV-2 viral variants circulating in the US collected through CDC's national genomic surveillance program is available at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html and may help guide treatment decisions. [73, 74] **Allocation of currently available SARS-CoV-2-specific mAbs for use under their respective EUAs** is being directed by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) in collaboration with state and territorial health departments and the manufacturers. Healthcare providers should contact the authorized US distributor (AmerisourceBergen) to obtain these mAbs. [46, 51, 70] Information on specific locations in the US administering the drugs may be available at the HHS protect public data hub (https://protect-public.hhs.gov/pages/therapeutics-distribution) or National Infusion Center Association (NICA) website (https://covid.infusioncenter.orgw. [56, 67, 69] **Bamlanivimab and Etesevimab: For additional information about the EUA,** consult the bamlanivimab and etesevimab EUA letter of authorization, [64] EUA fact sheet for healthcare providers, [65] and EUA fact sheet for patients, parents and caregivers. [66]

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			day 7. Initial results indicate **the two different dosage regimens of bamlanivimab and etesevimab result in similar virologic outcomes.** Day 7 data (range 7-9 days) indicate that 31% of the placebo group still had viral load by CT greater than 5.27 compared with 14% of the group treated with bamlanivimab 700 mg and etesevimab 1.4 g and 10% of the group treated with bamlanivimab 2.8 g and etesevimab 2.8 g. [65] Randomized, double-blind, placebo-controlled phase 3 trial initiated by the manufacturer (Eli Lilly) in collaboration with NIAID is evaluating efficacy and safety of **bamlanivimab used alone or with etesevimab** for **prevention** of SARS-CoV-2 infection in adult residents and staff of skilled nursing or assisted living facilities **(NCT04497987; BLAZE-2)**. [11] The manufacturer (Eli Lilly) announced results of data analyses for 965 study participants who tested negative for SARS-CoV-2 at baseline (299 residents and 666 staff) and were randomized to receive prophylaxis with **bamlanivimab** (4.2 g as a single dose) or placebo. At 8 weeks of follow-up, there was a significantly lower frequency of symptomatic COVID-19 (the primary end point) overall in the bamlanivimab group vs the placebo group (odds ratio 0.43). Subgroup analyses for the 299 residents also indicated a significantly lower frequency of symptomatic COVID-19 in the bamlanivimab group vs the placebo group (odds ratio 0.20); there were 4 deaths attributed to COVID-19 in the residents and all occurred in the placebo group. [62] **Multicenter, adaptive, randomized, placebo-controlled, phase 3 trial evaluating safety and efficacy of various therapeutics for hospitalized pts with COVID-19 sponsored by NIAID (NCT04501978; TICO; ACTIV-3):** Trial included a treatment arm to evaluate **bamlanivimab** with standard of care vs placebo with standard of care in **hospitalized** adults. [40, 41] NIAID announced that the bamlanivimab treatment arm was terminated following a recommendation from the independent data and safety monitoring board (DSMB) based on low likelihood of clinical benefit in hospitalized pts. [41] Data for the 314 enrolled pts		**Casirivimab and Imdevimab: For additional information about the EUA**, consult the casirivimab and imdevimab EUA letter of authorization, [48] EUA fact sheet for healthcare providers, [49] and EUA fact sheet for patients, parents and caregivers. [50] **NIH COVID-19 Treatment Guidelines Panel** states that, based on data available to date, use of **bamlanivimab and etesevimab *or* casirivimab and imdevimab is recommended** for treatment of **outpatients with mild to moderate COVID-19 who are at high risk of clinical progression** as defined by the EUA criteria. These experts state that SARS-CoV-2-specific mAb treatment should be given as soon as possible after COVID-19 diagnosis is confirmed by positive SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days after symptom onset. The panel **recommends against** use of SARS-CoV-2-specific mAbs in pts **hospitalized because of COVID-19, except in a clinical trial**; however, such treatment should be considered in those with mild to moderate COVID-19 who are hospitalized for reasons other than COVID-19 but who otherwise meet the EUA criteria. Although data are not available regarding the comparative efficacy and safety of bamlanivimab and etesevimab vs casirivimab and imdevimab and it is not known whether in vitro susceptibility data correlate with clinical outcomes, some panel members would preferentially use casirivimab and imdevimab in regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab and etesevimab are common. [57] **IDSA suggests** use of bamlanivimab and etesevimab or casirivimab and imdevimab rather than no SARS-CoV-2-specific mAb treatment **in outpatients with mild to moderate COVID-19 at high risk for progression** to severe disease since expected benefits likely outweigh any potential harms. These experts state that susceptibility of local

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			included in the prespecified interim futility assessment have been published. Enrolled pts were hospitalized with documented SARS-CoV-2 infection (duration of symptoms ≤12 days, no end-organ failure at baseline) and randomized 1:1 to receive bamlanivimab (163 pts) or placebo (151 pts). Pts also received remdesivir (95% of pts), corticosteroids (49% of pts), and supplemental oxygen when indicated. The futility assessment evaluated pulmonary function on day 5 based on a 7-category ordinal scale and indicated that **a single IV infusion of bamlanivimab did not result in better clinical outcomes at day 5 compared with placebo**. The odds ratio of being in a more favorable category in the bamlanivimab group compared with the placebo group was 0.85 (95% CI, 0.56 to 1.29; P = 0.45). Among 167 pts who were followed for at least 28 days or died within 28 days, 82 or 79% in the bamlanivimab or placebo group, respectively, had sustained recovery (rate ratio 1.06).The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar in the bamlanivimab and placebo group (19% and 14%, respectively). [59] **VIR-7831 (GSK4182136):** Manufacturer (Vir Biotechnology) in collaboration with GlaxoSmithKline initiated a randomized, double-blind, placebo- controlled, phase 2/phase 3 trial to assess safety, tolerability, efficacy, and pharmacokinetics of a single IV dose of VIR-7831 for **treatment** of mild or moderate COVID-19 in **outpatients** at high risk of disease progression **(NCT04545060; COMET-ICE)**. [14, 15] The manufacturers announced that interim results of the ongoing **phase 3 portion** of this study (not peer reviewed) indicate that a single IV dose of VIR-7831 (500 mg) reduced the risk of hospitalization or death by 85% compared with placebo. [78] Randomized, double-blind, placebo-controlled phase 2 study evaluating various mAb regimens for **treatment** in adult **outpatients** with mild to moderate COVID-19		SARS-CoV-2 variants may be considered when choosing the most appropriate SARS-CoV-2-specific mAb treatment. [68] **Pregnant women:** NIH panel states that **currently available SARS-CoV-2-specific mAbs** should not be withheld from a pregnant woman who has a condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefits outweigh potential risks. [57]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			(NCT04634409; BLAZE-4): One treatment arm is evaluating a regimen of **bamlanivimab with VIR-7831** (SARS-CoV-2-specific mAbs that bind to different regions of the S protein of SARS-CoV-2). [72, 75] The primary outcome measure is the percentage of pts with SARS-CoV-2 viral load >5.27 on day 7. The manufacturers (Lilly, VIR Biotechnology, and GlaxoSmithKline) announced that preliminary data (not peer reviewed) indicate that a single-dose regimen of IV bamlanivimab (700 mg) and VIR-7831 (500 mg) met the primary end point. The combined regimen resulted in a 70% relative reduction in persistently high viral load (>5.27; CT <27.5) at day 7 compared with placebo. In addition, the combined regimen resulted in a statistically significant reduction in the key virologic secondary end point (i.e., mean change in viral load from baseline to days 3, 5, and 7) compared with placebo. By day 29, there were no COVID-19-related hospitalizations or fatalities in either the bamlanivimab and VIR-7831 group or the placebo group. [75] **AZD7442:** Double-blind, placebo-controlled, phase 1 trial initiated by the manufacturer (AstraZeneca) to evaluate safety, tolerability, and pharmacokinetics of IV and IM doses of AZD-7442 in *healthy* adults **(NCT04507256)**. [19] Randomized, double-blind, placebo-controlled, phase 3 trial initiated by the manufacturer (AstraZeneca) to evaluate safety and efficacy of a single IM dose of AZD7442 for **treatment** of mild to moderate COVID-19 in **outpatient** adults **(NCT04723394; TACKLE)**. [71] Adaptive platform, randomized, placebo-controlled, phase 2/3 trial evaluating various drugs for the **treatment** of COVID-19 in **outpatients** includes a treatment arm to evaluate AZD7442 in such pts (**NCT04518410; ACTIV-2**). [47] Randomized, double-blind, placebo-controlled, phase 3 trials initiated by the manufacturer (AstraZeneca) to evaluate safety and efficacy of a single IM dose of		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			AZD7442 for **preexposure prophylaxis** (NCT04625725; PROVENT) or **postexposure prophylaxis** (NCT04625972; STORM CHASER) of SARS-CoV-2 infection in adults. [54, 55] **COVI-AMG (STI-2020):** Manufacturer (Sorrento Therapeutics) initiated a randomized, double-blind, placebo-controlled, phase 1/phase 2 study to evaluate safety and efficacy of single 40-, 100-, and 200-mg IV doses of COVI-AMG for **treatment** of COVID-19 in adult **outpatients (NCT04738175)**. [79] Manufacturer (Sorrento Therapeutics) initiated a randomized, double-blind, placebo-controlled, phase 2 study to evaluate safety and efficacy of single 100- and 200-mg IV doses of COVI-AMG for **treatment** in adults **hospitalized** with COVID-19 **(NCT04771351)**. [79]		
Umifenovir (Arbidol®) *Updated 1/14/21*	8:18.92 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [4] Although data limited, in vitro activity against SARS-CoV-1 [4] and SARS-CoV-2 [5] reported Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza [4]	Limited data do not suggest benefit in pts with COVID-19. Meta-analysis of 10 retrospective and 2 prospective, randomized controlled studies conducted in China (total of 1052 adults with laboratory-confirmed COVID-19; high heterogeneity) suggested that treatment with umifenovir was **not** associated with benefit in pts with COVID-19, as assessed by time to negative RT-PCR conversion, rate of negative RT-PCR on day 7, rate of fever or cough alleviation on day 7, hospital length of stay, or a composite endpoint of admission to intensive care unit, need for mechanical ventilation, or death, in studies that measured these endpoints. An increased rate of negative RT-PCR on day 14 was noted. [13] **Retrospective cohort study** in 50 adults with COVID-19 in China suggests better viral suppression with umifenovir vs LPV/RTV. All pts received conventional therapy, including interferon α-2b. At 7 days after hospital admission, SARS-CoV-2 was undetectable in 50% of pts treated with umifenovir vs 23.5% treated with LPV-RTV; at 14 days, viral load undetectable in all pts treated with umifenovir vs 44.1% treated with LPV/RTV. Duration of positive SARS-CoV-2 RNA positive test was shorter with umifenovir vs LPV-RTV [8]	**Dosage recommended for treatment of COVID-19 in China:** Adults, 200 mg orally 3 times daily for up to 10 days [5, 7] **Dosage used in COVID-19 clinical trials:** 200 mg orally 3 times daily for duration of 7-10 days or longer [2, 3, 6, 8] **Dosage recommended for treatment of COVID-19 in Russia:** 200 mg orally every 6 hours for 5 days [11]	Not commercially available in the US Has been included in COVID-19 treatment guidelines used in some other countries (e.g., China, Russia) [7, 11, 12] Efficacy for the treatment of COVID-19 not established

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Retrospective cohort study in 33 adults with COVID-19 in China suggests more favorable outcome with LPV/RTV plus umifenovir vs LPV/RTV alone: Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 12/16 pts (75%) treated with LPV/RTV plus umifenovir vs 6/17 pts (35%) treated with LPV/RTV alone; at 14 days, undetectable in 15/16 pts (94%) treated with both drugs vs 9/17 pts (53%) treated with LPV/RTV alone. At 7 days, chest CT scans were improving in 11/16 pts (69%) treated with both drugs vs 5/17 pts (29%) treated with LPV/RTV alone [1] **Retrospective cohort study** in 81 hospitalized, non-ICU adults with COVID-19 in China found *no difference* in clearance of SARS-CoV-2 virus between pts receiving umifenovir vs those who did not. At 7 days, SARS-CoV-2 undetectable in pharyngeal specimens in 33/45 pts (73.3%) treated with umifenovir vs 28/36 pts (77.8%) who did not receive umifenovir. No difference in median time from onset of symptoms to negative SARS-CoV-2 test (18 vs 16 days) [9] **Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 in China (ChiCTR200030254): When favipiravir was compared with umifenovir, clinical recovery rate was greater in those treated with favipiravir than in those treated with umifenovir. [6] (See Favipiravir in this Evidence Table.) **Randomized, single-center, partially blinded trial in China (NCT0425885)** evaluated efficacy of umifenovir in conjunction with standard care vs LPV/RTV in conjunction with standard care vs standard care without an antiviral in hospitalized adults with mild/moderate COVID-19. [2, 10] Data for the 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]		

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Anakinra (Kineret®) *Updated 4/15/21*	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]	There are case study data but no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19 [7] **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 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	Various dosage regimens are being studied [3, 8] Some studies under way in Europe are evaluating 100 mg given subcutaneously once to 4 times daily for 7 to 28 days 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
			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] **Various clinical trials evaluating anakinra alone or in conjunction with other drugs for treatment of COVID-19** are registered at clinicaltrials.gov. [3]		
Ascorbic acid *Updated 3/11/21*	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:** Open-label, randomized, nonblinded, controlled trial in 60 hospitalized adults with laboratory-confirmed or suspected severe COVID-19 (with manifestations of ARDS or myocarditis and SpO_2 <93%): Treatment with ascorbic acid (1.5 g IV every 6 hours for 5 days) plus standard care (daily regimen of lopinavir/ritonavir plus single hydroxychloroquine dose upon hospitalization) **failed to improve outcomes** compared with standard care alone. Body temperature and SpO_2 at discharge, length of ICU stay, and mortality rate were not significantly different between the treatment groups. Median hospital stay was longer in the ascorbic acid group compared with the control group (8.5 vs 6.5 days). Patients receiving ascorbic acid had lower mean	**IV ascorbic acid:** Various dosages of IV ascorbic acid used in COVID-19 studies. [1] In one study, ascorbic acid 1.5 g IV every 6 hours for 5 days failed to improve outcomes. [18] Various dosages of IV ascorbic acid used in sepsis studies; 50 mg/kg every 6 hours for 4 days used in CITRIS-ALI study; 50 mg/kg (maximum 3 g) every 12 hours for 48 hours used in ATESS study; 1.5 g every 6 hours used in VITAMINS, HYVCTTSSS, ACTS, and ORANGES studies, but treatment duration varied by study. [4, 8-10, 13-16]	Efficacy for the treatment of COVID-19 not established. NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of ascorbic acid for the treatment of COVID-19 in **critically ill patients**. The panel states that there are no completed controlled trials of ascorbic acid in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of ascorbic acid in patients with sepsis or ARDS have shown variable efficacy and few safety concerns. [12] NIH COVID-19 Treatment Guidelines Panel also states that there are insufficient data to recommend either for

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			body temperature on admission and on day 3 and higher mean SpO_2 on day 3. [18] 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 (including NCT04401150 [LOVIT-COVID]) are registered at clinicaltrials.gov. [1] **Oral ascorbic acid:** Randomized, open-label study (NCT04342728; COVID A to Z) in an outpatient setting in 214 adults with confirmed SARS-CoV-2 infection: A 10-day oral regimen of ascorbic acid (8 g daily given in 2 or 3 divided doses with meals), zinc gluconate (50 mg at bedtime), or both supplements in combination **failed to reduce the time required to achieve a 50% reduction in symptom severity** compared with usual care alone. The mean number of days from peak symptom score to 50% resolution of symptoms (including fever/chills, cough, shortness of breath, and fatigue, each rated on a 4-point scale) was 5.5 days with ascorbic acid, 5.9 days with zinc, 5.5 days with ascorbic acid and zinc, or 6.7 days with usual care alone. Target enrollment was 520 patients; **the study was stopped early for futility**. [17] Other clinical trials of outpatient oral ascorbic acid treatment are registered at clinicaltrials.gov. [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 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.[8] However, primary end	**Oral ascorbic acid:** NCT04342728 (COVID A to Z): Oral ascorbic acid dosage of 8 g daily, given in 2 or 3 divided doses, did not reduce duration of symptoms in outpatients. [17] NCT04395768 (outpatients): Ascorbic acid 1 g orally 3 times daily for 7 days following initial 200-mg/kg IV dose. [1] **Laboratory test interference:** May interfere with laboratory tests based on oxidation-reduction reactions (e.g., blood and urine glucose testing, nitrite and bilirubin concentrations, leukocyte counts). [11] High circulating vitamin C concentrations may affect accuracy of point-of-care glucometers. [12] Manufacturer states to delay oxidation-reduction reaction-based tests until 24 hours after infusion, if possible. [11] **Sodium content:** May be substantial with high-dose IV therapy (e.g., each mL of ascorbic acid 500-mg/mL injection provides 65 mg of sodium). [11] **Oxalate nephrolithiasis:** Potential for prolonged, high-dose IV therapy to increase risk of oxalate nephrolithiasis or nephropathy. [11, 14]	or against use of ascorbic acid for the treatment of COVID-19 in **noncritically ill patients**. The panel states that the role of ascorbic acid in this setting is unknown since patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation. [12]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			points not improved in CITRIS-ALI study (NCT02106975) in patients with sepsis and ARDS, HYVCTTSSS study (NCT03258684) in patients with sepsis or septic shock, or VITAMINS study (NCT03333278), ACTS study (NCT03389555), or ATESS study in patients with septic shock; one primary end point (resolution of shock [i.e., discontinuance of vasopressor support]) was improved but other primary end point (change in SOFA score) was not improved in ORANGES study (NCT03422159) in patients with sepsis or septic shock; variable findings reported with respect to certain primary or secondary outcomes. [9, 10, 13-16] Additional studies under way. [4, 6] 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]		
Azithromycin *Updated 3/11/21*	8:12.12 Macrolides	Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) [1, 3-5, 35] Some evidence of in vitro activity against SARS-CoV-2 in infected Vero E6 and Caco-2 cells; clinical importance unclear [36] 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, 35] 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	**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]	**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 or 500 mg once daily for 7 days has been used in conjunction with a 5-, 7-, or 10-day regimen of hydroxychloroquine [7, 18, 19, 23, 24, 29, 37]	Only limited information available regarding the frequency and microbiology of bacterial pulmonary coinfections or superinfections in pts with COVID-19. Empiric coverage for bacterial pathogens has been used, but is not required in all pts with confirmed COVID-19-related pneumonia. If bacterial pneumonia or sepsis is strongly suspected or confirmed, empiric antibacterial treatment should be administered. [21, 32] Although data are limited, bacterial pathogens in COVID-19 pts with community-acquired pneumonia (CAP) are likely the same as those seen in other pts with CAP. Therefore, if antibacterial coverage for CAP is indicated in COVID-19 pts, the usually recommended regimens for empiric treatment of CAP should be used. [32] Antimicrobial stewardship policies should be used to guide appropriate use of antibacterials in COVID-19 pts; such drugs should be discontinued if bacterial infection is not confirmed. [21]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]	**Clinical experience in pts with COVID-19:** Has been used for antibacterial coverage in hospitalized pts with COVID-19 [15] **Use in conjunction with hydroxychloroquine in pts with COVID-19:** Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), [7] open-label uncontrolled study in France (11 pts), [18] uncontrolled observational study in France (80 pts),[19] and larger uncontrolled observational study in France (1061 pts).[23] Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.) **Use in conjunction with hydroxychloroquine in hospitalized pts with COVID-19:** Data from 2 retrospective studies that analyzed outcome data for hospitalized pts in New York treated with hydroxychloroquine with or without azithromycin indicate that use of the 4-aminoquinoline antimalarial with or without azithromycin is **not** associated with decreased in-hospital mortality. [30, 31] (See Hydroxychloroquine in this Evidence Table.) **Open-label, randomized, multicenter trial in adults hospitalized with severe COVID-19 in Brazil (NCT04321278; COALITION II):** Patients were randomized 1:1 to receive oral azithromycin (500 mg once daily for 10 days) plus standard of care (n=214) or standard of care (control group; n=183). All pts received oral hydroxychloroquine (400 mg twice daily for 10 days) as part of standard of care; concomitant use of corticosteroids, other immunomodulators, antibiotics (no macrolides), and antivirals was allowed. Inclusion criteria required at least one severity criterion (use of oxygen supplementation at more than 4 L/minute, high-flow nasal cannula, noninvasive positive-pressure ventilation, or mechanical ventilation). Exclusion criteria included history of severe ventricular cardiac arrhythmia or QT_c ≥480 msec in any ECG performed before randomization. The primary outcome		Data from various randomized, controlled clinical trials and retrospective studies have not shown evidence of clinical benefit when azithromycin was used alone or in conjunction with hydroxychloroquine for the treatment of COVID-19 in hospitalized pts; [21, 22, 30, 31, 34, 37, 38] there are data indicating that combined use of azithromycin and chloroquine or hydroxychloroquine may be associated with an increased risk of adverse cardiac effects. [21, 22, 33] (See Hydroxychloroquine in this Evidence Table.) NIH COVID-19 Treatment Guidelines Panel **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in hospitalized pts and **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in nonhospitalized pts, except in the context of a clinical trial. [21] IDSA **recommends against** use of a combined regimen of hydroxychloroquine (or chloroquine) and azithromycin for the treatment of COVID-19 in hospitalized pts. [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, 33] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			was clinical status at day 15 based on a 6-level ordinal scale that ranged from not hospitalized (1) to death (6); the key secondary outcome was mortality at day 29. Results for the modified intention-to-treat (mITT) population (i.e., those with confirmed COVID-19) indicated that **addition of azithromycin to standard of care was not superior to standard of care alone**. At day 15, there was no difference in the proportional odds of being in higher categories on the 6-point ordinal scale between the azithromycin group and control group. At day 29, 42% of pts in the azithromycin group and 40% of those in the control group had died. There also was no difference between the groups in the proportion of pts with QT_c interval prolongation (20% in azithromycin group and 21% in control group). [34] **Azithromycin in randomized, controlled, open-label, adaptive, platform trial (NCT04381936; RECOVERY):** This study is enrolling pts with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the azithromycin arm (now terminated), 2582 pts were randomized to receive azithromycin (500 mg by mouth, NG tube, or IV once daily for 10 days or until discharge, whichever came first) plus standard of care and 5181 pts were randomized to standard of care alone. The primary outcome was all-cause mortality at day 28. **Results of this study indicated that azithromycin is not an effective treatment for pts hospitalized with COVID-19.** There was no difference in the 28-day mortality rate between the azithromycin plus standard of care group and the standard of care alone group (22% in both groups). In addition, the time to hospital discharge was similar (median 10 days in the azithromycin group and 11 days in the standard of care alone group) and, in those not requiring mechanical ventilation at baseline, azithromycin did not decrease the risk of progression to mechanical ventilation or death (25% in azithromycin group vs 26% in standard of care alone group). Results were consistent across all prespecified pt subgroups (age; sex; ethnicity; and symptom duration, level of respiratory support, and		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). [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, 33] (See Hydroxychloroquine in this Evidence Table.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			use of corticosteroids at time of randomization). [38] **Azithromycin in randomized, controlled, open-label, adaptive, platform trial in the UK (PRINCIPLE):** Adult outpatients with PCR-confirmed or suspected COVID-19 and ongoing symptoms for ≤14 days who were considered at increased risk of adverse outcomes (i.e., ≥65 years of age or ≥50 years of age with at least one comorbidity) were randomly assigned to various interventions with usual care or usual care alone. Patients randomized to the azithromycin intervention arm received oral azithromycin (500 mg once daily for 3 days) with usual care, and results were compared with those for pts randomized to usual care alone. The two coprimary end points were time to first self-reported recovery and COVID-19-related hospital admission or death (both end points measured within 28 days after randomization). **Results of this study indicated that use of azithromycin in symptomatic outpatients with known or suspected COVID-19 did not provide benefits in terms of reducing time to recovery or risk of hospitalization.** A Bayesian primary analysis for 500 pts treated with azithromycin and usual care and 823 pts treated with usual care alone indicated that 80% of those who received azithromycin and 77% of those who received usual care alone reported feeling recovered within 28 days (median time to first reported recovery was 7 and 8 days, respectively); 3% of pts in each group were hospitalized within 28 days; there were no deaths in either group. **Enrollment in the azithromycin arm of the study was terminated when analyses indicated the prespecified criterion for futility was met.** [39] **Various clinical trials evaluating azithromycin alone or in conjunction with other drugs for treatment of COVID-19** are registered at clinicaltrials.gov. [29]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Baricitinib (Olumiant®) *Updated 2/25/21*	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]	There is some clinical trial evidence that baricitinib may be beneficial in the treatment of patients with COVID-19 [11, 13, 18, 19, 24] 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] **Phase 3 adaptive, randomized, double-blind trial compared a regimen of remdesivir alone vs a regimen of remdesivir with baricitinib** in hospitalized adults (**NCT04401579; ACTT-2**): Inclusion criteria included laboratory-confirmed SARS-CoV-2 infection with at least one of the following: radiographic infiltrates by imaging, SpO_2 ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO. Patients were randomized 1:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily for a total treatment duration of 10 days or until hospital discharge) with either baricitinib (4 mg orally once daily for 14 days or until hospital discharge) with either baricitinib (4 mg orally or through a nasogastric tube once daily for 14 days or until hospital discharge) or placebo. [17, 19, 24] The primary end point was time to recovery through day 29 (defined as discharged without limitations on activities, discharged with limitations on activities and/or requiring home oxygen, or still hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care). Data for 1033 patients in the intent-to-treat population (515 in the remdesivir and baricitinib group and 518 in the remdesivir alone group) indicate that those who received the combined regimen were more likely to have better clinical outcomes than those who received remdesivir alone. Use of the combined regimen of remdesivir and baricitinib met the primary end point of reduced time to	Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1 [1, 2, 5] Optimal dosage and duration for treatment of COVID-19 not known (see Trials or Clinical Experience) **Emergency use authorization (EUA) baricitinib dosage for use in combination with remdesivir for treatment of COVID-19 in hospitalized adults and pediatric patients ≥9 years of age:** 4 mg orally once daily for 14 days or until hospital discharge, whichever comes first. For **pediatric patients 2 to <9 years of age**, 2 mg orally once daily for 14 days or until hospital discharge, whichever comes first. Not authorized for pediatric patients <2 years of age. Dosage adjustment is necessary for laboratory abnormalities, including renal and hepatic impairment. Consult the baricitinib EUA fact sheet for healthcare providers for additional dosage adjustment information. [19] NIH COVID-19 Treatment Guidelines Panel states that there are limited data on concurrent use of baricitinib and potent OAT3 inhibitors and that such combined use is generally not recommended. [11] If baricitinib and potent OAT3 inhibitors are used in combination, the EUA and NIH Panel recommend adjustment of baricitinib dosage. [11, 19]	**Emergency use authorization (EUA) for baricitinib in combination with remdesivir:** FDA issued an EUA on November 19, 2020 that permits use of baricitinib in combination with remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). FDA states that, based on review of data from a randomized, double-blind, placebo-controlled trial comparing baricitinib in combination with remdesivir to remdesivir alone (NCT04401579; ACTT-2), baricitinib data that were reviewed for the FDA-approved indication of rheumatoid arthritis, and data from populations studied for other indications (including pediatric patients), it is reasonable to believe that baricitinib may be effective in combination with remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in the patient population specified in the baricitinib EUA and, when used under the conditions described in the EUA, the known and potential benefits of baricitinib when used to treat COVID-19 in such patients outweigh the known and potential risks. [18] Consult the baricitinib EUA letter of authorization, [18] EUA fact sheet for healthcare providers, [19] and EUA fact sheet for patients, parents and caregivers [20] for additional information. **NIH COVID-19 Treatment Guidelines Panel** states that data are insufficient to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients when corticosteroids can be used. In rare circumstances when corticosteroids cannot be used, the panel recommends use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation. (See Remdesivir in this Evidence Table.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			recovery compared with use of remdesivir alone (median time to recovery was 7 days in those receiving the combined regimen vs 8 days in those receiving remdesivir). Patients treated with combined remdesivir and baricitinib were also more likely to have a better clinical status at day 15 compared with those receiving remdesivir alone. The proportion of patients who progressed to ventilation (noninvasive or invasive) by day 29 was lower in patients receiving combined remdesivir and baricitinib. In addition, the mortality rate at day 29 was 4.7% in those treated with the combined regimen and 7.1% in those treated with remdesivir alone.[19, 24] Based on results of this trial and other data, FDA issued an emergency use authorization (EUA) for baricitinib that permits use of the drug in combination with remdesivir. [18] **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] **Various clinical trials evaluating baricitinib alone or in conjunction with other drugs for treatment of COVID-19** are registered at clinicaltrials.gov. [25]		The panel **recommends against** the use of baricitinib without remdesivir, except in a clinical trial. The panel states that there are insufficient data to recommend either for or against use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both baricitinib and corticosteroids are potent immunosuppressants, there is potentially an additive risk of infection. [11] **NIH COVID-19 Treatment Guidelines Panel** states that use of baricitinib is not recommended in patients with hepatic or renal impairment (GFR <60 mL/min/1.73 m^2) (see Dosage). [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, 19]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Colchicine *Updated 4/30/21*	92:16 Antigout Agents	Exerts broad anti-inflammatory and immunomodulatory effects through multiple mechanisms, including inhibition of NOD-like receptor protein 3 (NLRP3) inflammasome assembly and disruption of cytoskeletal functions through inhibition of microtubule polymerization [2,3,5,6] May combat the hyperinflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines [2] NLRP3 inflammasome 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, 19] 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]	Limited anecdotal experience and clinical trial data reported to date in COVID-19; results pending from multiple clinical trials. [2, 4, 16, 17, 24] On March 5, 2021, researchers announced that enrollment into the colchicine arm of the RECOVERY trial had been halted on the advice of the data monitoring committee (DMC) when a preliminary analysis revealed no difference in mortality between hospitalized patients receiving colchicine for treatment of COVID-19 and those receiving usual care alone; full data are not available yet, but the researchers stated that the DMC found no convincing evidence that further recruitment would provide conclusive proof of worthwhile mortality benefit overall or in any prespecified subgroup. [26, 27] **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] **Hospitalized Patients:** Several **single-center, proof-of-concept or small comparative cohort studies** conducted in hospitalized patients with COVID-19 suggest beneficial effects of colchicine on mortality and other clinical outcomes; [20-22] in one observational study (not peer reviewed), mortality rate in patients with COVID-19 pneumonia was numerically lower in those receiving colchicine compared with those not receiving the drug, but the effect of the drug was not statistically significant; 80% of patients in the study received corticosteroids. [23] The studies had substantial limitations, and larger well-designed studies are needed to further evaluate efficacy. [20-23] **Open-label, randomized, 16-hospital clinical trial (NCT04326790, GRECCO-19) in hospitalized adults with RT-PCR-confirmed**	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 another ongoing trial: Colchicine 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose is 1 mg if body weight ≥80 kg); dosage is reduced for renal impairment. [18] Dosage in NCT04322682 (COLCORONA): Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days [1, 24] Other studies are evaluating various colchicine dosages and durations for treatment of COVID-19 [2] Consider possible need for colchicine dosage adjustment; [2] manufacturer-recommended dosages for labeled indications depend on patient's age, renal and hepatic function, and concomitant use of interacting drugs, including protease inhibitors (e.g., lopinavir/ritonavir), other moderate or potent CYP3A4 inhibitors, and P-glycoprotein (P-gp) inhibitors [5] Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated [5]	Safety and efficacy for treatment of COVID-19 not established The potential for toxic doses of colchicine to affect alveolar type II pneumocytes (which may inhibit surfactant release and contribute to ARDS) and increase the risk of multiple-organ failure and disseminated intravascular coagulation (DIC) has been raised as a possible concern with the use of colchicine in COVID-19 patients [14] **NIH COVID-19 Treatment Guidelines Panel** states that there are insufficient data to recommend either for or against use of colchicine for the treatment of **nonhospitalized** patients with COVID-19. The COLCORONA trial did not reach its primary efficacy end point of reducing hospitalizations and death, although a slight reduction in hospitalizations was observed in the subset of patients with PCR-confirmed disease. [28] **NIH COVID-19 Treatment Guidelines Panel** recommends against use of colchicine in **hospitalized** patients for the treatment of COVID-19, except in a clinical trial. [28] **Pregnancy:** Limited data are available on use of colchicine during pregnancy; data are lacking on use in pregnant women with acute COVID-19. Fetal risk cannot be ruled out. [5, 28] **Pediatric use:** Colchicine use in children is limited mainly to treatment of familial Mediterranean fever; data are lacking on use for treatment of acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C). [28]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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] **Interim analysis (not peer reviewed) of a single-center, randomized, double-blind, placebo-controlled trial in hospitalized adults with moderate to severe, RT-PCR-confirmed COVID-19 with pneumonia (not requiring ICU admission):** Analysis of first 38 patients randomized 1:1 to colchicine or placebo indicated **shorter duration of oxygen supplementation (3 vs 7 days) and shorter hospital stay (6 vs 8.5 days)** in colchicine group vs placebo group. One patient in each group required ICU admission. Median duration of symptoms prior to treatment was 9 days (colchicine group) or 7 days (placebo group). Colchicine dosage was 0.5 mg 3 times daily for 5 days, then 0.5 mg twice daily for 5 days (initial dose was 1 mg if body weight ≥80 kg); dosage was reduced for renal impairment. Standard concomitant treatment included 7-day azithromycin regimen, up to 10-day hydroxychloroquine regimen, and heparin with or without methylprednisolone (depending on oxygenation status). [18]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Nonhospitalized Patients: **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] **Phase 3, randomized, double-blind, placebo-controlled study (NCT04322682; COLCORONA)** (not peer reviewed): A total of 4488 adult outpatients (including 4159 patients with PCR-confirmed COVID-19) with at least 1 high-risk criterion were randomized within 24 hours of COVID-19 diagnosis to receive colchicine (0.5 mg twice daily for 3 days, then 0.5 mg once daily for 27 days) or placebo. The mean time from symptom onset to enrollment was 5.3 days. The primary end point was the composite of death or hospitalization due to COVID-19 within 30 days after randomization. Investigators (not the data safety monitoring board) decided to halt enrollment for logistical reasons prior to reaching the target of 6000 patients. In the intention-to-treat population, **colchicine did not result in a statistically significant reduction in the composite end point of death or hospitalization** due to COVID-19 compared with placebo (4.7 vs 5.8%, respectively) or in the individual end points of death, hospitalization due to COVID-19, or need for mechanical ventilation. In those with PCR-confirmed COVID-19, a statistically significant difference was observed between the colchicine and placebo groups in the composite end point of death or hospitalization (4.6 vs 6%, respectively) and in the rate of hospitalization, but not in the individual end points of death or need for mechanical ventilation. Pulmonary embolism occurred in 11 patients receiving colchicine compared with 2 placebo recipients. [24, 25]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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. [2,3]		
Corticosteroids (systemic) *Updated 4/30/21*	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 in other respiratory infections (e.g., SARS, MERS, influenza**): In these studies, corticosteroid use was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). [1, 24, 25] **Randomized controlled studies in acute respiratory distress syndrome (ARDS):** 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] **Randomized, controlled, open-label, adaptive trial with a Dexamethasone arm (NCT04381936; RECOVERY):** This trial was conducted to evaluate the effect of potential treatments (including low-dose dexamethasone) on all-cause mortality in hospitalized patients with COVID-19. The study enrolled patients with suspected or confirmed COVID-19 from 176 hospitals in the UK. In the dexamethasone treatment arm, 2104 patients were randomized to receive dexamethasone (6 mg once daily orally or IV for up to 10 days) plus standard care and 4321 patients were randomized to receive standard care alone. Preliminary data analysis indicates that overall 28-day mortality was reduced in patients receiving dexamethasone compared with those receiving standard care alone with the greatest benefit observed in patients requiring mechanical ventilation at enrollment. Overall, 22.9% of patients receiving dexamethasone and 25.7% of those receiving standard care died within 28 days of study enrollment. In patients receiving dexamethasone, the incidence of death was lower than that in the standard care group among those	The NIH COVID-19 Treatment Guidelines Panel recommends an **IV or oral Dexamethasone dosage of 6 mg daily for up to 10 days or until hospital discharge, whichever comes first,** in COVID-19 patients requiring mechanical ventilation and in patients who require supplemental oxygen but who are not mechanically ventilated. Although the clinical benefits of other corticosteroids (e.g., hydrocortisone, methylprednisolone, prednisone) are not clear, the panel recommends using total daily dosages of these drugs equivalent to dexamethasone 6 mg (IV or oral) as follows: **Hydrocortisone 160 mg, Methylprednisolone 32 mg, or Prednisone 40 mg**. Based on half-life and duration of action, frequency of administration varies among these corticosteroids. **Dexamethasone** is long-acting and administered once daily. **Methylprednisolone** and **Prednisone** are intermediate-acting and administered once daily or in 2 divided doses daily. **Hydrocortisone** is short-acting and administered in 2-4 divided doses daily. [24] Regimens used in early cases of COVID-19 in China were typically **methylprednisolone 40-80 mg IV daily for a course of 3-6 days.** 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	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, 43] **Non-severe or 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] The NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of dexamethasone or other corticosteroids in nonhospitalized patients with mild to moderate COVID-19 or in hospitalized patients with COVID-19 who do not require supplemental oxygen. [24] The WHO Guideline Development Group suggests not using systemic corticosteroids in the treatment of patients with **non-severe** COVID-19, regardless of hospitalization status. However, if the clinical condition of such non-severe patients worsens (e.g., increased respiratory rate, signs of respiratory distress, or hypoxemia), systemic corticosteroids are recommended for treatment. The WHO Guideline Development Group recommends against discontinuing systemic corticosteroids in patients with non-severe COVID-19 who are receiving systemic corticosteroids for chronic

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			receiving invasive mechanical ventilation (29.3 vs 41.4%) and among those receiving supplemental oxygen without invasive mechanical ventilation (23.3 vs 26.2%). However, no survival benefit was observed with dexamethasone and there was a possibility of harm in patients who did not require respiratory support at enrollment; the incidence of death in such patients receiving dexamethasone compared with standard care was 17.8 vs 14%, respectively. Dexamethasone was associated with a reduction in 28-day mortality among patients with symptoms for >7 days compared with those having more recent symptom onset. Dexamethasone treatment also was associated with a shorter duration of hospitalization and a greater probability of discharge within 28 days with the greatest effect observed among patients receiving invasive mechanical ventilation at baseline. [24, 32, 33] **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] **Dexamethasone randomized, controlled, open-label, multicenter study (NCT04327401; CoDEX):** This trial was conducted to determine whether IV dexamethasone increases the number of ventilator-free days among patients with COVID-19-associated ARDS. The study enrolled adults with COVID-19 and moderate or severe ARDS who were receiving mechanical ventilation from 41 ICUs in Brazil. In the dexamethasone treatment arm, 151 patients were randomized to receive dexamethasone (20 mg IV once daily for 5 days followed by 10 mg IV once daily for another 5 days or until ICU discharge) plus standard care; 148 patients were randomized to receive standard care alone. The primary study end point was ventilator-free days (defined as number of days alive and free from mechanical ventilation) during the first 28 days. Preliminary data analysis indicates that use of IV dexamethasone plus standard care was associated with a higher mean number of ventilator-free days (6.6 days) compared with those receiving	dosages of dexamethasone (i.e., 6 mg once daily for 10 days) were used in the RECOVERY trial. [32, 33] Higher dosages of IV **Dexamethasone** (i.e., 20 mg once daily for 5 days followed by 10 mg once daily for an additional 5 days or until ICU discharge, whichever came first) were used in the CoDEX trial in patients with COVID-19 and moderate or severe ARDS. [39] Continuous IV infusion of **Hydrocortisone** 200 mg/day for 7 days, followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days) was used in the CAPE COVID study. If a patient's respiratory and general status sufficiently improved by day 4, a shorter treatment regimen of **Hydrocortisone** was used at a dosage of 200 mg/day for 4 days followed by 100 mg/day for 2 days and then 50 mg/day for 2 days (total of 8 days). [40] A fixed dosage of IV **Hydrocortisone** (50 or 100 mg every 6 hours for 7 days) or a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours for up to 28 days in the presence of clinically evident shock) was used in the REMAP-CAP study. [41]	conditions (e.g., COPD, autoimmune diseases). [43] **Severely or critically ill patients:** The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) supports a **strong** recommendation to use a short course of systemic corticosteroids over not using corticosteroids in adults with severe or critical COVID-19. [52] However, these experts generally support a **weak** recommendation to use dexamethasone over other systemic corticosteroids when such therapy is considered for the treatment of adults with severe or critical COVID-19. [52] If dexamethasone is not available, these experts state that clinicians may use other systemic corticosteroids at dosages equivalent to dexamethasone 6 mg daily for up to 10 days. [52] Based on findings to date from the RECOVERY trial, the NIH COVID-19 Treatment Guidelines Panel recommends the use of **dexamethasone** (6 mg daily for up to 10 days or until hospital discharge, whichever comes first) in patients with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. [24] (See Remdesivir in this Evidence Table for recommendations from the NIH guidelines panel regarding use of dexamethasone with or without remdesivir in COVID-19 patients based on disease severity.) **Based on findings to date from the RECOVERY and REMAP-CAP studies, the NIH COVID-19 Treatment Guidelines Panel recommends the use of dexamethasone with or without remdesivir in hospitalized patients requiring oxygen delivery through a high-flow device or noninvasive ventilation. For such patients who were recently hospitalized with rapidly increasing oxygen needs and systemic inflammation, the panel also**

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			standard care alone (4 days). Although there was no significant difference in all-cause mortality at 28 days between the treatment groups, the trial was terminated early after results of the RECOVERY trial became available and, therefore, likely underpowered to determine secondary outcomes such as mortality. Dexamethasone was not associated with an increased risk of adverse effects in this study population of critically ill COVID-19 patients. [24, 39] **Hydrocortisone randomized, double-blind sequential trial (NCT02517489; CAPE COVID):** This trial was conducted to evaluate the effect of low-dose hydrocortisone compared with placebo on treatment failure in critically ill patients with COVID-19-related acute respiratory failure. The study enrolled adults with COVID-19-associated acute respiratory failure from 9 ICUs in France. In the hydrocortisone treatment arm, 76 patients received a continuous IV infusion of hydrocortisone at an initial dosage of 200 mg/day for 7 days followed by 100 mg/day for 4 days, and then 50 mg/day for 3 days (total of 14 days; some patients received a shorter regimen); 73 patients received placebo. The primary study end point was treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy) on day 21. Treatment failure on day 21 occurred in 42.1% of patients in the hydrocortisone group compared with 50.7% of patients in the placebo group. The difference between the treatment groups was not statistically significant; however, the study was discontinued early after results of the RECOVERY trial were announced and, therefore, likely underpowered to determine a statistically and clinically important difference in the primary outcome. [24, 40] **Hydrocortisone multicenter, ongoing, international open-label trial using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 corticosteroid domain, adults		**recommends the addition of tocilizumab to either monotherapy with dexamethasone or combination therapy with dexamethasone and remdesivir. The NIH panel also recommends use of dexamethasone plus tocilizumab for hospitalized patients with COVID-19 who are receiving invasive mechanical ventilation or ECMO and who are within 24 hours of ICU admission with rapid respiratory decompensation [24] (See Tocilizumab in this Evidence Table for recommendations from the NIH guidelines panel regarding use of dexamethasone with tocilizumab in COVID-19 patients.)** The NIH guidelines panel states that prolonged use of systemic corticosteroids in patients with COVID-19 may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus, strongyloidiasis, tuberculosis). The risk of reactivation of latent infections following a 10-day course of dexamethasone (6 mg once daily) is not well established. When initiating dexamethasone in patients with COVID-19, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in those at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) or fulminant reactivations of HBV should be considered. [24, 37, 38] The NIH guidelines panel also states that it is not known at this time whether other corticosteroids will have a similar benefit as dexamethasone. However, if dexamethasone is not available, the panel recommends using **alternative corticosteroids** (e.g., hydrocortisone, methylprednisolone, prednisone).[24] IDSA suggests the use of dexamethasone over no dexamethasone therapy in hospitalized patients with severe, but noncritical, COVID-19 (i.e., defined as patients with SpO_2 ≤94% on room air including those who require

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			from 8 countries with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive a fixed 7-day regimen of IV hydrocortisone (50 or 100 mg every 6 hours), a shock-dependent regimen of IV hydrocortisone (50 mg every 6 hours when shock was clinically evident), or no hydrocortisone or other corticosteroid. The primary study end point was organ support-free days (defined as days alive and free of ICU-based respiratory or cardiovascular support) within 21 days. The 7-day fixed regimen and the shock-dependent regimen of hydrocortisone were associated with a 93 and 80% probability of benefit in terms of organ support-free days compared with no hydrocortisone. However, the trial was discontinued early after results of the RECOVERY trial were announced and no treatment strategy met the prespecified criteria for statistical superiority, precluding definitive conclusions. In addition, serious adverse effects were reported in 2.6% of patients in the study (4 patients receiving the fixed-dosage regimen and 5 patients receiving the shock-dependent regimen compared with 1 patient receiving no hydrocortisone). [24, 41] **Prospective meta-analysis of studies using systemic corticosteroids (i.e., dexamethasone, hydrocortisone, or methylprednisolone) from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group**: This meta-analysis pooled data from 7 randomized clinical trials in 12 countries that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The primary outcome was all-cause mortality up to 30 days after randomization to treatment. Administration of systemic corticosteroids was associated with lower all-cause mortality at 28 days compared with usual care or placebo (222 deaths among 678 patients who received corticosteroids and 425 deaths among 1025 patients who received usual care or placebo). The effect of corticosteroids on reduced mortality was observed in critically ill patients who were and were not receiving mechanical ventilation at randomization and also in patients from the		supplemental oxygen). IDSA recommends the use of dexamethasone over no dexamethasone in hospitalized, critically ill patients with COVID-19 (i.e., defined as patients who are receiving mechanical ventilation or ECMO including those with end organ dysfunction as seen in cases of septic shock or ARDS). 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 **other corticosteroids** (e.g., methylprednisolone 32 mg, prednisone 40 mg) if dexamethasone is unavailable. However, IDSA suggests against using corticosteroids in hospitalized patients with nonsevere COVID-19 without hypoxemia (i.e., defined as patients with SpO_2 >94% on room air and not requiring supplemental oxygen). [25] The WHO Guideline Development Group strongly recommends the use of systemic corticosteroids (e.g., dexamethasone 6 mg orally or IV daily or hydrocortisone 50 mg IV every 8 hours for 7-10 days) over no systemic corticosteroid therapy for the treatment of patients with **severe and/or critical** COVID-19, regardless of hospitalization status. This treatment recommendation includes critically ill patients with COVID-19 who could not be hospitalized or receive oxygen supplementation because of resource limitations. This treatment recommendation is less clear for populations under-represented in recent clinical trials (e.g., children, patients with tuberculosis, immunocompromised individuals); however, the risk of not using systemic corticosteroids and depriving such patients of potentially life-saving therapy should be considered. The WHO treatment recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term dosage regimens, or prophylaxis. [43] **Cytokine storm:** There is no well-established or evidence-based

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			RECOVERY trial who required supplemental oxygen with or without noninvasive ventilation but who were not receiving invasive mechanical ventilation at the time of randomization. The odds ratios for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone. The optimal dosage and duration of corticosteroid treatment could not be determined from this analysis; however, there was no evidence suggesting that a higher dosage of corticosteroids was associated with greater benefit than a lower dosage. The authors also concluded that there was no suggestion of an increased risk of serious adverse effects associated with corticosteroid use. [24, 42] **Methylprednisolone randomized, parallel, double-blind, placebo-controlled, phase IIb trial (NCT04343729; Metcovid):** This trial was conducted to evaluate the effect of a short course of IV methylprednisolone compared with placebo in hospitalized adults with suspected COVID-19 infection from a single center in Brazil. Patients were enrolled prior to laboratory confirmation of COVID-19 to avoid treatment delays. The presence of COVID-19 was later confirmed based on RT-PCR testing in 81.3% of these patients. [24, 47] At time of enrollment, 34% of patients in each treatment group required invasive mechanical ventilation. Supplemental oxygen was required in 51% of patients receiving methylprednisolone and in 45% of those receiving placebo. [24] In the methylprednisolone treatment arm, 194 patients received IV methylprednisolone at a dosage of 0.5 mg/kg twice daily for 5 days; 199 patients received placebo. A modified intent-to-treat analysis was conducted; the primary study end point was 28-day mortality. Overall, the 28-day mortality rate was 37.1 or 38.2% in patients who received methylprednisolone or placebo, respectively, showing no significant difference in overall mortality between the treatment groups. However, a subgroup analysis found a lower mortality rate in patients >60 years of age who received methylprednisolone compared with placebo (46.6 vs 61.9%, respectively). Patients >60 years of age reportedly had a higher		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] **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] 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] 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 in patients with COVID-19 unless discontinuation is otherwise warranted by their clinical condition. Supplemental or stress dosages of corticosteroids may be indicated on an individual basis in patients with such conditions.[24] (See Corticosteroids [inhaled] in

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			degree of systemic inflammatory disease as manifested by increased median levels of C-reactive protein (CRP) compared with patients ≤60 years of age. In patients ≤60 years of age, there was a higher incidence of fatal outcomes in the methylprednisolone group. The authors concluded that caution is needed when using corticosteroids in patients with less severe COVID-19 since a trend toward more harm was noted in the younger age group. **Note:** Limitations of this study include the following: single-center study with a moderate sample size, longer median time from symptom onset to treatment administration compared with other corticosteroid studies, shorter treatment duration and higher equivalent corticosteroid dosage compared with the RECOVERY trial, and higher baseline mortality of the patient population possibly limiting the generalizability of the results to populations with lower baseline mortality. [24, 47] **Methylprednisolone multicenter, observational, longitudinal study (NCT04323592):** This trial was conducted to evaluate the association between use of prolonged, low-dose methylprednisolone treatment and ICU admission, intubation, or all-cause death within 28 days (composite primary end point) in patients with severe COVID-19 pneumonia admitted to 14 respiratory high-dependency units in Italy. A total of 173 patients were enrolled in the study with 83 patients receiving methylprednisolone plus standard care and 90 patients receiving standard care alone. In the methylprednisolone treatment arm, patients received a loading dose of IV methylprednisolone 80 mg at study entry followed by IV infusion of the drug at a dosage of 80 mg daily at a rate of 10 mL/hr for at least 8 days until achievement of either a PaO_2/FiO_2 (P/F ratio) >350 mm Hg or CRP levels <20 mg/L. Subsequently, twice-daily administration of either oral methylprednisolone 16 mg or IV methylprednisolone 20 mg was given until achievement of a P/F ratio >400 mm Hg or CRP levels reached <20% of the normal range. The composite primary end point was reached by 22.9 or 44.4% of patients in the group receiving methylprednisolone or standard care alone, respectively.		this Evidence Table for recommendations for use of inhaled corticosteroids in COVID-19 patients with asthma or COPD.) 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
			Therefore, use of methylprednisolone was associated with a reduction in the risk of ICU admission, invasive mechanical ventilation, or death within 28 days (adjusted hazard ratio: 0.41). Specifically, 18.1 or 30% of patients required ICU admission and 16.9 or 28.9% of patients required invasive mechanical ventilation in those receiving methylprednisolone or standard care alone, respectively. In addition, use of methylprednisolone was associated with a 28-day lower risk of all-cause mortality than use of standard care alone (7.2 vs 23.3%, respectively) with an adjusted hazard ratio of 0.29. Overall, there was no difference in adverse effects between treatment groups with the exception of increased reports of hyperglycemia and mild agitation in the methylprednisolone-treated patients; no adverse effects resulted in drug discontinuation. The authors concluded that early, low-dose, prolonged therapy with methylprednisolone resulted in decreased ICU burden, reduced need for invasive mechanical ventilation, and lower mortality along with improvement in systemic inflammation and oxygenation markers in hospitalized patients with severe COVID-19 pneumonia at high risk of progression to acute respiratory failure. [48] **Retrospective, case-control study using systemic corticosteroids (i.e., methylprednisolone, prednisone):** This trial was conducted to evaluate the efficacy of early, low-dose, short-term therapy with systemic methylprednisolone or prednisone in hospitalized adults from a single center in China with non-severe COVID-19 pneumonia. A total of 475 patients were enrolled with 55 of these patients receiving early, low-dose corticosteroids. Methylprednisolone 20 or 40 mg IV daily was administered to 50 of these patients for 3-5 days, and oral prednisone 20 mg daily (equivalent dosage to methylprednisolone) was administered to 5 such patients for 3 days. Corticosteroid therapy was initiated within a median of 2 days following hospital admission. A total of 420 patients received standard therapy (no corticosteroids); using propensity score matching, 55 of these patients were selected as matched controls. The primary outcome was the rate of patients who		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:** For pregnant women with COVID-19, the NIH COVID-19 Treatment Guidelines Panel states that a short course of corticosteroids that cross the placenta (i.e., betamethasone, dexamethasone) is routinely used for fetal benefit (e.g., to hasten fetal lung maturity). Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for this short course of corticosteroid therapy, the panel recommends the use of dexamethasone in pregnant women with COVID-19 who are receiving mechanical ventilation or in those who require supplemental oxygen but are not on mechanical ventilation. [24] The WHO Guideline Development Group recommends antenatal corticosteroid therapy for **pregnant** women at risk of preterm birth from 24-34 weeks' gestation when there is no clinical evidence of maternal infection and adequate maternal and newborn care are available. In cases where a pregnant woman presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroids may outweigh the risk of potential harm to the woman. The balance of benefits and risks for the woman and preterm infant should be considered during the informed decision-making process. [43] **Pediatric use:** The safety and efficacy of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Therefore, **caution is warranted when extrapolating recommendations for adults to patients <18 years of age**. Importantly, the RECOVERY trial

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			developed severe disease and mortality. In the corticosteroid treatment arm, 12.7% of patients developed severe disease compared with 1.8% of patients in the control group. There was one death in the group receiving methylprednisolone and none in the control group. Regarding secondary outcomes, duration of fever, virus clearance time, and length of hospital stay were all significantly longer in patients receiving corticosteroids compared with no corticosteroid therapy. [49] Because of the finding that early, low-dose, short-term systemic corticosteroid therapy was associated with worse clinical outcomes in hospitalized adult patients with non-severe COVID-19 pneumonia, the authors concluded that the study results do not support the use of corticosteroids in this population. [49] However, it is difficult to interpret these results because of potential confounding factors inherent in the nonrandomized study design. [24] It is unclear if the results of this study apply to corticosteroids other than methylprednisolone. [24] **Methylprednisolone multicenter quasi-experimental study with single pretest and posttest (NCT04374071):** This trial was conducted to evaluate the efficacy of early, short-term therapy with systemic methylprednisolone in hospitalized adults with confirmed moderate to severe COVID-19 from a multicenter health system in Michigan. A total of 213 patients were enrolled with 132 patients receiving early therapy with IV methylprednisolone at dosages of 0.5-1 mg/kg daily in 2 divided doses for 3 days plus standard care and 81 patients receiving early therapy with standard care alone. The primary end point was a composite based on the need for ICU transfer, progression to respiratory failure requiring mechanical ventilation, or in-hospital all-cause mortality. The primary composite end point occurred at a significantly lower rate in the group receiving early corticosteroid therapy (34.9%) compared with the group receiving early therapy with standard care alone (54.3%). The early corticosteroid group had a median time to initiation of methylprednisolone of 2 days compared with 5 days for the		did not include a significant number of pediatric patients, and mortality rates are significantly lower for pediatric patients with COVID-19 than for adult patients with the disease. Therefore, results of this trial should be interpreted with caution for patients <18 years of age. The NIH COVID-19 Treatment Guidelines Panel recommends use of dexamethasone for hospitalized pediatric patients with COVID-19 who are receiving high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or ECMO. Dexamethasone is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). For pediatric patients with COVID-19, the NIH panel recommends dexamethasone at a dosage of 0.15 mg/kg (maximum dose 6 mg) once daily for up to 10 days. If dexamethasone is not available, alternative corticosteroids such as hydrocortisone, methylprednisolone, or prednisone may be considered. Additional studies are needed to evaluate the use of corticosteroids for the treatment of COVID-19 in pediatric patients, including in those with multisystem inflammatory syndrome in children (MIS-C). Although immune globulin IV (IGIV) and/or corticosteroids generally have been used as first-line therapy in pediatric patients with MIS-C, the NIH COVID-19 Treatment Guidelines Panel recommends consultation with a multidisciplinary team when considering and managing immunomodulating therapy for children with this condition. The optimal choice and combination of immunomodulating therapies for children with MIS-C have not been definitely established. [24]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			standard care group. The median hospital length of stay was significantly reduced from 8 to 5 days in patients receiving early corticosteroid therapy compared with those receiving early therapy with standard care alone. ARDS occurred in 26.6% of patients receiving early corticosteroid therapy compared with 38.3% of those in the standard care group. The authors concluded that early, short-term therapy with methylprednisolone in patients with moderate to severe COVID-19 may prevent disease progression and improve clinical outcomes. **Note:** Limitations of this study include the following: differences were noted in the baseline characteristics of the comparator groups; some patients in the standard care group received corticosteroids, but initiation of therapy was significantly later than in the early corticosteroid group; and patient follow-up for both treatment groups was limited to 14 days. [51] **Methylprednisolone open-label, multicenter, randomized, controlled study (NCT04244591):** This recently completed trial compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to acute respiratory failure; results have not yet been posted. [23] **Retrospective, observational study of systemic corticosteroid use in patients with COVID-19 from a New York hospital (Keller et al):** Data are available for 1806 patients hospitalized with COVID-19 between Mar 11 and Apr 13, 2020. Patients included in the analysis were those treated with systemic corticosteroids (e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone) within the first 48 hours of hospital admission (140 patients) and those not treated with corticosteroids (1666 patients) as the control group. Treatment and control groups were similar except that corticosteroid-treated patients were more likely to have a history of COPD, asthma, rheumatoid arthritis, or lupus, or to have received corticosteroids in the year prior to admission. Primary goal of the study was to determine whether early systemic corticosteroid treatment was associated with		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			reduced mortality or need for mechanical ventilation. Overall, early use of systemic corticosteroids was not associated with in-hospital mortality or mechanical ventilation. However, there was a significant treatment effect based on C-reactive protein (CRP) levels. Early use of corticosteroids in patients with initial CRP levels of ≥20 mg/dL was associated with a significantly *reduced* risk of mortality or need for mechanical ventilation (odds ratio: 0.23). Conversely, such treatment in patients with initial CRP levels of <10 mg/dL was associated with a significantly *increased* risk of mortality or need for mechanical ventilation (odds ratio: 2.64). The authors state that these findings suggest that appropriate selection of COVID-19 patients for systemic corticosteroid treatment is critical to maximize the likelihood of benefit and minimize the risk of harm. **Note:** The limitations of the observational study design should be considered when interpreting these results. Corticosteroid dosages used in patients included in this study not provided. Further study is needed to determine the role of CRP levels in guiding the use of corticosteroid treatment in patients with COVID-19. [36] **Retrospective study of systemic corticosteroids and/or other immunosuppressive therapies and their effect on COVID-19 infection in patients with chronic immune-mediated inflammatory arthritis (Favalli et al):** This study evaluated the frequency and characteristics of symptomatic COVID-19 infection in relation to use of different immunosuppressive agents in such patients. Data are available from a cross-sectional survey administered to 2050 adults receiving follow-up care at arthritis outpatient clinics of 2 large academic hospitals in Italy. Patients surveyed had arthritis of long duration (median of 10 years) and 62% were receiving therapy with biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) alone or in combination with conventional synthetic DMARDs; approximately one-third of these patients were also receiving concomitant long-term treatment with systemic corticosteroids. Laboratory-confirmed COVID-19 or highly		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			suspected infection (based on close contact with a confirmed COVID-19 case within 14 days prior to onset of symptoms) was reported in 1.1 or 1.4% of patients, respectively. In this study, corticosteroid treatment was independently associated with an increased risk of COVID-19 infection, especially at prednisone dosages ≥ 2.5 mg daily. The use of corticosteroids was confirmed to independently predict increased risk of COVID-19 infection regardless of comorbidities, precautions taken to prevent infection, and contacts with COVID-19 cases. Conversely, treatment with biologic/targeted synthetic DMARDs was associated with a reduced risk of COVID-19 infection. Limitations of this study include its retrospective nature and the definition of COVID-19 cases based on patient survey results. The authors state these data should not result in indiscriminate discontinuance of systemic corticosteroids in patients with chronic immune-mediated inflammatory arthritis, but underscore the importance of a benefit-risk assessment in individual patients. [50] **Dexamethasone, hydrocortisone, methylprednisolone, or prednisone studies for treatment of COVID-19 pneumonia or ARDS:** Registered clinical trials that have been initiated or underway include: [22] NCT03852537 NCT04263402 NCT04329650 NCT04344730 NCT04348305 NCT04359511 NCT04395105 **Methylprednisolone non-randomized pilot study (NCT04355247):** Trial has been initiated to evaluate use of the drug for the *prevention* of COVID-19 cytokine storm and progression to respiratory failure. [22]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Corticosteroids (inhaled) ***Updated 5/13/21***	68:04 Adrenals	Inhaled corticosteroids may mitigate local inflammation and inhibit virus proliferation. [35, 44]	There are currently limited results from randomized controlled studies specifically evaluating use of inhaled corticosteroids in patients with COVID-19. [34, 44, 45, 53, 54] Early reports of an unexpectedly low prevalence of chronic respiratory conditions among outpatient and hospitalized COVID-19 patients resulted in speculation that respiratory treatments, specifically inhaled corticosteroids, may have a protective effect against SARS-CoV-2 infection. [45, 46, 53] **Retrospective, observational study of inhaled corticosteroid use in patients with COPD or asthma and associated risk of COVID-19-related death in the UK (Schultze et al):** This study was designed to assess the role of routine use of inhaled corticosteroids on COVID-19-related mortality. Data were extracted from primary care electronic health records and linked with mortality data for a cohort of patients with COPD (n = 148,557) and another cohort with asthma (n = 818,490) who were prescribed standard respiratory treatments within the 4 months prior to the index date. In patients with COPD, an increased risk of COVID-19-related death (hazard ratio: 1.39) was reported after adjusting for age and comorbidities among those who were prescribed inhaled corticosteroids combined with a long-acting β-agonist and/or long-acting antimuscarinic compared with those prescribed a long-acting β-agonist and long-acting antimuscarinic. In patients with asthma, an increased risk of COVID-19-related death (hazard ratio: 1.55) was reported in patients who were prescribed high-dose inhaled corticosteroids compared with those prescribed a short-acting β-agonist only; however, there was no increased risk of death (hazard ratio: 1.14) in asthma patients receiving low- or medium-dose inhaled corticosteroids compared with nonusers of inhaled corticosteroids. Sensitivity analyses suggest there may be other factors driving the increased risk of death observed with use of inhaled corticosteroids, including underlying disease differences between individuals that are not captured in the health records. The results of this study do not support evidence of benefit or harm with routine use	In the STOIC trial, inhaled budesonide was administered as a dry powder inhaler at a dosage of 800 mcg twice daily for 4-10 days. [53] **In the PRINCIPLE trial, inhaled budesonide was administered as a dry powder inhaler at a dosage of 800 mcg twice daily for 14 days.** [54] Initial dosage of orally inhaled ciclesonide used in the published case series from Japan of 3 patients with COVID-19 pneumonia was 200 mcg 2 times daily. If necessary, the dosage was increased to 400 mcg 3 times daily. The authors suggested continued use of ciclesonide oral inhalation for about 14 days or longer. [35]	NIH COVID-19 Treatment Guidelines Panel recommends that inhaled corticosteroids used daily for the management of asthma and COPD to control airway inflammation should not be discontinued in patients with COVID-19 unless discontinuation is otherwise warranted based on their clinical condition. The panel also states that no studies to date have investigated the relationship between inhaled corticosteroids in these clinical settings and virus acquisition, severity of illness, or viral transmission. [24] Currently, there is limited clinical evidence supporting adverse or beneficial effects of premorbid use or continued administration of inhaled corticosteroids in patients with acute respiratory infections due to coronaviruses. Randomized controlled clinical studies are needed to fully assess the benefits of inhaled corticosteroids for treatment of COVID-19 in patients with and without chronic respiratory conditions. [34, 44, 53]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			of inhaled corticosteroids on COVID-19-related mortality among individuals with COPD or asthma. [44, 45] **Phase 2, randomized, controlled, open-label, parallel group study evaluating the use of inhaled budesonide in adults with early COVID-19 (NCT04416399; STOIC):** This trial was conducted to evaluate the use of inhaled budesonide compared with usual care in 146 nonhospitalized adults from the UK within 7 days of the onset of mild symptoms suggestive of COVID-19. COVID-19 infection was later confirmed by RT-PCR in 94% of these patients. Prior to randomization, the median duration of symptoms was 3 days. Total of 70 patients were randomized to receive inhaled budesonide as a dry powder inhaler at a dosage of 800 mcg twice daily and 69 patients were randomized to receive usual care, with a total of 139 patients included in the per-protocol analysis. In the budesonide group, the drug was administered for a median duration of 7 days. The primary end point was defined as an urgent care visit, emergency department assessment, or hospitalization. This outcome occurred in 10 patients (14%) from the usual care group compared with 1 patient (1%) from the budesonide group. In addition, fewer patients receiving inhaled budesonide had persistent symptoms at days 14 and 28 compared with those receiving usual care. Study results suggest that early administration of inhaled budesonide reduces the likelihood of needing urgent medical care, emergency department consultation, or hospitalization in patients with early COVID-19 illness. Use of inhaled budesonide was also associated with self-reported reduced time to symptom resolution from COVID-19 infection. [53] **Multicenter, randomized, controlled, open-label, adaptive platform study (not peer reviewed) evaluating the use of inhaled budesonide in adults in the community with suspected COVID-19 at higher risk of adverse outcomes (PRINCIPLE):** This trial compared the use of standard care alone, standard care plus inhaled budesonide, or standard care plus other interventions in nonhospitalized adults in the UK who had		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			suspected COVID-19 and were ≥65 years of age or ≥50 years of age with comorbidities. COVID-19 infection was later confirmed in 2617 (56%) of these patients, of which 2422 had follow-up data and, therefore, were included in the primary analysis. Patients were randomized to receive standard care alone (n=1028), standard care plus inhaled budesonide at a dosage of 800 mcg twice daily for 14 days (n=751), or standard care plus other interventions (n=643). The coprimary end points were time to first self-reported recovery and COVID-19-related hospitalization or death (both end points measured within 28 days after randomization). Inhaled budesonide appeared to reduce time to recovery by a median of 3 days in adults with COVID-19 who had comorbidities that put them at higher risk for complications. Among patients in the inhaled budesonide group who had 28 days of follow-up data, a lower rate of COVID-19-related hospitalization or death was observed compared with patients in the standard care group (8.5 versus 10.3%, respectively). Final data analysis is pending completion of 28-day follow up for all patients randomized to receive inhaled budesonide. [54] A small case series from Japan observed possible clinical benefit in 3 patients with mild to moderate COVID-19 pneumonia following oral inhalation of ciclesonide; however, without a control group, it is not known whether the patients would have improved spontaneously. [35] Various clinical trials evaluating the use of inhaled corticosteroids (e.g., budesonide, ciclesonide) in patients with COVID-19 are registered at clinicaltrials.gov. [22]		
Inhaled prostacyclins (e.g., epoprostenol, iloprost) *Updated 1/28/21*	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]	Available evidence suggests that inhaled prostacyclins can improve oxygenation, but have no known mortality benefit, in patients with ARDS.[3, 6-9] It is not clear whether or how COVID-19-associated ARDS differs from ARDS related to other etiologies. [14-16] Results of a retrospective, single-center, observational study in intubated patients	In patients with ARDS, various dosages of inhaled epoprostenol have been used; dosages up to 50 ng/kg per minute (titrated to response) have been used in clinical studies. [1-4, 6, 9]	The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against the use of inhaled prostacyclins in COVID-19 patients with severe ARDS[10]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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 similar 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]	with COVID-19 and refractory hypoxemia did not show significant improvement in oxygenation metrics following treatment with inhaled epoprostenol or inhaled nitric oxide. In this study, 38 patients initially received inhaled epoprostenol (starting dose of 0.05 mcg/kg per minute, continued based on PaO_2 response); 11 patients who did not respond to epoprostenol were transitioned to inhaled nitric oxide (starting dose of 20 ppm, titrated up to 80 ppm based on PaO_2 response). Although 42.1% of patients who received epoprostenol and 63.6% of patients who received nitric oxide were considered responders (defined as an increase in PaO_2/FiO_2 by >10%), there were no significant changes in other oxygenation parameters or clinical outcomes. [14] In another retrospective observational study in 80 mechanically ventilated COVID-19 patients, clinically significant improvement in PaO_2/FiO_2 (defined as an increase by 10% from baseline values) was observed in 50% of the patients following treatment with inhaled epoprostenol (initial dose of 50 ng/kg per minute delivered through the ventilator tubing); however, the benefit was generally modest and there was wide variability in response. [15] Numerous limitations of the observational studies described above preclude definitive conclusions. [14, 15] Inhaled prostacyclins may be included in some COVID-19 clinical trials registered at clinicaltrials.gov.[13]	In several observational studies in mechanically ventilated patients with COVID-19, inhaled epoprostenol was administered at an initial dosage of 50 ng/kg per minute (based on ideal body weight). [14,15]	The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment [10, 12]
Interferons *Updated 3/11/21*	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]	**Only limited clinical trial data available** to date specifically evaluating efficacy of IFNs for treatment of COVID-19; [10, 15, 20, 21-23, 25, 27] 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. Various clinical trials evaluating **IFN beta-1a, IFN beta-1b**, or **peginterferon [pegIFN] beta-1a**, generally added to other antivirals, for treatment of COVID-19 are registered at clinicaltrials.gov. [16] PegIFN beta-1a also is being evaluated for postexposure prophylaxis of SARS-CoV-2 infection. [16]	**IFN beta:** Various sub-Q dosages of IFN beta-1a and IFN beta-1b are being evaluated for treatment of COVID-19. [10, 16] IFN beta-1a has been administered IV in some patients (IV preparation not commercially available in US). [23] Sub-Q and IV routes of administration may not be equivalent. Bioavailability is lower following sub-Q injection, suggesting potential for less efficient distribution to central target organs, especially in critically ill patients. [24]	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 severe or critical COVID-19, except in the context of a clinical trial. The panel also states there are insufficient data to recommend either for or against use of IFN beta for the treatment of early (i.e., <7 days from

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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 -C0V-2 in Vero cells at clinically relevant concentrations; [1, 26] in vitro study suggests SARS-CoV-2 is more sensitive than SARS-CoV-1 to IFN alfa [1, 3] However, lack of clinical benefit observed with use of type 1 IFNs, generally in combination with ribavirin, for treatment of SARS and MERS [2, 8, 9, 11, 12] IV IFN beta-1a did not reduce ventilator dependence or mortality in a placebo-controlled trial in patients with acute respiratory distress syndrome (ARDS) [11, 17] **Type 3 IFNs (IFN lambda)** are thought to provide important immunologic defense against respiratory viral infections [3, 4, 6, 7, 19] and may have less potential than type 1 IFNs to produce systemic inflammatory response, including inflammatory effects on respiratory tract; [4, 7, 19] IFN lambda receptor is expressed mainly on epithelial (including respiratory epithelial) cells and	**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 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 adults hospitalized with severe COVID-19: Regimen of IFN beta-1b** (250 mcg sub-Q every other day for 2 weeks) plus Iran national protocol medications was compared with national protocol alone (control). Protocol included a 7- to 10-day regimen of lopinavir/ritonavir or atazanavir/ritonavir and hydroxychloroquine. All patients required respiratory support (mainly oxygenation through facemask [80%]) but none were intubated at baseline. Median time from symptom onset to randomization was 8 days. Total of 80 patients were randomized (40 to each treatment group); analyses were based on data for 33 patients per treatment group after exclusion of those who withdrew consent, were enrolled in another study, or received <4 IFN doses. Median time to clinical improvement (defined as ≥2-category improvement in a 6 -category ordinal scale) was shorter in the	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] In an open-label, randomized study in hospitalized adults with severe COVID-19, **IFN beta-1b** 250 mcg was given sub-Q every other day for 2 weeks. [25] In the SOLIDARITY study, most IFN-treated patients received three 44-mcg doses of **IFN beta-1a** sub-Q over 6 days. [23] In an open-label, randomized study in hospitalized adults with severe COVID-19, **IFN beta-1a** 12 million units was given sub-Q 3 times weekly for 2 weeks. [20] **IFN alfa:** National guidelines from China suggest IFN alfa dosage of 5 million units (or equivalent) twice daily via inhalation for up to 10 days for treatment of COVID-19. [13] **PegIFN lambda-1a:** For *treatment* of COVID-19 in adults (NCT04354259): a single 180-mcg sub-Q dose of pegIFN lambda-1a was given. [32] 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]	symptom onset) mild or moderate COVID-19. No benefit was observed with use of IFNs for treatment of other severe or critical coronavirus infections (SARS, MERS), and toxicity of IFNs outweighs the potential for benefit. IFNs may have antiviral activity early in the course of SARS-CoV-2 infection; however, there are insufficient data to assess the potential benefit of IFN use during early disease versus the risk of toxicity. [11] Interferon alfa via inhalation is included in national guidelines from China as a possible option for treatment of COVID-19. [13]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]	IFN group than in the control group (9 vs 11 days). A smaller proportion of IFN-treated patients required ICU admission (42 vs 67%). There was no difference in duration of hospitalization, intubation rate, length of ICU stay, or all-cause 28-day mortality. [25] **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. Diagnosis of COVID-19 was based on RT-PCR testing (64%) or clinical manifestations/imaging findings (36%). Other concomitant therapies included corticosteroids and immune globulin (IFN beta-1a group: 62 and 36%, respectively; control group: 44 and 26%, respectively). Patients were recruited from general, intermediate, and ICU wards; 45% of the IFN beta-1a-treated patients and 59% of the control patients were admitted to ICU; 36 and 44%, respectively, required invasive mechanical ventilation. Mean time from symptom onset to treatment initiation was 11.7 days for the IFN beta-1a group and 9.3 days for the control group. [20]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Large, multinational, open-label, randomized, adaptive trial launched by the World Health Organization (WHO) to evaluate effects of 4 different treatments compared with local standard of care in adults hospitalized with COVID-19 and not previously treated with any of the study drugs (SOLIDARITY; NCT04315948): The protocol-specified primary outcome is in-hospital mortality; protocol-specified secondary outcomes are initiation of ventilation and duration of hospitalization. **Interim results have been reported, including results for the IFN beta-1a treatment arm.** From March 22 to October 4, 2020, 2063 patients were randomized to receive IFN (given in conjunction with lopinavir and ritonavir [n = 651] or standard of care [n = 1412]) and 2064 patients were randomized to IFN control (either lopinavir and ritonavir or standard of care, for the respective IFN regimens). Most IFN-treated patients received three 44-mcg doses of IFN beta-1a sub-Q over 6 days; where IV IFN was available, patients on high-flow oxygen, ventilators, or ECMO received 10 mcg IV once daily for 6 days. Preliminary data analysis for the intention-to-treat (ITT) population indicated that IFN did not reduce in-hospital mortality (either overall or in any subgroup defined by age or ventilation status at study entry) and did not reduce the need for initiation of ventilation or the duration of hospitalization. The log-rank death rate ratio for IFN in the ITT population was 1.16; 243/2050 patients treated with IFN (12.9%) and 216/2050 control patients (11%) died. About one-half of the patients randomized to receive IFN or IFN control received corticosteroids; this did not appear to affect the death rate ratio. The clinical relevance of the difference in the pharmacokinetic profiles of sub-Q and IV IFN is unclear. [23, 28] **Phase 2, randomized, double-blind, multicenter, placebo-controlled study (NCT04385095; SG016) evaluating SNG001 (inhaled IFN beta-1a) in adults with COVID-19:** In the in-hospital portion of the study, patients received SNG001 (IFN beta-1a 6 million units via nebulizer once daily for up to 14 days) plus standard care or placebo		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			plus standard care. The intention-to-treat population for the interim analysis included 48 patients treated with SNG001 and 50 patients given placebo. More patients in the SNG001 group had hypertension (69 vs 41%) and received oxygen at baseline (77 vs 58%), while more patients in the control group had diabetes mellitus (33 vs 12%) or cardiovascular disease (30 vs 19%). Median duration of symptoms before initiation of treatment was 10 days. Clinical outcomes were assessed on the WHO ordinal scale for clinical improvement; statistical models were adjusted for baseline and demographic factors. Hazard ratio for time to recovery (2.19) during the 14-day treatment period and odds ratios for recovery (3.19) and for improvement (2.32) on day 15 or 16 favored SNG001 over placebo. The study has been extended to include 120 patients in the home setting. [16, 22, 27, 29] **Aerosolized IFN alfa** (not commercially available in U.S.) has been used in China in children and adults for treatment of COVID-19, [13, 14, 15] but limited clinical data presented to date. [11] In a retrospective study of 77 hospitalized adults with moderate COVID-19 disease who received aerosolized IFN alfa-2b (5 million units twice daily) (n = 7), umifenovir (Arbidol®) (n = 24), or both drugs (n = 46), time from symptom onset to negative RT-PCR result in throat swab appeared to be shorter in those receiving IFN alfa-2b alone or in combination with umifenovir compared with those receiving umifenovir alone; this exploratory study was small and nonrandomized, and treatment groups were of unequal size and demographically unbalanced in age, comorbidities, and time from symptom onset to treatment. [15] **Retrospective cohort study** in 446 hospitalized patients who received antiviral therapy for COVID-19 suggested that **early IFN alfa-2b therapy** (within first 5 days of hospitalization) was associated with reduced in-hospital mortality while **late IFN alfa-2b therapy** was associated with increased mortality and delayed recovery. In this study, 48.4% of patients received early IFN therapy, 6% received late IFN therapy, and		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			46% received no IFN. Median time from symptom onset to admission was 6 days, and median time from admission to first IFN dose was 2 or 8.5 days in the early or late IFN group, respectively. Median duration of IFN therapy was 10 or 8.5 days in the early or late IFN group, respectively. [30] Preliminary, retrospective, single-center, matched case-control study in 104 patients hospitalized with COVID-19 suggested that **IFN alfa-2b therapy** (100,000 units by inhalation 4 times daily for 7 days) **did not reduce the duration of viral shedding**. Duration of viral shedding (based on 2 consecutive negative RT-PCR results) was not significantly different between the matched-pair groups (12 days in 32 IFN-treated patients vs 15 days in 32 control patients [no IFN treatment]). [31] **Randomized, double-blind, placebo-controlled trial** (NCT04354259) in 60 adults with confirmed SARS-CoV-2 infection: Patients who received **pegIFN lambda-1a** (single 180-mcg sub-Q injection) within 7 days of symptom onset or first positive nasal swab test (if asymptomatic) had **greater reduction in viral load** compared with those receiving placebo. By day 7 after treatment, 80% of pegIFN lambda-1a recipients and 63% of placebo recipients had undetectable SARS-CoV-2 RNA. After controlling for a higher baseline viral load in the pegIFN lambda-1a group compared with the placebo group (6.16 vs 4.87 $\log_{10}$ copies/mL; 5 vs 10 patients in these respective groups had undetectable SARS-CoV-2 RNA on day of randomization), patients in the pegIFN lambda-1a group were more likely to have undetectable viral RNA by day 7 after treatment (odds ratio 4.12; 95% CI 1.15-16.73). At low viral loads, viral clearance tended to occur rapidly regardless of treatment assignment. Studies establishing clinical benefit (e.g., effects on morbidity, mortality, or virus transmission) still required. [32] **Other trials evaluating sub-Q pegIFN lambda-1a** (not commercially available in U.S.) for *treatment* or *postexposure prophylaxis* of SARS-CoV-2 infection are registered at clinicaltrials.gov. [5]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Nitric oxide (inhaled) *Updated 1/28/21*	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, 19] In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV-1) has been demonstrated [1, 14. 19] In a small pilot study (Chen et al.) conducted during the SARS outbreak, treatment with inhaled nitric oxide was found to reverse pulmonary hypertension, improve severe hypoxia, and shorten the duration of ventilatory support in critically ill SARS patients [2, 3] Genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential benefit in patients with COVID-19 [1, 14]	The available evidence indicates that inhaled nitric oxide can modestly improve oxygenation in patients with ARDS, but has no mortality benefit and may cause possible harm (e.g., renal impairment). [4-6, 9] It is not clear whether or how COVID-19-associated ARDS differs from ARDS related to other etiologies. [18, 20] Evidence supporting the use of inhaled nitric oxide in COVID-19 patients is currently limited. [15, 16] Various case reports, case series, and observational studies have described the use of inhaled nitric oxide in mechanically ventilated patients with COVID-19. [13, 15, 16] Findings generally have been inconsistent, with some improvement in oxygenation reported in some studies and minimal to no improvement in others; various dosages of inhaled nitric oxide were used and patients were receiving other therapies confounding interpretation of the data.[13, 15-17, 23-25] In a small cohort (n=6) of pregnant women with hypoxic respiratory failure secondary to COVID-19, intermittent twice-daily treatments with high-dose inhaled nitric oxide (160-200 ppm for 30 minutes to 1 hour administered to spontaneously breathing patients using a mask) improved systemic oxygenation. The decision to use a high dose of inhaled nitric oxide was based on prior reports showing broad antimicrobial effects of such high doses. However, fetal parameters and the development of acute kidney injury (a known complication of nitric oxide therapy) were not monitored. [19] Results of a retrospective, single-center, observational study in intubated patients with COVID-19 and refractory hypoxemia did not show significant improvement in oxygenation metrics following treatment with inhaled epoprostenol or inhaled nitric oxide. In this study, 38 patients initially received inhaled epoprostenol (starting dose of 0.05 mcg/kg per minute, continued based on PaO_2 response); 11 patients who did not respond to epoprostenol were transitioned to inhaled nitric oxide (starting dose of 20 ppm, titrated up to 80 ppm based on PaO_2 response). Although 42.1%	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] Dosages of inhaled nitric oxide used in patients with COVID-19 have varied. (See Trials or Clinical Experience.)	The NIH COVID-19 Treatment Guidelines Panel and the Surviving Sepsis Campaign **recommend against** the routine use of inhaled nitric oxide in mechanically ventilated adults with COVID-19 and ARDS.[10, 12] These experts state that a trial of inhaled pulmonary vasodilator may be considered as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia; however, if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment [10, 12]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			of patients who received epoprostenol and 63.6% of patients who received nitric oxide were considered responders (defined as an increase in PaO_2/FiO_2 by >10%), there were no significant changes in other oxygenation parameters or clinical outcomes. Limitations of the study include its retrospective nature and small sample size. [18] In a report describing administration of inhaled nitric oxide (initial dose 30 ppm; mean duration of therapy 2.1 days) to 39 spontaneously breathing patients with laboratory-confirmed COVID-19 (29 were initially admitted to the general medical floor and 24 of these patients later required transfer to the ICU), approximately half of the patients did not require invasive mechanical ventilation after treatment. These findings suggest a role of inhaled nitric oxide in preventing progression of hypoxic respiratory failure; however, randomized controlled studies are needed. [21] In a single-center prospective study, 34 critically ill adults with COVID-19 received inhaled nitric oxide (10 ppm administered through the inspiratory limb of the ventilator tubing when PaO_2/FiO_2 <150). A response (defined as improvement in PaO_2/FiO_2 of >20% during the 30 minutes following administration) was achieved in 65% of the patients. [22] Nitric oxide may be included in some COVID-19 clinical trials registered at clinicaltrials.gov.[3]		
Ruxolitinib (Jakafi®) *Updated 4/29/21*	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] May reduce inflammation via JAK inhibition, but study based on artificial intelligence (AI)-derived methodology suggests that clinically tolerated concentrations of ruxolitinib may be unlikely to reduce viral infectivity by disrupting	Although some small studies have suggested possibility of benefit from ruxolitinib in patients with COVID-19, 2 placebo-controlled, phase 3 trials have failed to meet key end points. **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;	Various dosages are being evaluated [3, 10] **Phase 3 study (NCT04362137; RUXCOVID):** Ruxolitinib 5 mg orally twice daily for 14 days with possible extension to 28 days (study failed to demonstrate efficacy). [10, 19] **Phase 3 study (NCT04377620; RUXCOVID-DEVENT; 369 DEVENT):** Ruxolitinib 5 or 15 mg orally twice daily (study failed to meet primary end point). [12, 21]	NIH COVID-19 Treatment Guidelines Panel **recommends against** use of JAK inhibitors other than baricitinib (see Baricitinib entry in this table) for the treatment of COVID-19 except in the context of a clinical trial. [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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		regulators of endocytosis (e.g., AP2-associated protein kinase 1 [AAK1]). [16] (See Baricitinib entry in this table.) 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]	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 = 20) 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; most patients in both treatment groups received systemic corticosteroids (71%) and antivirals (90%). Study excluded critically ill and ventilator-dependent patients. Interpretation is limited by small sample size. [13] **Compassionate use of ruxolitinib in mainly older adults with RT-PCR-confirmed COVID-19 with severe respiratory manifestations but not requiring invasive mechanical ventilation in Italy:** Patients (n = 34) received ruxolitinib (5 mg twice daily, increased to 10 mg twice daily or 25 mg daily if respiratory function not improved); ruxolitinib was initiated at a median of 8 days after symptom onset; median dose was 20 mg daily and median treatment duration was 13 days. Median patient age was 80.5 years (53% were ≥80 years of age and 35% were 60-79 years of age); 85% of patients had ≥2 comorbidities. Concomitant therapies included hydroxychloroquine (91%),		second patient; these cases differed in the timing of ruxolitinib initiation and the severity of COVID-19 illness. [11] However, clinical trials have identified no substantial safety concerns with ruxolitinib in patients with COVID-19. [19]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			antimicrobials (77%), antivirals (62%), and corticosteroids (29%). Cumulative incidence of clinical improvement (decrease of ≥2 categories on a 7-category ordinal scale within 28 days) was 82%; overall survival at day 28 was 94%. Clinical improvement was not affected by low-flow versus high-flow oxygen support but was less frequent in patients with PaO_2/FiO_2 ratio <200. [17] **Compassionate use of ruxolitinib in combination with eculizumab** (a terminal complement inhibitor) in adults with RT-PCR-confirmed COVID-19 and associated pneumonia or acute respiratory distress syndrome (ARDS) in Italy: Consecutive patients received ruxolitinib (10 mg twice daily for 14 days) and eculizumab (900 mg IV once weekly for 2 or 3 doses) (n = 7) or best available therapy (n = 10; control). Greater improvement in median PaO_2 and PaO_2/FiO_2 ratio and greater increase in platelet count observed on day 7 in patients receiving ruxolitinib and eculizumab compared with control patients. All patients received antibiotic prophylaxis (azithromycin) and all patients except 2 in control group received hydroxychloroquine; greater proportion of patients in the ruxolitinib and eculizumab group compared with the control group received low-dose corticosteroids (5/7 vs 3/10) and sub-Q heparin (7/7 vs 5/10). Randomized, controlled trials needed to confirm these preliminary data. [15] **Small retrospective cohort study of adults with RT-PCR-confirmed COVID-19 and associated ARDS:** Total of 18 patients with PaO_2/FiO_2 ratio of 100 to <200 and rapid clinical worsening of respiratory function received ruxolitinib (20 mg twice daily for initial 48 hours, with subsequent stepwise dosage reductions based on response, for a maximum of 14 days of treatment); ruxolitinib was initiated at a median of 9 days after symptom onset. Other therapies were used according to local practice. Clinical improvements in respiratory function within 48 hours and avoidance of mechanical ventilation reported in 16 patients; spontaneous breathing with pO_2 >98% reported on day 7 in 11 patients; no response reported in 2 patients. No patients died. [18]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Phase 3 randomized, double-blind, placebo-controlled, global clinical trial (NCT04362137; RUXCOVID) **failed to confirm efficacy of ruxolitinib** in 432 patients ≥12 years of age with COVID-19-associated cytokine storm (sponsored by Novartis/Incyte). [1, 10, 19] Manufacturer announced results (not peer reviewed) indicating that ruxolitinib (5 mg orally twice daily for 14 days, with possible extension to 28 days) plus standard care did not reduce the proportion of patients experiencing severe complications (death, respiratory failure requiring mechanical ventilation, or ICU admission) by day 29, compared with standard care alone (12 vs. 11.8%); in addition, no clinically relevant benefits were observed among secondary or exploratory end points, including mortality rate by day 29 and time to recovery. [19] **Phase 3, randomized, double-blind, placebo-controlled clinical trial (**NCT04377620; RUXCOVID-DEVENT; 369 DEVENT) **failed to confirm the primary efficacy end point** for ruxolitinib in 211 patients ≥12 years of age with COVID-19-associated acute respiratory distress syndrome (ARDS) who required mechanical ventilation (sponsored by Incyte). [12, 20, 21] Manufacturer announced results (not peer reviewed) indicating that ruxolitinib (5 or 15 mg orally twice daily) plus standard care did not reduce all-cause mortality (adjusted for ARDS severity) through day 29 compared with placebo plus standard care (5 mg vs. placebo: 55.2 vs. 74.3%; 15 mg vs. placebo: 51.8 vs. 69.6%). Manufacturer announced that a mortality benefit was observed when data for both dosages were pooled; a mortality benefit also was observed for both the 5- and 15-mg dosages in the subset of patients enrolled in the U.S. (n = 191). Most patients received concurrent or prior therapy with remdesivir (55%) and corticosteroids (90%). The study was terminated at the time of the above planned interim analysis. Initial targeted enrollment was 500 patients. [21] **Expanded-access (managed-access, compassionate use) program** (NCT04337359) for adults and children ≥6 years of age with		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			severe or very severe COVID-19 illness: No longer available. [1, 2] **Expanded-access program** (NCT04355793) 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, 20, 21, 22] Other clinical trials evaluating ruxolitinib in COVID-19 also may be registered at clinicaltrials.gov. [3]		
Sarilumab (Kevzara®) *Updated 4/30/21*	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]	Results from randomized clinical trials evaluating efficacy of sarilumab in the treatment of patients with COVID-19 have been conflicting. [7, 11, 12, 13] 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 was performed. [3, 4, 7, 9, 10, 12] Patients in this study were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Randomization was stratified by severity of illness (e.g., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids. [7, 12] In the phase 2 part of the study, sarilumab at both dosages reduced C-reactive protein (CRP) levels. [7] The primary efficacy outcome measure in phase 3 was the change on a 7-point scale; this phase was modified to focus on the 400-mg dose of sarilumab in the critically ill patient group. [7] During the course of the trial, there were many amendments that increased the sample size and modified the dosing strategies, and multiple interim analyses were performed. [7, 9] The results did not demonstrate a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. [7, 9, 12] **A second manufacturer-sponsored phase 3 clinical trial was conducted in countries outside the U.S.** (Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Spain) in 420 severely or critically ill patients hospitalized with COVID-19 did not	**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) **In the REMAP-CAP trial, patients received a single** 400-mg IV dose [13] Note: IV formulation not commercially available in the U.S., but was studied in the above-mentioned clinical trial. The sub-Q formulation is not FDA-labeled to treat cytokine release syndrome (CRS) in the U.S. [7]	NIH COVID-19 Treatment Guidelines Panel states that there are **insufficient data** for the Panel **to recommend either for or against** use of sarilumab for hospitalized patients with COVID-19 who are within 24 hours of admission to the ICU and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO_2/30 L/min oxygen flow) [7] (See Tocilizumab in this Evidence Table.) No new safety findings observed with use in COVID-19 patients [9]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			meet its primary endpoint and key secondary endpoint when sarilumab was compared with placebo in addition to usual hospital care. Although not statistically significant, trends were observed toward a decrease in duration of hospital stay, an acceleration in time to improved clinical outcomes, reduced mortality in the critically ill patient group not seen in the severely ill group, and a shortened time to discharge. [9, 11] **Multicenter, ongoing, international open-label trial using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 immune modulation therapy domain, adults with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive either tocilizumab (353 patients; 8 mg/kg by IV infusion over 1 hour; dose may be repeated 12-24 hours later) or sarilumab (48 patients; single 400-mg dose by IV infusion over 1 hour) or standard care (402 patients; control group; corticosteroids were included as standard of care) within 24 hours of commencing organ support in an intensive care unit. Over 80% of the patients in the study received corticosteroids. The primary outcome was an ordinal scale combining in-hospital mortality and days free of organ support to day 21. Compared with standard care, treatment with sarilumab or tocilizumab decreased in-hospital mortality (mortality was 22% for sarilumab and 28% for tocilizumab vs 36% for the standard of care). Compared with standard of care, sarilumab and tocilizumab also improved in-hospital survival and increased the number of organ support-free days. [7, 13] **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).		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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] **Various clinical trials evaluating sarilumab for the treatment of COVID-19** are registered at clinicaltrials.gov. [10]		
Siltuximab (Sylvant®) *Updated 4/30/21*	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]	Only limited, unpublished data available describing efficacy in patients with COVID-19 **Italy:** Non-peer-reviewed findings from an observational cohort study of 30 patients with COVID-19 and pneumonia/acute respiratory distress syndrome (ARDS) who participated in a compassionate use program in one hospital in Italy (SISCO study; NCT04322188) and were followed for at least 30 days showed reduced C-reactive protein (CRP) levels by day 14. The siltuximab-treated patients were compared with 30 propensity score-matched patients receiving best supportive care. The 30-day mortality rate was substantially lower in the siltuximab group compared with the matched-control cohort. Out of the 30 patients treated with siltuximab, 16 (53%) were discharged from the hospital, 4 (13%) remained hospitalized on mechanical ventilation, and 10 patients died. [4, 6] **Various clinical trials evaluating siltuximab for the treatment of COVID-19** are registered at clinicaltrials.gov [10]	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 [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 NIH COVID-19 Treatment Guidelines Panel **recommends against** use of siltuximab in the treatment of COVID-19, except in a clinical trial [9] **Pediatric use:** Safety and efficacy of siltuximab have not been established in pediatric patients [1, 9]
Sirolimus (Rapamune®) *Updated 3/25/21*	92:44 Immunosuppressive agent; mammalian target of rapamycin (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	A few clinical trials evaluating sirolimus for the treatment of COVID-19 are registered at clinicaltrials.gov	Various dosing regimens are being evaluated in registered trials [4]	Although possible clinical application, current data not specific to COVID-19; additional study needed [5]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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] T cell dysregulation has been observed in patients with severe COVID-19 and is thought to be a possible cause of cytokine storm; when given early prior to the cytokine storm phase, sirolimus may prevent progression to severe COVID-19 by restoring T-cell functionality [7]			
Tocilizumab (Actemra®) ***Updated 5/13/21***	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. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients [1-3, 6, 9,10, 14]	Results from randomized clinical trials evaluating efficacy of tocilizumab in the treatment of patients with COVID-19 have been conflicting. [9, 15, 16, 18-22] 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] **In the REMAP-CAP trial, patients received a single** dose of 8 mg/kg based on actual body weight (up to a maximum of 800 mg) by IV infusion; this dose could be repeated 12-24 hours later at the discretion of the treating clinician [21] **Based on the results from the REMAP-CAP and RECOVERY trials,** the NIH COVID-19 Treatment Guidelines Panel recommends **a single 8-mg/kg dose (based on actual body weight) of tocilizumab by IV infusion (up to a maximum of 800 mg) in addition to dexamethasone (6 mg daily for ≤10 days) in certain patients (see Comments column). An alternative corticosteroid to dexamethasone may be used in a therapeutically-equivalent dosage. The Panel states that data are insufficient to determine which patients, if any, would benefit from an additional dose of tocilizumab.** [9]	NIH COVID-19 Treatment Guidelines Panel has revised recommendations regarding the use of tocilizumab in patients with COVID-19 based on the collective evidence from clinical trials reported to date. [9] **The Panel recommends use of tocilizumab (single IV dose of 8 mg/kg of actual body weight, up to 800 mg) in combination with dexamethasone (6 mg daily for ≤10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation caused by COVID-19:** [9] 1) **Recently hospitalized patients (e.g., within 3 days) admitted to the ICU** within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO_2/30 L/min oxygen flow) by nasal cannula. [9] 2) **Recently hospitalized patients (e.g., within 3 days) not admitted to the ICU** with rapidly increasing oxygen needs who require noninvasive ventilation or high-flow nasal cannula oxygen and who have significantly increased markers of inflammation (CRP ≥75 mg/L). [9]

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] **France:** An investigator-initiated, multicenter, open-label, randomized clinical trial (CORIMUNO-TOCI, NCT04331808) evaluated tocilizumab in patients hospitalized at Assistance Publique – Hôpitaux de Paris hospitals in Paris. [15, 16, 20] Sixty-four out of 131 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 67 patients were randomized to receive standard of care alone. Tocilizumab did not reduce scores on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) to <5 on day 4 but may have reduced the risk of noninvasive ventilation, mechanical ventilation, or death by day 14. No difference in day 28 mortality was found. [20] **US/Global randomized, placebo-controlled**	**US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA):** Evaluated an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose was given if symptoms worsened or showed no improvement [8, 18] **Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial** used a single 8-mg/kg IV dose (up to a maximum dose of 800 mg) [19]	**For hospitalized patients with hypoxemia who require conventional oxygen therapy, the Panel states that there is currently insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also use tocilizumab in patients exhibiting rapidly increasing oxygen needs while on dexamethasone and who have a CRP ≥75 mg/L, but who do not yet require noninvasive ventilation or high-flow oxygen as described above.** [9] The Panel states that use of tocilizumab **should be avoided** in patients with significant immunosuppression, particularly in those with a history of recent use of biologic immunomodulating drugs; alanine transaminase levels >5 times the upper limit of normal; high risk for GI perforation; uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection; or absolute neutrophil count <500 cells/µL; platelet count <50,000 cells/µL, or known hypersensitivity to tocilizumab. [9] In addition, the Panel states the following: **Tocilizumab should only be given in combination with dexamethasone (or another corticosteroid at an equivalent dose).** [9] Some clinicians may assess a patient's clinical response to dexamethasone first before deciding whether tocilizumab is needed. [9] Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the treating physician's discretion, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug. [9] Cases of severe and disseminated strongyloidiasis reported with the use of tocilizumab and corticosteroids in patients with COVID-19. Prophylactic

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			trial: Manufacturer (Roche) conducted a randomized, double-blind, placebo-controlled phase 3 trial (COVACTA; NCT04320615) in collaboration with the US Health and Human Services' Biomedical Advanced Research Development Authority (BARDA). The study evaluated safety and efficacy of tocilizumab in combination with standard of care compared with placebo in adults hospitalized with severe COVID-19 pneumonia. The trial failed to meet its primary endpoint of improved clinical status at week 4 (determined using a 7-point scale to assess clinical status based on need for intensive care and/or ventilator use and requirement for supplemental oxygen) and several key secondary endpoints, including the key secondary endpoint of reduced patient mortality.[18] **Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial: In this investigator-driven, randomized, placebo-controlled trial** (NCT04356937), 243 adults with confirmed severe COVID-19, hyperinflammatory states, and at least 2 of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or need for supplemental oxygen in order to maintain SpO_2 >92% were randomly assigned in a 2:1 ratio to receive standard care plus a single IV dose of either tocilizumab (8 mg/kg) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. Secondary efficacy outcomes were clinical worsening and discontinuation of supplemental O_2 among patients who had been receiving it at baseline, both assessed in time-to-event analyses. 58% of the enrolled patients were men, median age was 59.8 years (range: 21.7 to 85.4 years), and 45% of patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group compared with the placebo group was 0.83 (P = 0.64), and the hazard ratio for disease worsening was 1.11 (P = 0.73). At 14 days, 18% of the pts in the tocilizumab group and 14.9% of those in the placebo group had worsening of disease. Median time to discontinuation of supplemental O_2 was 5 days in the tocilizumab group and 4.9 days in the placebo group (P = 0.69). At 14 days, 24.6% of patients in the tocilizumab group and 21.2%		ivermectin should be considered for individuals who are from areas where strongyloidiasis is endemic. [9] **Pediatric use:** There are insufficient data to recommend either for or against tocilizumab for the treatment of hospitalized children with COVID-19 or multisystem inflammatory syndrome of children (MIS-C). Tocilizumab has been used in children to treat cytokine release syndrome associated with CAR-T cell therapy and systemic and polyarticular juvenile idiopathic arthritis. [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
			of those in the placebo group were still receiving supplemental O_2. Patients who received tocilizumab had fewer serious infections than patients who received placebo. Tocilizumab was not found to be effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19 in this study. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide. [19] **Multicenter, ongoing, international open-label trial using a randomized, embedded multifactorial adaptive platform (NCT02735707; REMAP-CAP):** This trial randomized patients to multiple interventions within multiple domains. In the COVID-19 immune modulation therapy domain, adults with suspected or confirmed COVID-19 following admission to an ICU for respiratory or cardiovascular organ support were randomized to receive either tocilizumab (353 patients; 8 mg/kg by IV infusion over 1 hour; dose may be repeated 12-24 hours later) or sarilumab (48 patients; single 400-mg dose by IV infusion over 1 hour) or standard care (402 patients; control group; corticosteroids were included as standard of care) within 24 hours of commencing organ support in an intensive care unit. Over 80% of the patients in the study received corticosteroids. The primary outcome was an ordinal scale combining in-hospital mortality and days free of organ support to day 21. Compared with standard care, treatment with sarilumab or tocilizumab decreased in-hospital mortality (mortality was 22% for sarilumab and 28% for tocilizumab vs 36% for the standard of care). Compared with standard of care, sarilumab and tocilizumab also improved in-hospital survival and increased the number of organ support-free days. [9, 21] **** Randomized, controlled, open-label, platform trial (NCT04381936; RECOVERY): The RECOVERY trial is assessing several possible treatments in patients hospitalized with COVID-19 in hospitals throughout the UK.** Up to 21 days following the initial (main) randomization and regardless of the initial treatment allocation, participants in the RECOVERY trial with clinical		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			evidence of progressive COVID-19 characterized by hypoxia (O_2 saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (CRP concentrations ≥75 mg/L) could be considered for randomization in a 1:1 ratio to tocilizumab (400-800 mg, based on weight, by IV infusion; a second dose could be given within 12-24 hours) plus usual care or usual care alone. Between April 23, 2020 and January 24, 2021, 4116 adults of 21,550 patients enrolled in the RECOVERY trial were included in the assessment of tocilizumab, including 3385 patients (82%) who were receiving systemic corticosteroid therapy. The mean age of enrolled patients was 63.6 years. The primary outcome measure was 28-day mortality; **621 of 2022 patients (31%) in the tocilizumab group died within 28 days compared with 729 of 2094 patients (35%) in the standard of care group. Patients who received tocilizumab also were more likely to be discharged from the hospital alive within 28 days than those receiving standard of care alone (57 versus 50%, respectively)**. Among patients not receiving invasive mechanical ventilation at baseline, **tocilizumab was associated with a substantially lower risk of progressing to invasive mechanical ventilation or death compared with standard of care alone (35 versus 42%, respectively)**. These benefits were seen in all prespecified patient subgroups, including those receiving invasive mechanical ventilation, non-invasive respiratory support, or no respiratory support other than simple oxygen. **Patients concurrently receiving corticosteroids and tocilizumab showed a clear benefit.** There was no evidence that tocilizumab had any effect on the chance of successful cessation of invasive mechanical ventilation. [22] **Various clinical trials evaluating tocilizumab for the treatment of COVID-19** are registered at clinicaltrials.gov. [5]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Vitamin D ***Updated 4/30/21***	88:16 Vitamin D	Vitamin D receptor is expressed on immune cells (e.g., B cells, T cells, antigen-presenting cells); these cells can synthesize and respond to active vitamin D. [10, 13] Vitamin D modulates innate and adaptive immune responses; may downregulate proinflammatory cytokines and upregulate anti-inflammatory cytokines, increase T regulatory cell activity, and reduce cytokine storm induced by innate immune system. [10, 12, 13] In an animal model of gram-negative bacterial-induced acute lung injury (ALI), vitamin D modulated expression of renin, angiotensin II, angiotensin-converting enzyme (ACE) 1, and ACE2, and attenuated ALI; studies needed to determine relevance to SARS-CoV-2 infection. [30, 31] Vitamin D deficiency is associated with increased autoimmunity and increased susceptibility to infection. [10, 13] In observational studies, low vitamin D concentrations have been associated with increased risk of community-acquired pneumonia in older adults and upper respiratory viral infections in children. [1, 8, 9] Vitamin D deficiency is common in the U.S., particularly in Hispanic and Black populations (groups overrepresented among U.S. COVID-19 cases). [1, 14, 20]	Only limited prospective clinical trial evidence regarding efficacy of vitamin D supplementation for treatment or prevention of COVID-19. **Prevention of respiratory infections:** Efficacy of vitamin D supplementation for prevention of influenza or other respiratory infections is unclear. [10] Meta-analysis of 25 randomized, double-blind, placebo-controlled trials including a total of 11,321 participants, either healthy or with comorbidities, indicated a protective effect for oral vitamin D supplementation against acute respiratory infection. [5] A second systematic review and meta-analysis of 15 randomized controlled trials involving approximately 7000 healthy individuals found that vitamin D supplementation did not reduce the risk of respiratory infections compared with placebo or no treatment. [11] **Outcomes in critically ill patients:** Results of 2 randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with vitamin D deficiency (but not with COVID-19) indicated that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D_3; patients in VITdAL-ICU also received oral maintenance doses (90,000 units monthly for 5 months). [6, 7] **Outcomes in patients with COVID-19: Retrospective study (NCT04560608) in frail geriatric patients** (mean age: 88 years; range: 78-100 years) hospitalized with COVID-19 suggested lower frequency of severe COVID-19 disease and lower 14-day mortality in those who received regular oral vitamin D supplementation (50,000 units monthly or 80,000 or 100,000 units every 2–3 months) over the prior year (n = 29) compared with those who received no supplementation, either over the prior year or following COVID-19 diagnosis (n = 32).	Various dosages of vitamin D are being evaluated for prevention or treatment of COVID-19. [4] High concentrations of vitamin D may cause hypercalcemia and nephrocalcinosis; [1] currently no convincing scientific evidence that very high intake of vitamin D will be beneficial in preventing or treating COVID-19. [14] National Academy of Sciences (NAS) guidelines for **adequate dietary intake of vitamin D for bone health in US population**: Estimated Average Requirement (EAR) in children and adults 1-70 years of age is 400 units (10 mcg) daily; Recommended Dietary Allowance (RDA) in these age groups is 600 units (15 mcg) daily. In adults >70 years of age, EAR is 400 units (10 mcg) daily and RDA is 800 units (20 mcg). These reference values assume minimal sun exposure. [26] NAS states that data indicate that a serum 25-hydroxyvitamin D concentration of 50 nmol/L is sufficient to meet the needs of 97.5% of the population and concentrations <30 nmol/L are associated with clinical deficiency. [26]	Efficacy of vitamin D supplementation in the prevention or treatment of COVID-19 has not been established. [1, 2, 3] Some experts recommend maintaining recommended levels of vitamin D intake during the COVID-19 pandemic to maintain bone and muscle health and avoid deficiency. [2, 3, 14] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of vitamin D for prevention or treatment of COVID-19. [1] Joint guidance from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF), and International Osteoporosis Foundation (IOF) emphasizes importance of obtaining the recommended daily dosage of vitamin D; for those unable to obtain recommended durations of direct sun exposure during the pandemic, recommended intake of vitamin D can be obtained through supplemental vitamin D. The joint guidance states that current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19. [2] Recommendations from the UK National Institute for Health and Care Excellence (NICE) state that there is insufficient evidence to recommend use of vitamin D supplements solely to prevent or treat COVID-19, except as part of a clinical trial. However, all individuals should continue to follow current recommendations on daily vitamin D supplementation to maintain bone and muscle health during the pandemic. [3]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Vitamin D deficiency also is more common in older patients and patients with obesity and hypertension (factors potentially associated with worse COVID-19 outcomes). [1, 20, 21, 23-25, 27] Association also suggested between vitamin D and diabetes mellitus (a condition also associated with worse COVID-19 outcomes). [20, 22, 27] Clinical trials are evaluating the relationship between vitamin D concentration and COVID-19 disease severity and mortality; [4] some retrospective observational data suggest an association between vitamin D concentration and COVID-19 risk or severity/mortality, [15-18, 28, 29, 32] but may not account for potential confounding factors. [17-19, 29] Meta-analysis of 26 observational studies reporting vitamin D concentrations in adults and elderly patients with COVID-19 suggested an association between vitamin D deficiency and COVID-19 severity; however, potential for bias in most of the studies was considered high. [36] Prospective observational study in non-elderly adults admitted to a COVID-19 care center indicated higher prevalence of vitamin D deficiency (defined as serum 25-hydroxyvitamin D concentration <20 ng/mL) on admission (97 versus 32%) in patients with severe COVID-19 disease requiring ICU admission	Supplemental oral vitamin D (single 80,000-unit dose) given shortly after COVID-19 diagnosis (n = 16) did not improve outcomes. [35] **App-based community survey, conducted mainly in the UK:** COVID-19 Symptom Study app subscribers in the UK who self-reported regular use of vitamin D supplements (>3 times/week for ≥3 months) had a **modest 9% lower risk of testing positive for SARS-CoV-2** than those who did not report regular use; stratification of data by sex showed an association in women but not in men. The analysis included data for 372,720 UK app users who reported having had a SARS-CoV-2 test and completed a dietary supplement questionnaire. The overall finding of an association between vitamin D supplementation and lower risk of testing positive for SARS-CoV-2 was replicated in smaller numbers of US and Swedish app users; however, findings based on sex varied in the different cohorts. [39] **Randomized, open label, pilot study in hospitalized adults with confirmed COVID-19:** Total of 76 patients were randomized 2:1 to receive oral calcifediol (0.532 mg on day of admission, then 0.266 mg on days 3 and 7 followed by 0.266 mg weekly until discharge or ICU admission) in conjunction with standard care (including 6-day hydroxychloroquine regimen and 5-day azithromycin regimen) or standard care alone (control). ICU admission was reported for 1/50 calcifediol-treated patients (2%) and 13/26 control patients (50%). All calcifediol-treated patients were discharged; 24 control patients were discharged and 2 died. The odds ratio for ICU admission in calcifediol-treated patients vs control patients was 0.02; odds ratio was 0.03 after adjustment for the higher prevalence of hypertension and type 2 diabetes mellitus in the control group. Data on serum vitamin D concentrations were not available. Larger placebo-controlled trials with well-matched groups are needed to confirm these pilot results. [33] **Randomized, double-blind, placebo-controlled trial** (NCT04449718) in 240		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		(n = 63) compared with asymptomatic, SARS-CoV-2 -positive patients admitted to isolation ward (n = 91); inflammatory markers (ferritin, interleukin-6) were elevated in vitamin D -deficient versus non-deficient patients. [37] Results of a Mendelian randomization study (not peer reviewed) **do not support a protective role** for increased 25-hydroxyvitamin D concentrations with respect to COVID-19 outcomes and may suggest harm. The study used genetic determinants of serum 25-hydroxyvitamin D from a genome-wide association study and meta-analysis of >443,734 individuals of European ancestry to estimate the effect of increased 25-hydroxyvitamin D concentrations on COVID -19 susceptibility and severity. Genetically increased concentrations of the vitamin had no clear effect on susceptibility, but tended to increase the odds ratio of hospitalization (2.34) and severe disease requiring hospitalization and respiratory support (2.21). Some analyses suggested worse outcome with increasing concentrations of the vitamin. [34]	hospitalized adults with moderate to severe COVID-19: Vitamin D supplementation (single oral 200,000-unit dose of cholecalciferol) **increased 25-hydroxyvitamin D concentrations but failed to improve clinical outcomes** compared with placebo. No significant differences in median duration of hospital stay (7 vs 7 days), in-hospital mortality rate (7.6 vs 5.1%), ICU admission (16 vs 21.2%), or need for mechanical ventilation (7.6 vs 14.4%) were observed between the vitamin D and placebo groups, respectively. Mean time from symptom onset to enrollment was 10.3 days. Mean baseline 25-hydroxyvitamin D concentration was approximately 21 ng/mL in both groups. Following the intervention, 86.7% of vitamin D recipients vs 10.9% of placebo recipients had 25-hydroxyvitamin D concentrations >30 ng/mL, and 6.7% of vitamin D recipients vs 51.5% of placebo recipients had 25-hydroxyvitamin D deficiency (concentration <20 ng/mL). [38] Other clinical trials evaluating vitamin D supplementation in the prevention or treatment of COVID-19 may be registered at clinicaltrials.gov. [4]		
Zinc *Updated 4/30/21*		Trace mineral involved in immune function, including antibody and white blood cell production; an important cofactor for many enzymes; [1,3] may improve wound healing [8] Zinc deficiency increases proinflammatory cytokine	No evidence from controlled trials that zinc is effective in the prevention or treatment of COVID-19 [5, 6] **Retrospective observational study in New York City (Carlucci et al; non-peer-reviewed):** Data were collected from electronic medical records to compare outcomes between hospitalized patients with COVID-19 who received hydroxychloroquine, azithromycin, and zinc (411 patients)	Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day [3, 8] Some clinicians have recommended an elemental zinc intake of 30-50 mg/day in the short-term treatment of influenza and coronavirus infections [3, 4]	Despite some anecdotal claims in the media that zinc is effective in treating COVID-19,[6] it remains unclear whether zinc supplementation is beneficial in the prophylaxis and/or treatment of COVID-19; further study is needed [1, 3, 6] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		concentrations (interleukin -1 [IL-1], IL-6, TNF alpha) and decreases antibody production; zinc supplementation increases the ability of polymorphonuclear cells to fight infection[1] Possible antiviral activity; zinc appears to inhibit virus RNA polymerase activity and viral replication in an in vitro and cell culture model of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). [1, 7] High-dose zinc supplementation reduced the duration but not severity of common cold symptoms compared with placebo in a meta-analysis [1, 3, 7] Zinc enhances cytotoxicity and induces apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine): chloroquine can enhance intracellular zinc uptake in vitro [9] Elderly patients and patients with certain concurrent medical conditions are at higher risk of zinc deficiency [2, 3, 8]	and those who received hydroxychloroquine and azithromycin alone (521 patients). Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or duration of ICU stay, but patients in the treatment group that included zinc were discharged home more frequently and the need for ventilation, ICU admission, and mortality or transfer to hospice for patients not admitted to the ICU were all reduced in univariate analyses. After adjusting for the timing of when zinc was added to the protocol, findings remained significant for increased frequency of being discharged home and reduction in mortality or transfer to hospice in the zinc-treated patients. Because of the study design and its limitations, the authors state that this study should not be used to guide clinical practice, but that the observations do support initiation of randomized controlled trials investigating zinc in patients with COVID-19. [10] **Multicenter, retrospective, cohort study in New York City hospitals (Yao et al; non-peer-reviewed):** This study reviewed the records of 3473 hospitalized adults with laboratory-confirmed COVID-19 who were admitted to 4 New York City hospitals between March 10 and May 20, 2020. The primary aim of the study was to compare rates of in-hospital mortality among patients who received zinc plus hydroxychloroquine and those not receiving this combination. Out of 3473 patients, 1006 (29%) received zinc and hydroxychloroquine in combination and 2467 (71%) received hydroxychloroquine without zinc. Zinc plus hydroxychloroquine was associated with a 24% reduced risk of in-hospital mortality compared with patients who did not receive the combination (12 versus 17% respectively; p<0.001). In addition, hospital discharge rates were substantially higher in patients receiving the combination versus those who did not (72 versus 67%; p=0.003). Neither zinc nor hydroxychloroquine alone were associated with decreased mortality rates. [14] There are several limitations to this study. It was a	Appropriate dosage regimens not established in either the prophylaxis or treatment of COVID-19; various supplementation regimens being evaluated in clinical trials, with a maximum dosage of zinc sulfate of 220 mg (50 mg of elemental zinc) twice daily [2, 5, 6, 9, 10, 11, 12, 13] NCT04342728 (COVID A to Z): Oral zinc gluconate 50 mg (of elemental zinc) once daily, given at bedtime for 10 days after diagnosis, did not reduce duration of symptoms in outpatients [11] Oral zinc supplementation likely safe in dosages up to 40 mg of elemental zinc daily in adults; safety of dosages exceeding those used in the management of the common cold not known [3, 6, 8]	or against use of zinc in the *treatment* of COVID-19 [9] NIH COVID-19 Treatment Guidelines Panel **recommends against** using zinc supplementation above the RDA for the *prevention* of COVID-19, except in a clinical trial [9] Zinc concentrations are difficult to measure accurately since it is distributed as a component of various proteins and nucleic acids [9] Adverse effects may include nausea (possibly dose dependent), vomiting, and changes in taste [1, 6, 7, 8] Long-term zinc supplementation may cause copper deficiency with adverse hematologic (e.g., anemia, leukopenia) and neurologic effects (e.g., myelopathy, paresthesia, ataxia, spasticity); zinc supplementation for as little as 10 months has been associated with copper deficiency [9] Intranasal administration should be avoided because of reports of prolonged or permanent loss of the sense of smell; intranasal zinc formulations are no longer commercially available in the US [6, 8] Potential for interactions with iron and copper, certain antibiotics (e.g., quinolones, tetracyclines), and other medications [8]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			retrospective in design and patients were not randomized to treatments. In addition, it was not known whether patients were taking zinc and/or hydroxychloroquine prior to admission. The treatment groups were not balanced; patients receiving zinc plus hydroxychloroquine were more likely to be male and Black and to have a higher body mass index and diabetes. Patients receiving zinc plus hydroxychloroquine were also treated more often with corticosteroids and azithromycin and less often with lopinavir/ritonavir than those who did not receive this combination. [9, 14] **Randomized, open-label study (NCT04342728; COVID A to Z)** in an outpatient setting in 214 adults with confirmed SARS-CoV-2 infection: A 10-day oral regimen of ascorbic acid (8 g daily given in 2 or 3 divided doses with meals), zinc gluconate (50 mg at bedtime), or both supplements in combination **failed to reduce the time required to achieve a 50% reduction in symptom severity**, as compared with usual care alone. The mean number of days from peak symptom score to 50% resolution of symptoms (including fever/chills, cough, shortness of breath, and fatigue, each rated on a 4-point scale) was 5.5 days with ascorbic acid, 5.9 days with zinc, 5.5 days with ascorbic acid and zinc, or 6.7 days with usual care alone. Target enrollment was 520 patients; the study was stopped early for futility. [11] **Randomized clinical trial conducted at 3 major university hospitals in Egypt** (NCT04447534): 191 patients with a laboratory-confirmed diagnosis of COVID-19 were randomized to receive either zinc sulfate 220 mg (50 mg of elemental zinc) twice daily in combination with hydroxychloroquine or hydroxychloroquine alone for 5 days; patients in both treatment groups also received standard of care therapy. Hydroxychloroquine was given in a dosage of 400 mg twice daily on the first day, then 200 mg twice daily for 5 days. The primary efficacy endpoints were recovery within 28 days, the need for mechanical ventilation, and death. No significant differences were found between the 2 groups of patients in the percentage of patients who		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			recovered within 28 days (79.2% in the zinc plus hydroxychloroquine group and 77.9% in the hydroxychloroquine group), the need for mechanical ventilation, or overall mortality. [12] **Retrospective observational study at a single institution (Hoboken University Medical Center):** This study collected data on 242 patients with laboratory-confirmed COVID-19 who were admitted to the hospital. 196 of the patients (81%) received a total daily dosage of zinc sulfate 440 mg (100 mg of elemental zinc); 191 of these patients (97%) also received hydroxychloroquine. The primary outcome was days from admission to in-hospital mortality. The primary analysis explored the causal relationship between zinc administration and patient survival. There were no significant differences in baseline characteristics between the 2 groups of patients. 73 patients (37.2%) died in the zinc group compared with 21 patients (45.7%) in the control group. In the primary analysis, which used inverse probability weighting (IPW), the effect estimate of zinc therapy was an additional 0.84 days of survival. This finding was considered imprecise. On multivariate Cox regression analysis with IPW, zinc therapy was not significantly associated with a change in the risk of in-hospital mortality and the use of interleukin-6 inhibitors was associated with reduced mortality. Older patients, male patients, and those with severe or critical disease were significantly associated with increased mortality. [14] Zinc is being evaluated in a number of clinical trials in both the prophylaxis and treatment of COVID-19, sometimes in combination with other supplements (including vitamin C and vitamin D) and drugs (including hydroxychloroquine) [1, 2, 5, 6, 9]		

OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) *Updated 4/30/21*	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]	Only limited data available to date evaluating the effect of these drugs on COVID-19 infection.[1-3, 9, 15-18] **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 from Feb 21 to Mar 11, 2020 who were		American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) recommend continuation of treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.[2, 3] These experts state there is a lack of experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients receiving ACE inhibitors or ARBs. Further study is needed.[2, 3] NIH COVID-19 Treatment Guidelines Panel states patients who are receiving an ACE inhibitor or ARB for cardiovascular disease (or other non-COVID-19 indications) should not discontinue these drugs during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition. The panel **recommends against** use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial. These experts state that it is unclear whether use of ACE inhibitors or ARBs has a positive or negative impact on the treatment and clinical outcomes of COVID-19. Meta-analyses and ongoing reviews have not found an association between the use of such medications and the likelihood of a positive result from SARS-CoV-2 testing or on the severity or outcomes of COVID-19 infection.[9] Patients with cardiovascular disease are at an increased risk of severe COVID-19.[1, 4, 9] 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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] **Multicenter, prospective study in a cohort of hospitalized pts with confirmed COVID-19 infection to evaluate the association of antihypertensive therapy with ACE inhibitors or ARBs and the risk of severe COVID-19 or worsening of clinical outcomes**		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			(NCT04357535; Hakeam et al): Data are available for 338 patients from 4 hospitals in Saudi Arabia. On the day of hospital admission, 245 of these patients (72.5%) were receiving ACE inhibitors or ARBs; 197 of these patients continued such antihypertensive therapy during hospitalization. On the day of hospital admission, 93 patients (27.5%) were receiving antihypertensive therapy (e.g., calcium-channel blockers, β-blockers, thiazide diuretics) that did not include either ACE inhibitors or ARBs. The primary study end point was the rate of developing severe COVID-19 on the day of hospitalization. The key secondary end point was a composite of mechanical ventilation and in-hospital mortality. In the study cohort, 98 patients (29%) met the WHO criteria for severe COVID-19 on the day of hospitalization. However, use of ACE inhibitors or ARBs was not associated with development of severe COVID-19 (odds ratio: 1.17). Use of ACE inhibitors or ARBs prior to hospitalization also was not associated with ICU admission, mechanical ventilation, or in-hospital mortality. In addition, continuing such antihypertensive therapy during non-ICU hospitalization was associated with decreased mortality (odds ratio: 0.22). The authors concluded that patients with hypertension or cardiovascular disease receiving therapy with ACE inhibitors or ARBs prior to hospitalization for COVID-19 do not appear to be at increased risk for severe infection upon hospital admission. In addition, ICU admission, mechanical ventilation, and mortality are not associated with use of ACE inhibitors or ARBs prior to hospitalization. Because of a lower risk of mortality, the authors advise that ACE inhibitor or ARB therapy be continued in pts with COVID-19 during hospitalization. However, because of study limitations, randomized controlled trials are needed for further assessment of the effects of ACE inhibitors or ARBs on COVID-19. [15] **Multicenter, open-label, randomized study in hospitalized pts with mild to moderate COVID-19 to evaluate the effect of discontinuation versus continuation of ACE inhibitors or ARBs on clinical outcomes (NCT04364893; Lopes et al):** Data are		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			available for 659 adults from 29 hospitals in Brazil who were receiving ACE inhibitors or ARBs prior to hospitalization. In the primary analysis, 334 of these patients were randomized to discontinue ACE inhibitors or ARBs and 325 patients were assigned to continue use of such medication for 30 days. The primary study end point was the number of days alive and out of the hospital from randomization through 30 days. Key secondary end points included death during the 30-day follow-up period, cardiovascular death, and COVID-19 progression. No significant difference was observed in the mean number of days alive and out of the hospital for patients in the discontinuation group (21.9 days) compared with patients in the continuation group (22.9 days). There were also no significant differences between the discontinuation and the continuation groups in the incidence of death (2.7 versus 2.8%, respectively), cardiovascular death (0.6 versus 0.3%, respectively), or COVID-19 progression (38.3 versus 32.3%, respectively). The authors concluded that these findings do not support the routine discontinuation of ACE inhibitors or ARBs among hospitalized patients with mild to moderate COVID-19 when there is an indication for such use. Limitations of this trial include the open-label study design and the lack of generalizability of results to COVID-19 patients in other settings. The study also was not designed to evaluate the effect of ACE inhibitors or ARBs on susceptibility to COVID-19. [18] Clinical trials completed; results not yet published (losartan): Initiation of losartan in adults with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score (NCT04312009). Initiation of the drug in adults with COVID-19 not requiring hospitalization; primary outcome measure: treatment failure resulting in hospital admission (NCT04311177). [7] Other clinical trials evaluating the effect of continuing or discontinuing treatment with ACE inhibitors or ARBs on clinical outcomes in patients with COVID-19 are registered at clinicaltrials.gov. [7]		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Anticoagulants ***Updated 5/13/21***	20:12.04 Anticoagulants	Patients with COVID-19, particularly those with severe disease, may develop a hypercoagulable state, which can contribute to poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death).[1-6, 14, 16, 28, 29, 44] Most common pattern of coagulopathy 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 associated with endothelial cell activation and other factors contributing to an uncontrolled immunothrombotic response to the virus.[16, 17, 27-29, 32, 48] Lupus anticoagulants have been detected in some patients with COVID-19 who present with prolonged aPTT;[4, 54] however, clinical significance of these antibodies is not known.[4, 44, 49] Such thrombotic findings are the basis for anticoagulant therapy in COVID-19 patients; some anticoagulant agents also may have antiviral and anti-inflammatory properties.[2, 4, 5, 14, 25, 27, 40, 51, 54]	**Retrospective study in China**: Reduced mortality was observed 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 cohort study using data (n=4297) from the US VA system**: Early initiation of prophylactic anticoagulation (within 24 hours of admission for COVID-19) was associated with a 27% decreased risk of 30-day mortality compared with no anticoagulation; post-hoc analysis indicated that evidence of benefit appeared to be most pronounced in patients who did not require ICU care within the first 24 hours of admission. Results of this study provide some evidence to support recommendations for use of prophylactic anticoagulation in hospitalized COVID-19 patients (see Comments column).[65] Several retrospective studies suggest that high-intensity prophylactic anticoagulation or therapeutic anticoagulation may be associated with lower mortality compared with standard VTE prophylaxis in severe COVID-19 patients.[31, 38, 42, 45, 50] **Retrospective study in a large cohort (n=786) of hospitalized patients with COVID-19**: Systemic anticoagulation was associated with reduced risk of mortality; in the subgroup of patients who required mechanical ventilation, mortality rate was reduced with the use of therapeutic anticoagulation compared with no anticoagulation (29 versus 63%; median survival of 21 versus 9 days).[28, 31, 54] **Subsequent retrospective study involving a larger cohort of patients (n=4389) from the same health system**: Use of prophylactic or therapeutic anticoagulation was associated with lower in-hospital mortality compared with no anticoagulant therapy (adjusted hazard reductions of 50 and 47%, respectively). Overall bleeding rates were low, but higher in the therapeutic anticoagulation group (3%) compared with the prophylactic or no anticoagulation groups.	See Comments column for available dosage-related information.	The available evidence to inform the clinical management of COVID-19-associated coagulopathy is continuously evolving.[9, 11, 27-29, 44, 54, 59] Several organizations (e.g., NIH, WHO, CDC, American Society of Hematology (ASH), International Society for Thrombosis and Haemostasis, Anticoagulation Forum, Surviving Sepsis Campaign, Mayo Clinic) have published interim guidance for anticoagulation management in patients with COVID-19.[4, 5, 9, 15, 25, 27, 28, 30, 32, 44, 48, 51, 54, 56, 59, 64] These experts agree that hospitalized patients with COVID-19 should receive prophylactic-dose anticoagulation to reduce the risk of thromboembolism unless there are contraindications.[4, 5, 15, 28, 44, 64] However, many questions regarding the best prophylactic strategy in COVID-19 patients remain unanswered (e.g., type and intensity of anticoagulation, duration of anticoagulation, use of biomarkers for VTE risk stratification).[28, 55] VTE risk should be assessed in all hospitalized patients with COVID-19.[4, 5, 10, 17, 18, 27, 28, 32, 54, 56] While initial reports suggested that bleeding is infrequent in COVID-19 patients, more information regarding the risk of bleeding is emerging.[5, 30, 60] 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] **The NIH COVID-19 Treatment Guidelines Panel issued the following recommendations for VTE prophylaxis in COVID-19 patients:** 1) **Hospitalized nonpregnant adults with COVID-19**: Prophylactic-dose anticoagulation is recommended.[28] 2) **Pregnant patients hospitalized with severe COVID-19**: Prophylactic-dose anticoagulation is recommended unless contraindicated; if antithrombotic therapy is prescribed prior to the diagnosis

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Among 26 autopsies performed in this cohort of patients, 42% had evidence of thromboembolic disease not otherwise suspected premortem; the majority of these patients were not treated with therapeutic anticoagulation. [40] In other observational studies, intermediate-dose or therapeutic-dose anticoagulation in COVID-19 patients did not provide a mortality benefit over standard-dose prophylaxis and/or was associated with an increased risk of clinically significant adverse effects (e.g., bleeding). [46, 61, 62, 69] All of the aforementioned studies have important limitations such as their retrospective nature, small sample size, confounding variables (e.g., other treatments administered), and lack of information and consistency with regard to anticoagulation indication, doses, and regimens; therefore, confirmation of findings in randomized controlled studies is required. [28, 31, 38, 40, 42, 44, 45, 50, 52, 61, 62, 69] Some retrospective studies have evaluated the impact of a tailored anticoagulant approach (e.g., risk stratification based on D-dimer and other clinical and laboratory parameters) or an escalated-dose thromboprophylaxis approach based on severity of disease. [52, 57] **Phase 2 randomized open-label study (HESACOVID):** Administration of therapeutic-dose enoxaparin in 20 mechanically ventilated COVID-19 patients was associated with improved oxygenation (PaO_2/FiO_2 ratio), decreased D-dimer levels, and a higher rate of successful liberation from mechanical ventilation compared with prophylactic-dose anticoagulation. The study was insufficiently powered to assess mortality. [53] **Meta-analysis of 5 observational studies in critically ill or acutely ill COVID-19 patients conducted by the American Society of Hematology:** No difference was observed in risk of VTE and mortality between patients treated with prophylactic dose anticoagulation and those treated with higher doses of anticoagulation; critically ill patients who received intermediate- or		of COVID-19 in a pregnant patient, such therapy should be continued. [28] 3) **Hospitalized children with COVID-19**: Indications for VTE prophylaxis should be the same as those for children without COVID-19. [28] 4) **Nonhospitalized patients with COVID-19:** Anticoagulants should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for such therapy or is participating in a clinical trial. [28] LMWH is generally preferred for VTE prophylaxis; however, specific drug characteristics (e.g., pharmacokinetics, route of administration, drug interaction potential), 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, 28, 30, 32, 44, 54, 59] There is currently debate about the appropriate intensity of anticoagulation for VTE prevention in COVID-19 patients. [43, 44] Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, some clinicians suggest a more aggressive anticoagulation strategy using intermediate or therapeutic dosages of anticoagulants in such patients; however, current data is limited (see Trials or Clinical Experience Column) and well-designed randomized controlled studies are needed to evaluate these approaches. [8, 11, 14-17, 20-24, 26-28, 30-32, 34, 36, 39, 43, 44, 48, 59] Based on expert opinion, interim guidance from the Anticoagulation Forum (published in July 2020) 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]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			therapeutic-dose anticoagulation had lower odds of PE (OR 0.09) but higher odds of major bleeding (OR 3.84). [28, 66] **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4 trials)**: NIH launched this series of adaptive platform trials to evaluate safety and efficacy of various anticoagulants in different COVID-19 patient populations including outpatient, inpatient, and convalescent. [41] **Large multiplatform, adaptive-design trial that includes 3 global studies (REMAP-CAP, ATTACC, ACTIV-4A):** This trial was initiated to address the question of whether more intensive anticoagulation is indicated in critically ill or moderately ill COVID-19 patients; the primary outcome of this trial is "organ-support-free days." [4, 15] As of December 21, 2020, enrollment of patients requiring ICU-level care (defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or ECMO support) was paused due to results of an interim pooled analysis demonstrating futility of full-dose anticoagulation in reducing the need for organ support and mortality compared with usual care prophylactic-dose anticoagulation. [4, 28, 58] Enrollment is continuing for hospitalized patients not requiring ICU support (i.e., moderately ill patients) in these trials to determine whether there is any benefit from full-dose anticoagulation. [58] On January 22, 2021, NIH reported interim results of the above multiplatform trials in the moderately ill cohort. Based on data collected from more than 1000 moderately ill hospitalized patients with COVID-19 (identified as those not in the ICU and not receiving organ support such as mechanical ventilation at trial enrollment), preliminary findings showed that full-dose anticoagulation was superior to prophylactic doses in reducing mortality or the need for organ support. [15, 63] Peer-review of the finalized multiplatform trial data is pending. [15] **** Randomized open-label trial comparing intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the ICU (INSPIRATION trial; NCT04486508):**		Based on more recent evidence (as of February 2021), **ASH guideline panel** issued the following recommendations for anticoagulation therapy in patients with COVID-19: 1) **Patients with COVID-19-related critical illness (defined as those with an immediately life-threatening condition who would typically be admitted to the ICU, such as patients requiring hemodynamic support, ventilatory support, or renal replacement therapy) who do not have suspected or confirmed VTE**: The ASH guideline panel suggests using prophylactic-intensity over intermediate- or therapeutic-intensity anticoagulation in these patients; however, a conditional recommendation is given based on very low certainty of evidence. (See information on the multiplatform, adaptive-design trial that includes REMAP-CAP, ATTACC, and ACTIV-4A in the Clinical Trials and Experience column). ASH discourages the empiric use of full-dose heparin or LMWH outside a clinical trial in critically ill COVID-19 patients who do not have any other indication for therapeutic anticoagulation. 2) **Hospitalized patients with COVID-19-related acute illness not requiring intensive care (e.g., those with dyspnea or mild to moderate hypoxia) who do not have suspected or confirmed VTE**: ASH suggests the use of prophylactic-intensity over intermediate- or therapeutic-intensity anticoagulation; a conditional recommendation is given based on very low certainty of evidence. Although preliminary findings in the moderately ill patient cohort (those requiring hospitalization but not ICU-level care) suggest that full-dose anticoagulation is superior to usual prophylactic-dose anticoagulation in this population, ASH states that, until peer-reviewed data are available, clinicians should use clinical judgment when managing individual patients and carefully consider the benefits and harms of higher-intensity anticoagulation. [66]

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			No evidence of benefit from intermediate-dose anticoagulation versus standard-dose prophylactic anticoagulation was observed based on a composite primary outcome of venous or arterial thrombosis, treatment with ECMO, or mortality within 30 days. Patients in the intermediate-dose anticoagulation group received enoxaparin 1 mg/kg daily and patients in the standard-dose prophylactic anticoagulation group received enoxaparin 40 mg daily with modification according to body weight and renal function. Among 562 patients who were included in the efficacy analysis, the primary outcome occurred in 45.7% of patients in the intermediate-dose group and 44.1% of patients in the standard-dose prophylaxis group. Although bleeding events were rare, there was a small but nonsignificant increase in major bleeding in the intermediate-dose group (2.5 versus 1.4%). The authors state that these results do not support the routine empiric use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the ICU for COVID-19. [68] **As of December 16, 2020, there were 75 ongoing or completed randomized controlled trials of antithrombotic therapy in patients with COVID-19 registered at clinicaltrials.gov or the World Health Organization clinical trials registry. [12, 43, 47, 67] Several ongoing trials are evaluating anticoagulants (e.g., LMWHs, DOACs) in the outpatient setting. These trials are mostly open-label in design and include COVID-19 patients with a hyperinflammatory or procoagulant state who do not have a high risk of bleeding. [67] In addition, numerous ongoing randomized controlled studies are evaluating various antithrombotic regimens (most commonly LMWHs and UFHs) in hospitalized COVID-19 patients (both ICU and non-ICU). Results of these studies are expected to provide additional evidence on use of intermediate/therapeutic anticoagulation versus standard prophylactic regimens. [67]		3) **COVID-19 patients who experience recurrent clotting of access devices** (e.g., central venous catheters, arterial lines): ASH states that, although of unproven benefit, it may be reasonable to increase the intensity of anticoagulation or switch to a different anticoagulant in these patients. [15] NIH states that there are currently insufficient data to recommend for or against the use of doses higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial setting. [28] The most recent guideline from WHO includes a conditional recommendation to administer standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients with COVID-19 who do not have an established indication for higher dose anticoagulation; this recommendation was made based on a low certainty of evidence. [25] 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]

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COVID-19 Convalescent Plasma *Updated 4/29/21*		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 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]	While there is some evidence suggesting possible benefits of COVID-19 convalescent plasma in the treatment of COVID-19, the specific role of convalescent plasma for the treatment of COVID-19 in patients with or without humoral immunity is unclear and additional data are needed from well-controlled, adequately powered, randomized clinical trials. Data from case reports, case series, and a retrospective case-control study suggest benefit of convalescent plasma in patients with various primary and secondary humoral immunodeficiencies. [25] **Randomized, controlled, open-label, adaptive, platform trial assessing several possible treatments in patients hospitalized with COVID-19 in the UK (NCT04381936; RECOVERY):** Preliminary (non-peer-reviewed) data for 5763 patients randomized to receive standard care and 5795 patients randomized to receive standard care plus convalescent plasma demonstrated **no significant differences in 28-day mortality** between the two groups (risk ratio: 1.00). Convalescent plasma for this study was prepared using only plasma donations with sample to cut-off (S/CO) ratio of ≥6.0 as detected by the EUROIMMUN IgG ELISA test. [54] **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	**Emergency use authorization (EUA) high-titer COVID-19 convalescent plasma dosage and administration for hospitalized patients and those with impaired humoral immunity**: Consider initiating therapy with one high-titer unit (approximately 200 mL) of COVID-19 convalescent plasma given IV through a peripheral or central venous catheter according to standard institutional transfusion guidelines. Additional high-titer COVID-19 convalescent plasma units may be administered based on the prescribing physician's medical judgment and the patient's clinical response. [37, 38] Smaller volumes or prolonged transfusion times may be necessary in patients with impaired cardiac function and heart failure. [38]	Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. [11, 25] Several case reports indicate that patients with humoral immunity may experience persistent SARS-CoV-2 viral replication and, therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies following therapy with convalescent plasma. [25] **There are no convalescent blood products currently licensed by the FDA. COVID-19 convalescent plasma is regulated as an investigational product.** [11, 37] **Emergency use authorization (EUA) for high-titer COVID-19 convalescent plasma:** FDA issued an EUA on August 23, 2020 that permitted use of convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA was reissued in its entirety on February 4, 2021 to authorize the use of **high-titer** COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19, early in the course of disease, and in those hospitalized with COVID-19 who have impaired humoral immunity. **Use of low-titer COVID-19 convalescent plasma is no longer authorized under the EUA.** This EUA is based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) for COVID-19 convalescent plasma sponsored by the Mayo Clinic, and additional studies (including randomized controlled trials). [37] The EUA requires healthcare providers to provide convalescent plasma recipients with the Fact Sheet for Patients and Parents/ Caregivers and to inform recipients of the significant known and potential risks and benefits of emergency use of COVID-19 convalescent plasma. [37, 38] Healthcare facilities and healthcare providers administering high-titer COVID-19 convalescent plasma must

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			symptoms before admission. Overall, survival was improved in patients in the convalescent plasma group compared to the control group; after adjusting for covariates, data suggest a significant improvement in survival in non-intubated patients (hazard ratio: 0.19) receiving convalescent plasma, but not in the small cohort of intubated patients (hazard ratio: 1.24). Subgroup analyses suggested a survival benefit of convalescent plasma among nonintubated patients, in those who received treatment earlier in the course of disease, and those who received therapeutic anticoagulation. No significant transfusion-related morbidity or mortality was observed in patients receiving convalescent plasma. [32] **Uncontrolled case series in US (Salazar et al):** 316 adults with severe and/or life-threatening COVID-19 disease received convalescent plasma (one or two units) in addition to multiple other treatments (e.g., antivirals, anti-inflammatory agents). [26, 48] At the time of an interim analysis, outcomes of 136 convalescent plasma recipients who reached day 28 post-transfusion were compared with two sets of propensity score-matched controls at 28 days after admission. [25, 48] These data suggested a trend toward benefit of convalescent plasma, particularly in patients who were transfused early (i.e., within 72 hours of admission) with high-titer convalescent plasma (i.e., anti-spike protein receptor binding domain titer ≥1:1350). [25, 48] **Cochrane systematic review:** Analysis of 19 published studies (2 RCT, 8 controlled non-randomized studies of interventions [NRSIs], 9 non-controlled NRSIs) evaluating convalescent plasma in adults with COVID-19 (total of 38,160 study participants, of whom 36,081 received COVID-19 convalescent plasma) found low to very low confidence in the efficacy and safety of this treatment approach. [42, 52] **Systematic review (Joyner et al; non-peer-reviewed):** Analysis of pooled data (total of 804 COVID-19 patient outcomes) from 12 studies (3 RCT, 5 matched-control, 4 case series) evaluating convalescent plasma in hospitalized adults with severe or life-threatening COVID-19 found evidence		comply with certain mandatory record keeping and reporting requirements (including adverse event reporting). [38] Consult the EUA, [37] EUA fact sheet for healthcare providers, [38] and EUA fact sheet for patients and parents/caregivers [41] for additional information. The EUA states that high-titer COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. FDA states that adequate and well-controlled randomized trials remain necessary to determine optimal product attributes and to identify appropriate subpopulations for its use and that ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on issuance of the EUA. [37] **The NIH COVID-19 Treatment Guidelines Panel has made the following recommendations regarding the use of convalescent plasma for the treatment of COVID-19:** 1). The panel **recommends against** the use of **low-titer convalescent plasma**. [25] 2). **Hospitalized patients without impaired immunity:** The panel **recommends against** the use of convalescent plasma in those requiring mechanical ventilation. In those not requiring mechanical ventilation, the panel **recommends against** use of high-titer convalescent plasma, except in a clinical trial. [25] 3). **Hospitalized patients with impaired immunity:** The panel states that there are insufficient data to either recommend for or against the use of high-titer convalescent plasma. [25] 4). **Nonhospitalized patients:** The panel states that there are insufficient data to recommend either for or against the use of high-titer convalescent plasma. [25] The Surviving Sepsis Campaign COVID-19 subcommittee suggests that convalescent plasma not be used routinely in

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			favoring efficacy of this therapeutic approach. The risk of death was substantially reduced in hospitalized COVID-19 patients transfused with convalescent plasma compared to matched patients receiving standard therapy (OR: 0.43, p <0.001). **Note:** There were several limitations to this analysis including aggregating mortality data across study populations that varied by dose and timing of convalescent plasma administration, geographic region, and duration of follow-up. [34] **Open-label, randomized, controlled study in Netherlands (Gharbharan et al; Con-COVID study):** Preliminary (non-peer-reviewed) data from a study of 86 hospitalized adults with COVID-19 found no significant difference in mortality, duration of hospital stay, or disease severity on day 15 in patients treated with convalescent plasma (300 mL of convalescent plasma containing anti-SARS-CoV-2 neutralizing antibody titers of ≥1:80 as determined by a SARS-CoV-2 plaque reduction neutralization test) compared with standard of care. [44] **Note:** Anti-SARS-CoV-2 antibodies were detected at baseline in 53/66 patients who had been symptomatic for 10 days prior to study enrollment. Neutralizing antibodies were detected in 44/56 (79%) patients tested with median titers comparable to the donors (1:160). These findings raised concerns about the potential benefit of convalescent plasma in the study population and the study was terminated. [44] **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		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] Current data suggest clinical benefit is associated with transfusion of high-titer convalescent plasma early in the course of the disease (e.g., prior to respiratory failure requiring intubation and mechanical ventilation) and in those with impaired humoral immunity. [1, 2, 16, 17, 20, 24, 25, 36-38] Limited clinical evidence suggests the potential therapeutic window following symptom onset may be longer in patients with suppressed or deficient humoral immunity. [38] Available data suggest that serious adverse effects following administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. Risks associated with COVID-19 convalescent plasma therapy include 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, febrile nonhemolytic reactions, hemolytic reactions, hypothermia, metabolic complications, and post-transfusion purpura. Theoretical risks of COVID-19 convalescent plasma therapy include antibody-dependent enhancement of SARS-CoV-2 infection and long-term immunosuppression. [25] May be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusions. [38] The NIH COVID-19 Treatment Guidelines Panel recommends consulting a transfusion medicine specialist for

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			that preclude any definite conclusions, including the possibility of being under-powered 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] **Open-label, single-arm, phase 2 study (Ibrahim et al):** Data from a study of 38 severely or critically ill hospitalized adults with COVID-19 who received convalescent plasma (up to 2 transfusions of 200 mL of convalescent plasma containing IgG titers of 1:320) found a significant reduction in mortality (13 versus 55%, respectively) and hospital length of stay (15.4 versus 33 days, respectively) in those who were severely ill compared with those who were critically ill. **Note:** Severely ill patients received convalescent plasma approximately 4.6 days following hospital admission and 12.6 days following symptom onset while on high-flow oxygen supplementation without evidence of acute respiratory distress syndrome (ARDS). Critically ill patients received convalescent plasma approximately 16.4 days following hospital admission and 23.1 days following symptom onset after developing ARDS; these patients also had been on ventilation support for an average of 10.6 days prior to transfusion of convalescent plasma. Transient transfusion reaction (fever and hematuria) was observed within 2 hours of transfusion of convalescent plasma in one patient with severe illness. [45] **Open-label, randomized, controlled study in India (Agarwal et al; PLACID trial):** Preliminary (non-peer-reviewed) data from a study of 464 moderately ill adults hospitalized with COVID-19 found no significant difference in 28-day mortality or progression to severe disease in patients treated with convalescent plasma (2 transfusions of 200 mL) plus standard of care compared with standard of care alone. Convalescent plasma therapy was well tolerated by the majority of patients; adverse effects included local infusion site reaction, chills, nausea, bradycardia, dizziness, pyrexia, tachycardia, dyspnea, and IV catheter blockage. [46]		patients with a history of severe allergic or anaphylactic transfusion reactions. [25] **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established; a decision to use high-titer convalescent plasma in patients <18 years of age should be based on an individualized assessment of risks and benefits in consultation with a pediatric infectious disease specialist. [25, 38] The **NIH COVID-19 Treatment Guidelines Panel** states that there are **insufficient data to either recommend for or against** the use of convalescent plasma for the treatment of COVID-19 **in hospitalized children who do not require mechanical ventilation.** The Panel **recommends against** use of convalescent plasma for the treatment of COVID-19 **in mechanically ventilated pediatric patients.** [25] **Pregnancy:** Safety and effectiveness of convalescent plasma during pregnancy have not been evaluated; however, pathogen-specific immunoglobulins are used clinically during pregnancy to prevent infection from varicella-zoster virus (VZV) and rabies virus. [25] **FDA does not collect COVID-19 convalescent plasma and does not provide such plasma**; healthcare providers and acute care facilities obtain convalescent plasma from FDA-registered or licensed blood establishments. [11, 37] Information on obtaining such plasma may be available at www.redcrossblood.org or www.aabb.org. [14, 15] **FDA issued a guidance for industry to provide recommendations to healthcare providers and investigators regarding COVID-19 convalescent plasma, which may be used under the EUA, and investigational COVID-19 convalescent plasma, which does not meet all conditions of the EUA and/or is being used under an investigational new drug application (IND)**. This guidance document includes recommendations regarding pathways available for administering or studying COVID-19

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			Open-label, randomized, controlled study in Chile (Balcells et al): Preliminary (non-peer-reviewed) data from a study of 58 adults hospitalized within 7 days of COVID-19 symptom onset with risk factors for disease progression and without mechanical ventilation found no significant difference in composite outcome of death, mechanical ventilation, or prolonged hospital admission (>14 days) in patients who received convalescent plasma (up to two transfusions of 200 mL) immediately following hospital admission compared with those who received convalescent plasma at clinical deterioration. Two patients developed severe respiratory deterioration within 6 hours after transfusion of convalescent plasma and were categorized as possible transfusion-associated acute lung injury (TRALI) type II. [47] **Expanded access IND protocol in US (Joyner et al):** Analysis of 35,322 adults hospitalized with laboratory-confirmed SARS-CoV-2 infection who had or were considered at high risk of progression to severe or life-threatening COVID-19 who participated in a US FDA Expanded Access Program (NCT04338360) suggests that 7- and 30-day mortality rates are substantially reduced in patients transfused with convalescent plasma within 3 days of COVID-19 diagnosis. Patients received at least one unit (approximately 200 mL) of ABO-compatible COVID-19 convalescent plasma IV according to institutional transfusion guidelines. A statistically significant difference in crude 7-day mortality was observed between patients transfused with convalescent plasma within 3 days of COVID-19 diagnosis compared with those transfused with convalescent plasma 4 or more days after COVID-19 diagnosis (8.7 vs 11.9%). Similar findings were observed for 30-day mortality rate (21.6 vs 26.7%). A reduction in 7- and 30-day mortality rate also was observed in patients transfused with convalescent plasma containing higher IgG antibody levels (>18.45 signal-to-cut-off [S/Co] ratio) compared with those transfused with convalescent plasma containing IgG antibody levels ≤18.45 S/Co. [36] Analysis of key safety indicators in 20,000 adults who participated in this Expanded Access Program		convalescent plasma, collection of such plasma (including donor eligibility and qualifications, testing such plasma for anti-SARS-CoV-2 antibodies, product labeling, and recordkeeping. [11] **Additional pathways (outside of the EUA) for administering or studying the use of investigational COVID-19 convalescent plasma**: 1). **Clinical Trials:** Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional IND regulatory pathway. [11] 2). **Intermediate-size Population Expanded Access IND:** FDA is accepting requests for expanded access INDs for use of COVID-19 convalescent plasma in patients with serious or immediately life-threatening COVID-19 who are not eligible or are unable to participate in randomized clinical trials. Consult the FDA guidance document for specific information on applying for an expanded access IND for more than a single patient. [11] 3). **Single Patient Emergency Expanded Access IND (IND)**: Licensed physicians seeking to administer COVID-19 convalescent plasma to individual patients with serious or life-threatening COVID-19 may request an individual patient expanded access IND from the FDA. Consult the FDA guidance document for specific information on applying for a single patient IND. [11] **Donor eligibility**: The FDA guidance states that COVID-19 convalescent plasma for use under the EUA or for use under an IND may be collected from individuals who meet the following qualifications: [11] 1). Laboratory-confirmed evidence of COVID-19 infection in individuals who had symptoms or laboratory-confirmed evidence from 2 different tests in those who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19. [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			suggests that IV transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. Within the first 4 hours after transfusion, 146 serious adverse events (i.e., transfusion-associated circulatory overload, 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 13/146 serious adverse events were judged by the treating clinician as related to convalescent plasma transfusion. [31] Within 7 days after transfusion, 1136 other serious adverse events were reported (i.e., thromboembolic or thrombotic event, sustained hypotensive event requiring IV vasopressor, cardiac event); however, 55/87 thromboembolic or thrombotic complications and 569/643 cardiac events were judged to be unrelated to convalescent plasma transfusion. [31] **Retrospective subset analyses of Mayo Clinic expanded-access protocol in US**: Retrospective analysis of a subset of 3082 hospitalized adults with COVID-19 who were treated with convalescent plasma at 680 acute care facilities in the US as part of an expanded-access program indicated 30-day mortality was improved following transfusion of high-titer COVID-19 convalescent plasma compared with low-titer convalescent plasma in patients who did not require mechanical ventilation prior to transfusion (relative risk: 0.66); however, **no effect on mortality was observed in patients who required mechanical ventilation** prior to transfusion of convalescent plasma (relative risk: 1.02). [25, 53] **Randomized, embedded, multifactorial adaptive platform trial (REMAP-CAP):** Preliminary analysis of 912 hospitalized adults with severe COVID-19 requiring ICU admission indicated that convalescent plasma was unlikely to benefit such patients; however, the study continues to recruit hospitalized patients who do not require ICU admission. [25, 55] **Open-label, prospective study (Madariaga et al):** The relationship between clinical and serologic parameters in a group of COVID-19 convalescent plasma donors and		2). 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] 3). Male donors, female donors who have never been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies. [11] To ensure that COVID-19 convalescent plasma collected from donors contains antibodies directly related to an immune response to SARS-CoV-2 infection, the FDA guidance states that COVID-19 convalescent plasma should **not** be collected from the following individuals: 1). Those who have received an investigational COVID-19 vaccine in a clinical trial or received an authorized or licensed COVID-19 vaccine, unless they had symptoms of COVID-19 *and* a positive test result from a diagnostic test approved, cleared, or authorized by FDA *and* received the COVID-19 vaccine after diagnosis of COVID-19 *and* are within 6 months after complete resolution of COVID-19 symptoms. 2). Those who received an Investigational COVID-19 monoclonal antibody in a clinical trial or received an authorized or licensed COVID-19 monoclonal antibody (SARS-CoV-2-specific mAb), unless it is ≥3 months after receipt of such therapy.[11] **SARS-CoV-2 antibody titers in donor plasma:** COVID-19 convalescent plasma for use under the EUA or an IND must be tested to determine suitability before release. [11] **Information on tests acceptable for use in the manufacture of high-titer COVID-19 convalescent plasma and respective qualifying results may be found in the EUA.** [37]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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 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] **Randomized, double-blind, placebo-controlled study in Argentina (Libster et al):** Results of this study in 160 geriatric patients (≥75 years of age or 65–74 years of age with ≥1 coexisting condition) with mild COVID-19 who received convalescent plasma (250 mL with a SARS-CoV-2 anti-spike antibody titer of >1:1000) or placebo (250		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			mL of 0.9% sodium chloride injection) within 72 hours of symptom onset found a significant reduction in risk of progression to severe respiratory disease (16 versus 31%, respectively; relative risk 0.52). However, the study was terminated early because of the lack of available patients and, therefore, is likely underpowered. [51] **Retrospective matched cohort study (Rogers et al; non-peer-reviewed)** of hospitalized COVID-19 patients at 3 Rhode Island medical centers indicated no significant difference in in-hospital mortality or rate of hospital discharge in patients who received convalescent plasma within a median of 7 days after symptom onset; however, subgroup analysis suggested a significantly increased hospital discharge rate among convalescent plasma recipients 65 years of age or older. [43] **Retrospective matched cohort study (Yoon et al; non-peer-reviewed)** of hospitalized COVID-19 patients at a New York medical center indicated no significant difference in all-cause mortality at 28 days in adults who received convalescent plasma (200 mL containing SARS-CoV-2 anti-spike antibody titers >1:2430) within 72 hours of admission. Subgroup analysis suggested a 4-fold decrease in mortality (8.8 vs 29.4%) and deterioration in oxygenation or mortality (11.8 vs 35.3%) in convalescent plasma recipients <65 years of age compared with propensity score-matched patients who did not receive convalescent plasma. [50] **Retrospective study (Salazar et al; non-peer-reviewed)** of adults diagnosed with COVID-19 and hospitalized with pneumonia in 215 hospitals in Argentina suggested clinical benefit of convalescent plasma in such patients; a significant reduction in 28-day unadjusted mortality was observed in convalescent plasma recipients compared with those who did not receive convalescent plasma (25.5 vs 38%). [49] **Multiple clinical trials are ongoing 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 are registered at clinicaltrials.gov.		

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Famotidine *Updated 4/30/21*	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] However, computer-aided modeling suggested binding affinity is weak and combined use with other antivirals would likely be required. [14] In vitro data suggest famotidine does not bind to SARS-CoV–2 proteases, although antiviral activity was not tested in cell lines that express H_2 receptors. [11, 12] No in vitro antiviral activity against SARS-CoV-2 observed in infected Vero E6 cells. [11] A possible role for dysfunctional mast cell activation and histamine release in mediating clinical manifestations of COVID-19 has been postulated; it is further postulated that the principal action of famotidine in COVID-19 may relate to activity at H_2 receptors. [10, 11] **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	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] Other randomized clinical trials evaluating famotidine for treatment of COVID-19 may be registered at clinicaltrials.gov. [5] **Retrospective cohort study** (NCT04389567) 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] **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	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. IDSA suggests against using famotidine for the sole purpose of treating COVID-19 in hospitalized patients with severe COVID-19 outside of the context of a clinical trial. [9]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		(14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors [3]	(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] **Retrospective, matched, single-center, observational study** in hospitalized patients with RT-PCR-confirmed COVID-19: **In-hospital mortality (14.5 vs 26%) and the combined end point of death or intubation (7.2 vs 13.8%) were reduced in patients who received famotidine** (n = 83) compared with a propensity score-matched group of patients who did not receive the drug (n = 689). Famotidine use was identified from electronic medical records and was defined as IV or oral use at any dosage within 7 days before or after COVID-19 screening and/or hospitalization; in the famotidine group, 66% received the drug in hospital only, and 29% received the drug both before and during hospitalization. Median total in-hospital dose was 80 mg (range: 40-160 mg) given over a median of 4 days (range: 2-8 days). There were no significant differences between the groups with respect to baseline demographics, comorbidities, or severity of illness or in concomitant use of hydroxychloroquine, remdesivir, azithromycin, or corticosteroids. [10] **Retrospective territory-wide cohort study** (not peer reviewed) in Hong Kong investigating the association between famotidine use and COVID-19 severity: In this cohort of 952 adults hospitalized with COVID-19, 51 patients (5.4%) had severe disease; 23 patients (2.4%) received famotidine and 4 patients (0.4%) received proton-pump inhibitors (PPIs), as determined on the day of		

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			admission. Multivariable logistic regression analysis showed **no significant association between severe COVID-19 disease and use of famotidine or PPIs.** [15] **Retrospective, matched, multiple-hospital study** investigating the association between in-hospital famotidine use (within 24 hours of admission) and mortality in patients with confirmed COVID-19: Famotidine users and nonusers were matched by age, gender, race and ethnicity, body mass index, comorbidities, and in-hospital hydroxychloroquine use. Patients who died or required intubation within 48 hours of admission were excluded. The post-match cohort included 410 patients (35.5%) who received famotidine and 746 matched controls (64.5%). Multivariable logistic regression analysis within the matched cohort showed **no association between in-hospital famotidine use and 30-day mortality** after adjustment for WHO severity rating, smoking status, and use of antiviral and supportive therapies. [16] **Retrospective, multihospital, cohort study** in hospitalized patients with an electronic health record (EHR) diagnosis of COVID-19: **Famotidine use did not reduce mortality or the combined end point of death plus intensive intervention** (mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation [ECMO]) at 30 days after admission compared with nonuse of famotidine or compared with use of proton-pump inhibitors (PPIs) or hydroxychloroquine. Medication use was determined from dispensing records on the day of admission; famotidine nonuse was defined as no history of exposure to the drug on or before the day of admission. Patients receiving intensive services on or within 30 days prior to admission were excluded. The study included 1816 famotidine users, 2193 PPI users, 5950 hydroxychloroquine users, and 26,820 nonusers of famotidine. Most famotidine users received the drug orally (64%) at a low dose of 20 mg (73%) on the day of admission. After propensity score stratification, the hazard ratio for death was 1.03, 1.14, or 1.03 for famotidine use vs.		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			no famotidine use, vs. PPI use, or vs. hydroxychloroquine use, respectively. Results for the combined end point were similar. [17] **Meta-analysis** of the above 5 retrospective studies, [7, 10, 15-17] which included a total of 36,635 patients, found **no significant protective effect** for famotidine in reducing the risk of progression to severe illness, death, or intubation in patients with COVID-19 (odds ratio = 0.82 [95% CI = 0.52-1.3]). [18] Uncontrolled series of hospitalized patients with COVID-19 receiving open-label, **combined H_2 and H_1 antagonist therapy (famotidine and cetirizine)** for ≥48 hours: Total of 110 patients at a single hospital received famotidine 20 mg and cetirizine hydrochloride 10 mg orally or IV every 12 hours; concomitant therapy included hydroxychloroquine (85%), tocilizumab (51%), methylprednisolone (31%), and convalescent plasma (30%). Findings included a 16.4% overall rate of intubation, 7.3% rate of intubation after ≥48 hours of treatment, 15.5% mortality rate, and 11-day average hospital stay. **Note:** Comparisons were limited to published outcome data from other locales for patients receiving "standard-of-care" regimens. [13]		
Fluvoxamine (Luvox CR®) *Updated 4/30/21*	28:16.04.20 Selective Serotonin-reuptake Inhibitors	Precise mechanism against SARS-CoV-2 not known; fluvoxamine is an antidepressant with high affinity at the sigma-1 receptor, which potentially could help prevent clinical deterioration in patients with COVID-19. [1, 3] The sigma-1 receptor in the endoplasmic reticulum was essential for cytokine production in a mouse model of septic shock; fluvoxamine is associated with enhanced survival in mouse models of inflammation and sepsis and inhibition of the inflammatory response in human peripheral blood cells. [1, 2, 3]	**Randomized, double-blind, placebo-controlled, fully remote (contactless) trial** (Lenze et al; NCT04342663) evaluated whether fluvoxamine could prevent clinical deterioration in adult outpatients with symptomatic (symptom onset within 7 days prior to randomization) and laboratory-confirmed COVID-19 with an O_2 saturation of ≥92%. Patients enrolled from the St Louis metropolitan area were randomly assigned to receive either fluvoxamine 100 mg or placebo orally 3 times daily for 15 days (see Dosage column). The primary efficacy outcome was clinical deterioration within 15 days of randomization, which was defined as meeting both of the following criteria: 1) shortness of breath or hospitalization for shortness of breath or pneumonia and 2) O_2 saturation <92% on room air or need for supplemental oxygen to achieve an O_2 saturation of ≥92%. Out of 152 randomized patients, 115 (76%) completed the trial. Clinical deterioration occurred in 0 of 80	Fluvoxamine dosage in NCT04342663: 50 mg once in the evening on day 1, then dosage was increased to 100 mg twice daily as tolerated on days 2 and 3, then increased to 100 mg 3 times daily as tolerated through day 15. [3] Fluvoxamine dosage in NCT04668950: Initial dosage of 50 mg once daily then 100 mg twice daily for approximately 15 days; dosage can be adjusted based on tolerability. [4] Fluvoxamine dosage in the open-label cohort was initial dose of 50-100 mg, then 50 mg twice daily for 14 days. [5]	NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of fluvoxamine for the treatment of COVID-19. The panel states that results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of fluvoxamine in the treatment of COVID-19. [6] Some potential advantages of fluvoxamine include that it's a relatively safe, inexpensive, and available drug that can be given orally. Unlike some selective serotonin-reuptake inhibitors, fluvoxamine is not associated with QT-interval prolongation. In addition, it has been widely used in children and adults and may help treat depressive and anxiety symptoms that may occur in patients with COVID-19. However, fluvoxamine

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Further studies needed to establish whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the COVID-19 setting. [6]	patients in the fluvoxamine group and in 6 of 72 patients (8.3%) in the placebo group. This preliminary study had several limitations, including a relatively small sample size, a single geographic area, a limited number of events occurred, and a short follow-up period. In addition, ascertaining clinical deterioration of patients was difficult because all assessments were made remotely. [3, 6] A larger, fully remote, randomized, placebo-controlled, phase 3 trial (the StopCovidTrial) evaluating fluvoxamine in adults with COVID-19 (expected enrollment 880) is currently under way by the same group of investigators as the Lenze et al study above (NCT04668950). [4] Seftel and Boulware reported on a **prospective open-label cohort of patients in whom fluvoxamine was given during a mass COVID-19 outbreak** at a horse racing track in California. A total of 65 patients with laboratory-confirmed COVID-19 chose to receive fluvoxamine (loading dose of 50-100 mg, then 50 mg twice daily for 14 days) and 48 patients declined the drug and received observed only. Hospitalization occurred in 0% of the fluvoxamine-treated patients compared with 12.5% of those receiving observation alone (2 of these patients required ICU treatment with mechanical ventilation and one of these patients died). At 14 days, residual symptoms persisted in none of the fluvoxamine-treated patients compared with 60% of those receiving observation alone. No serious adverse events were reported in the patients taking fluvoxamine. Limitations of this study include that it was a nonrandomized trial with a small sample size and limited data were collected during the course of the study. [5, 6] Other clinical trials evaluating use of fluvoxamine in patients with COVID-19 may be registered at clinicaltrials.gov. [4]		may cause clinically important drug interactions because it is a potent inhibitor of CYP isoenzymes 1A2 and 2C19 and a moderate inhibitor of CYP isoenzymes 2C9, 2D6, and 3A4. [1, 3, 5, 6] **Pediatric use:** No data available to date on use of fluvoxamine for prevention or treatment of COVID-19 in pediatric patients. [6]

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HMG-CoA Reductase Inhibitors (statins) *Updated 4/30/21*	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 pts with COVID-19. Retrospective cohort studies in various settings and meta-analyses conducted using data from observational studies have yielded conflicting results regarding the benefit of statin treatment on disease severity or mortality and/or recovery time in pts with COVID-19. [10-16, 22-30] **Retrospective cohort studies:** In a study of 13,981 pts 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 pts who received statins during hospitalization compared with pts who did not receive statins. Among propensity-score-matched pts (861 pts in the statin group vs 3444 matched pts in the non-statin group), the risk of 28-day all-cause mortality was 42% lower in pts 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 pts. The authors note that pts in the statin group were older and had a higher prevalence of comorbidities and more severe symptoms at baseline; matched non-statin pts therefore had more severe baseline symptoms and comorbidities than unmatched pts, which could account for the increased mortality in the non-statin group after propensity score matching. [11] In a national registry-based cohort study in Denmark, statin use was **not** associated with decreased risk of all-cause mortality or severe disease in patients with COVID-19. This study captured data from 4842 pts with a hospital encounter (e.g., inpatient, outpatient, ED visit) and COVID-19; 17.4% were receiving statin therapy (defined as individuals having filled a prescription for a statin within 6 months prior to COVID-19 diagnosis). After adjusting for baseline characteristics, including comorbidities (e.g., history of ischemic heart disease, stroke, diabetes mellitus, hypertension, malignancy, chronic kidney disease, liver disease) and concomitant medications,		NIH COVID-19 Treatment Guidelines Panel states pts who are receiving statin therapy for an underlying medical condition should not discontinue such therapy unless discontinuation is otherwise warranted by their clinical condition. [2] The panel **recommends against** use of statins for the treatment of COVID-19 except in the context of a clinical trial. [2] Pts with cardiovascular disease are at an increased risk of serious COVID-19 infections. [3] In pts 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) pts are on guideline-directed statin therapy. [3]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			there was no difference between statin and non-statin pts in the 30-day risk of all-cause mortality, severe disease, and a composite of both outcomes. The study also found no differences in these outcomes among statin pts when stratified by specific statin or statin intensity. [23] In a study of 2157 pts hospitalized with COVID-19 at multiple centers in Spain (NCT04407273; STACOV), statin use prior to hospitalization was associated with a lower in-hospital mortality rate compared with no statin use (19.8 vs 25.4%), particularly in pts who continued statin therapy during hospitalization (17.4%). Approximately 58% of the 581 pts receiving statins prior to hospitalization continued therapy at the same dosage during hospitalization. In this study, propensity matching failed to achieve similar baseline characteristics between statin and non-statin pts; pts were therefore matched using a genetic matching method. [20] A study of 2147 pts hospitalized with COVID-19 at 2 hospitals in China found an association between statin use and lower mortality and improved clinical outcomes compared with no statin use. In this study, 11.6% of patients were receiving statin therapy prior to admission that was continued during hospitalization. After propensity score matching, statin use was associated with a lower risk of death, ARDS, and ICU admission compared with no statin use (adjusted hazard ratios: 0.251, 0.232, and 0.381, respectively). [24] In a study of 842 pts hospitalized with COVID-19 at multiple centers in Italy, statin use was not associated with a difference in in-hospital mortality compared with no statin use. In this study, 21% of pts were receiving statin therapy prior to admission. After propensity score matching, although pts receiving statin therapy presented with worse disease severity (as assessed by the National Early Warning Score [NEWS]) and worse radiological features compared with non-statin pts, there was no difference in in-hospital mortality between statin and non-statin pts. The study also found that,		

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			although pts receiving high- or moderate-intensity statin therapy had worse clinical presentation of disease compared with those receiving low-intensity statin therapy, in-hospital mortality was similar between the groups. [25] In a study of 170 pts hospitalized for COVID-19 at a single US center, statin use prior to admission was associated with reduced risk of developing severe disease and, among those without severe disease, faster time to recovery. In this study, 27% of pts reported using statins within 30 days prior to hospitalization for COVID-19. Statin use was associated with a 71% lower risk of severe outcome (i.e., death or ICU admission). In addition, rate of recovery in pts without severe disease was higher (hazard ratio for recovery: 2.69) and median time to recovery was shorter for those who received statins. The beneficial effect of statin use on reduction of severe outcomes in pts with COVID-19 was greater than that observed in a large control cohort of COVID-19-negative pts. [12] In a study of 249 pts hospitalized with COVID-19 at multiple US centers, statin use prior to hospitalization was associated with lower risk of invasive mechanical ventilation in some models, but there was no substantial association between statin use and in-hospital death or ICU admission. [16] In a cohort analysis of 541 pts hospitalized with COVID-19 at a single center in Italy, the association between statin use prior to hospitalization and reduced mortality or disease severity was not statistically significant. [21] Statin use was associated with a small, but statistically significant, decrease in mortality compared with no statin use in a multicenter US-based study comparing 2297 COVID-19 pts receiving statins (defined as pts with a medication order for a statin within 10 days before and 7 days after positive SARS-CoV-2 test) with 4594 propensity score-matched non-statin pts. In this study, the mortality rate was 16.1% in statin users and ranged from 18-20.6%, depending on		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			propensity score iteration, in non-statin users. [30] In a study using the Korean National Health Insurance Service database, prior statin use was associated with a lower risk of mortality in hospitalized COVID-19 pts. This study included 10,448 pts hospitalized for COVID-19 (5.1% were statin users based on prescription records). After propensity score matching, the risk of mortality was 36% lower in statin users compared with non-statin users. [29] **Intensive care pts:** In a study of 87 pts admitted to the ICU with COVID-19 at a single US center, treatment with atorvastatin (40 mg daily) was associated with a reduced risk of death (adjusted hazard ratio: 0.38). [13] **Non-hospitalized pts:** In a study of 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 pts receiving statin therapy remained asymptomatic compared with 22% of the 123 pts not receiving statins. [10] In a retrospective cohort study in Korea, statin use was associated with lower odds of developing COVID-19 compared with no statin use. This study included 122,040 individuals without COVID-19 in the National Health Insurance Service database in Korea (18.5% were statin users based on prescription records). The primary endpoint was COVID-19 diagnosis. After propensity score matching, the odds of developing COVID-19 were 35% lower in statin users compared with non-statin users. However, among the 7780 pts diagnosed with COVID-19, there was no substantial difference in hospital mortality between statin users and those not receiving statins. [28] **Meta-analyses**: Preliminary findings from a **meta-analysis** (Kow & Hasan) of 4 cohort or case-control studies which included a total of 8990 pts with COVID-19 suggest that statin use is		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			associated with a 30% reduction in risk of severe or fatal outcome in pts with COVID-19. [14] However, another **meta-analysis** of 9 cohort or case-control studies (Hariyanto & Kurniawan) did not find an association between statin use and improved severity or mortality outcomes in pts with COVID-19. This meta-analysis included a total of 3449 pts with COVID-19 and included 2 of the same studies used in the Kow & Hasan analysis. [15] A larger **meta-analysis** of observational studies (Scheen) found that statin use was not associated with reduced in-hospital mortality (13 studies with a total of 42,722 pts) or disease severity (11 studies with a total of 14,022 pts). In studies using multivariate analyses or adjusting for covariates, statin use was associated with lower rates of in-hospital mortality and reduced disease severity (adjusted odds ratio: 0.73). In addition, studies that utilized propensity-score matching for comparison found a statistically significant lower risk of in-hospital mortality in statin users compared with those not receiving statins (hazard ratios ranging from 0.48 to 0.88). The authors note that there was considerable heterogeneity between studies. [22] Another meta-analysis (Pal et al.), which included 14 observational studies with a total of 19,988 pts, found that although analysis of *unadjusted* data indicated current and/or in-hospital statin use was not associated with differences in clinical outcomes (e.g., mortality, ICU admission), when analysis was limited to the 5 studies that reported *adjusted* odds and/or hazard ratios, statin use was associated with a 36-49% reduced risk of adverse clinical outcomes. [26] Another meta-analysis (Permana et al.; 13 observational studies with a total of 52,122 pts) investigated whether in-hospital use of statins had an effect on mortality in patients with COVID-19. In 8 studies that specifically reported the use of statins *during* hospitalization, in-hospital statin use was associated with a 46% lower risk of mortality compared with no statin use.		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			In the remaining 5 studies where statin use was discontinued or not explicitly stated as being continued during hospitalization, no difference in mortality was observed between pre-hospitalization statin use and no prior statin use. [27] **In pts with diabetes mellitus** hospitalized with COVID-19, observational studies have also yielded conflicting results with regards to statin use. [17, 18, 19] In a US single-center observational study, among 2266 pts with diabetes mellitus hospitalized with COVID-19, statin use during hospitalization was associated with reduced in-hospital mortality (hazard ratio 0.51). [19] In addition, a large registry-based cohort study in England found an association between statin use (i.e., having a prescription for statins) and reduced COVID-19-related mortality in pts with type 2 diabetes mellitus. [17] However, a cohort study of 2449 pts with type 2 diabetes mellitus hospitalized with COVID-19 at multiple centers in France (CORONADO study) found that statin use prior to hospitalization was associated with higher 7- and 28-day mortality compared with no statin use (odds ratio 1.74 and 1.46, respectively). [18] **Other respiratory conditions:** 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 pts hospitalized with influenza and/or pneumonia. [3-6] Other clinical trials evaluating use of statins in pts with COVID-19 may be registered at clinicaltrials.gov. [9]		
Immune Globulin *Updated 10/28/20*	80:04 Immune Globulin	**Commercially available immune globulin (non-SARS-CoV-2-specific IGIV, IVIG, γ-globulin):** Immune globulin derived from pooled plasma containing many antibodies normally present in adult human blood; used for replacement therapy or treatment of various immune and inflammatory disorders	**Investigational Anti-SARS-CoV-2 Hyperimmune Globulin (anti-SARS-CoV-2 hIGIV)** Several manufacturers are collaborating to provide investigational anti-SARS-CoV-2 hIGIV on behalf of the CoVIg-19 Plasma Alliance for the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) study (NCT04546581). The ITAC study is an international, multi-center, randomized, double-blind, placebo-controlled, adaptive phase 3 study sponsored by the NIAID to	Commercially available immune globulin (non-SARS-CoV-2-specific 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, 20]	Role of commercially available immune globulin (non-SARS-CoV-2-specific IGIV) and investigational anti-SARS-CoV-2 hyperimmune globulin (anti-SARS-CoV-2 hIGIV) in the treatment of COVID-19 is unclear. [16] The NIH COVID-19 Treatment Guidelines Panel recommends against the use of commercially available IGIV (non-SARS-CoV-2-specific IGIV) for the treatment of COVID-19 except in the context

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		(e.g., primary or secondary humoral immunodeficiency, immune thrombocytopenic purpura) and also used to provide *passive* immunity to certain viral infections in other individuals. [1, 21, 22] Commercially available immune globulin (non-SARS-CoV-2-specific IGIV) 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] **Investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hyperimmune globulin intravenous [hIGIV]):** Concentrated immune globulin preparation containing specific antibody derived from pooled plasma of individuals who have recovered from COVID-19.[16, 23] Investigational anti-SARS-CoV-2 hIGIV preparations potentially could reduce dissemination and accelerate clearance of SARS-CoV-2 and theoretically may provide both immediate and long-term protection against the virus (e.g., for as long as one month). [2, 16, 23, 24]	evaluate safety, tolerability, and efficacy of anti-SARS-CoV-2 hIGIV for treatment of hospitalized adults at risk for serious complications of COVID-19 disease. All enrolled patients will receive treatment with remdesivir. [12, 25] (See Remdesivir in this Evidence Table.) **Commercially Available Immune Globulin (non-SARS-CoV-2-specific IGIV)** **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] **Open-label, prospective, randomized, controlled study in the US (Sakoulas et al; NCT04411667):** Preliminary (non-peer-reviewed) data from a study of 33 adults with COVID-19 and moderate to severe hypoxia (defined as SpO_2 ≤96% requiring ≥4 liters O_2 by nasal cannula) but not on mechanical ventilation found that IGIV significantly improved hypoxia and reduced hospital length of stay and progression to mechanical ventilation in patients with alveolar-arterial (A-a) gradient ≤200 mm Hg treated with IGIV (Octagam® 10% 0.5 g/kg daily for 3 days) plus standard of care compared with standard of care alone. All 16 patients in the IGIV group received premedication with methylprednisolone (40 mg IV) prior to each IGIV dose and 5 of these received additional glucocorticoid therapy; 10/17 patients in the standard of care group received some glucocorticoid therapy. [20] **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]		of a clinical trial and states that current IGIV preparations are not likely to contain SARS-CoV-2 antibodies. [16] This does not preclude the use of IGIV when it is otherwise indicated for the treatment of complications arising during the course of COVID-19 disease. [16] NIH states that there are insufficient data to recommend either for or against the use of investigational SARS-CoV-2 immune globulin (anti-SARS-CoV-2 hIGIV) for the treatment of COVID-19. [16] The Surviving Sepsis Campaign COVID-19 subcommittee suggests that commercially available IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, such 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
			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 (non-SARS-CoV-2-specific IGIV) or anti-SARS-CoV-2 hyperimmune globulin (anti-SARS-CoV-2 hIGIV) in patients with COVID-19, including the following trials: [12] NCT04264858 NCT04350580 NCT04381858 NCT04261426 NCT04411667 NCT04400058 NCT04480424 NCT04546581		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Ivermectin (Stromectol®) ***Updated 4/30/21***	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]	Limited published clinical data to date evaluating use 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 cohort study of COVID-19 pts treated with ivermectin (Rajter et al):** Outcome data for 173 pts with confirmed COVID-19 who received oral ivermectin at any time during hospitalization (0.2-mg/kg dose; 13 pts received a second dose) in addition to usual care were compared with outcome data for 107 pts who received usual care. Usual care included hydroxychloroquine and/or azithromycin in most pts in both groups; use of these drugs and ivermectin was at the discretion of the treating physician. The primary outcome measure was all-cause in-hospital mortality; secondary outcome measures included mortality in the subgroup of pts with severe pulmonary involvement, length of hospital stay, and extubation rates in mechanically ventilated pts. For the unmatched cohort, overall mortality was lower in the ivermectin group (15%) than in the group not treated with ivermectin (25.2%); overall mortality in the matched cohort also was lower in the ivermectin group (13.3 vs 24.5%). Data for the		No published data to date from randomized, controlled clinical trials to support use in the treatment or prevention of COVID-19 NIH COVID-19 Treatment Guidelines Panel states that **data are insufficient to date to recommend either for or against** the use of ivermectin for the **treatment** of COVID-19. These experts state that clinical trials reported to date have significant methodological limitations and incomplete information; results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19. [13] NIH panel **recommends against** use of ivermectin for preexposure prophylaxis (**PrEP**) or postexposure prophylaxis (**PEP**) for **prevention** of SARS-CoV-2 infection, except in a clinical trial. [13] Only limited clinical trial data are available to date regarding use of ivermectin for PrEP or PEP. Although some potentially promising results were reported in a few initial studies (some not peer reviewed), [13, 18, 19, 20] these findings are limited by design of the studies, small sample sizes, and lack of details regarding safety and efficacy of the drug. [13] IDSA **suggests against** use of ivermectin for **treatment** of severe COVID-19 in hospitalized patients and use of ivermectin for treatment of COVID-19 in outpatients outside of the context of a clinical trial. [17] Manufacturer (Merck) states that, to date, there is no scientific basis from preclinical studies for a potential therapeutic effect of ivermectin against COVID-19, no meaningful evidence of clinical activity or clinical efficacy of the drug in patients with COVID-19, and a concerning lack of safety data in the majority of studies. In addition, available data do not support the safety and efficacy of ivermectin beyond the doses

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			subgroup of pts with severe pulmonary involvement also indicated lower mortality in the ivermectin group (38.8 vs 80.7%). There was no difference in duration of hospitalization between the groups in either the unmatched or matched cohorts (median of 7 days for both groups). There also was no significant difference in extubation rates between groups in either the unmatched or matched cohorts. **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 standard care and variances in clinical benefits of such drugs) is not known. [12] **Randomized, double-blind, placebo-controlled trial in hospitalized adults (Ahmed et al):** A total of 72 adults with COVID-19 were randomized to receive ivermectin (12 mg orally once daily for 5 days), ivermectin (single 12-mg oral dose) with doxycycline (200 mg orally on day 1, then 100 mg every 12 hours for 4 days), or placebo. The primary end points were time required for virologic clearance (i.e., negative RT-PCR on nasopharyngeal swab) and remission of fever and cough within 7 days. The mean time to viral clearance was 9.7 days in the 5-day ivermectin group, 11.5 days in the ivermectin with doxycycline group, and 12.7 days in the placebo group. There was no significant difference between groups in remission of fever and cough. [14] **Randomized, double-blind, placebo-controlled trial in adults with mild COVID-19 (López-Medina et al; NCT04405843):** A total of 476 adults (hospitalized or outpatients) with mild disease and symptom onset within the previous 7 days were randomized 1:1 to receive a 5-day regimen of ivermectin (300 mcg/kg daily as an oral solution) or placebo. The primary outcome was the time from randomization to complete resolution of symptoms within the 21-day follow-up. The primary efficacy analysis population included 398 pts (200 received ivermectin and 198 received placebo). Baseline demographic and disease		and populations indicated in regulatory agency-approved prescribing information. [16] 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
			characteristics were well balanced between groups. **Ivermectin treatment did not significantly improve time to resolution of symptoms** in pts with mild COVID-19 (median of 10 or 12 days in the ivermectin or placebo group, respectively). At day 21, 82 or 79% of the ivermectin or placebo group, respectively, had complete resolution of symptoms. [21] **Randomized, double-blind, placebo-controlled pilot study to evaluate ivermectin for reduction of SARS-CoV-2 transmission (Chaccour et al):** Twelve adults with nonsevere COVID-19 who had no risk factors and symptom onset within the last 72 hours were randomized 1:1 to receive ivermectin (single dose of 400 mcg/kg) or placebo. The primary outcome measure was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab at day 7. Results indicated no difference in the proportion of PCR-positive patients between the ivermectin group and placebo group at day 7 (100% of pts in both groups still had positive PCR). [15] Various clinical trials evaluating ivermectin used alone or in conjunction with other drugs for the treatment or prevention of COVID-19 are registered at clinicaltrials.gov. [10]		
Nebulized drugs *Updated 2/11/21*		**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, 7, 8]	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, 7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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, as well as use of protective measures. [5, 7] 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] CDC states that it is unclear whether the potential association between nebulizer therapy and increased risk of transmission of COVID-19 infection is related to the aerosol-generating procedure or to increased contact between those administering the nebulized therapy and infected patients. [8] If clinicians need to be present during nebulizer use among patients who have symptoms or a diagnosis of COVID-19, recommended infection control precautions (e.g., social distancing, use of negative-pressure rooms, discarding or disinfecting personal protective equipment after each use) should be followed when aerosol-generating procedures are performed. [7, 8]
Niclosamide *Updated 3/25/21*	8:08 Anthelmintic	Antiparasitic agent that also has broad antiviral activity [2] In vitro evidence of activity against SARS-CoV-1 and MERS-CoV; [1,2] inhibited replication and antigen synthesis of SARS-CoV-1 in vitro, but did not interfere with attachment to and entry into cells [1] In drug repurposing screens, niclosamide was found to inhibit replication of SARS-CoV-2 in vitro in Vero E6 cells [4, 5]	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 Niclosamide may be included in some COVID-19 clinical trials registered at clinicaltrials.gov [3]	Protocol in one ongoing trial (NCT04399356) specifies a niclosamide dosage of 2 g orally once daily for 7 days for treatment of mild to moderate COVID-19 in adults [3] Protocol in one ongoing trial (NCT04603924) specifies a niclosamide dosage of 1 g orally twice daily for 7 days for treatment of moderate or severe COVID-19 in hospitalized adults [3]	Not commercially available in the US Although suggested as a potential treatment for COVID-19 based on its broad antiviral activity, including in vitro activity against coronaviruses, [1,2] there are no data to support the use of niclosamide in the treatment of COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Nitazoxanide (Alinia®) *Updated 2/25/21*	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, 14] 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]	Only very limited data available 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] **Randomized, double-blind, placebo-controlled trial in adults with mild COVID-19 (Rocco et al; NCT04552483):** Total of 392 outpatients were randomized 1:1 to receive nitazoxanide (500 mg 3 times daily) or placebo for 5 days; median time from symptom onset to first dose was 5 days. Percentage of pts experiencing complete resolution of symptoms (i.e., dry cough, fever, fatigue) at 5 days did not differ between pts treated with nitazoxanide or placebo. Nitazoxanide significantly reduced SARS-CoV-2 viral load at 5 days compared with placebo. [13] **Two randomized, double-blind, placebo-controlled clinical trials** were initiated by the manufacturer (Romark) to evaluate efficacy and safety for preexposure and postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers and others at increased risk of SARS-CoV-2 infection (NCT04359680) or postexposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (NCT04343248) [8]	**Dosages investigated for treatment of influenza and influenza-like illness or being investigated for other viral infections:** Adults and adolescents (≥12 years of age): 500 or 600 mg orally twice daily for 5 days [6, 7, 8] Protocols in registered trials evaluating the drug for treatment of COVID-19 in adults generally specify a nitazoxanide dosage of 500 or 600 mg two, three, or four times daily for 5-14 days or 1 g twice daily for 7 or 14 days [8] Protocol in two ongoing trials sponsored by the manufacturer (NCT04343248, NCT04359680) evaluating preexposure and/or postexposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks in adults; [8] another study (NCT04435314) specifies a dosage of 600 mg 3 times daily for 7 days for postexposure prophylaxis in adults [8] Another study (NCT04561063) evaluating prophylaxis for prevention of symptomatic COVID-19 in healthcare workers at high risk of exposure specifies a nitazoxanide dosage of 500 mg every 12 hours for 7 days, then 1 g every 12 hours thereafter [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]	Initially investigated as a potential treatment for COVID-19 based on its broad antiviral activity, including in vitro activity against SARS-CoV-2 and MERS-CoV; [1,4,5,14] however, there are no data to support the use of nitazoxanide in the treatment of COVID-19 While nitazoxanide is one of several agents being investigated for postexposure prophylaxis, [8] NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of any agents for postexposure prophylaxis for prevention of SARS-CoV-2 infection, except in a clinical trial [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Nitazoxanide, alone or in combination with other drugs, may be included in some COVID-19 clinical trials registered at clinicaltrials.gov [8]		
Nonsteroidal Anti-inflammatory Agents (NSAIAs) ***Updated 4/30/21***	28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)	**Ibuprofen:** Speculative link between ibuprofen and increased ACE2 expression, which possibly could lead to worse outcomes in COVID-19 patients [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]	Results from large cohort studies have **not** found associations between NSAIA use and increased risk of COVID-19 incidence or severity. [14-17] In a national **registry-based cohort study** in Denmark, NSAIA use was *not* associated with increased 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in individuals who tested positive for SARS-CoV-2. In this study, of the 9236 individuals who had a positive PCR test for SARS-CoV-2, 2.7% had used NSAIAs (defined as individuals having filled a prescription for an NSAIA within 30 days prior to a positive SARS-CoV-2 test) based on national community pharmacy records. The authors note that in Denmark, NSAIAs are available only by prescription with the exception of low-dose ibuprofen (200 mg) sold over the counter (OTC) in packages of no more than 20 tablets, and such OTC purchases of ibuprofen constituted 15% of total ibuprofen sales and a smaller proportion of total NSAIA sales. This definition of NSAIA use was a major limitation of the study [14] NSAIA use was **not** associated with increased incidence of COVID-19 (suspected or confirmed) or all-cause mortality in a UK database-based study comparing 13,202 pts with osteoarthritis who were prescribed NSAIAs with 12,457 propensity-matched pts who were prescribed comparator analgesics (acetaminophen and codeine/dihydrocodeine). [16] In addition, 2 other large UK database-based cohort studies did **not** find an association between NSAIA use and increased risk of COVID-19-related death in the general population or in pts with rheumatoid arthritis or osteoarthritis. These studies defined current NSAIA users as individuals with a prescription for an NSAIA within 4 months prior to study entry and compared 536,423 current NSAIA users with		Concerns that anti-inflammatory drugs such as ibuprofen may worsen COVID-19 circulated widely in the early months of the pandemic. [5, 12, 14] These reports were based largely on a letter published in *The Lancet Respir Med* stating that increased expression of ACE2 could facilitate infection with COVID-19 and that ibuprofen can increase ACE2. [1, 4] In addition, there were unconfirmed reports of younger, healthy patients who had used ibuprofen to treat early symptoms of COVID-19 and later experienced severe outcomes. [10, 12, 14] A statement attributed to the WHO recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position by the WHO has not been substantiated. WHO subsequently performed a rapid review of the literature and concluded that there was no evidence at that time of severe adverse events or effects on acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIAs. [9] FDA has stated that it is not aware of scientific evidence connecting the use of NSAIAs, such as ibuprofen, with worsening COVID-19 symptoms and will communicate publicly when more information is available. FDA also noted that all prescription NSAIA labels warn that by reducing inflammation, and possibly fever, these drugs may diminish the utility of diagnostic signs in detecting infections.[11] Although there currently is no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19, **some experts have recommended preferentially using acetaminophen for treatment of fever** [2, 3, 4, 10]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			1,927,284 NSAIA nonusers from the general population; among pts with rheumatoid arthritis or osteoarthritis, 175,495 current NSAIA users were compared with 1,533,286 NSAIA nonusers. In multivariate analyses, an increased risk of COVID-19-related death was **not** observed in NSAIA users. [17] **Ibuprofen:** In a **retrospective cohort study** of 403 hospitalized patients with COVID-19 at a single center in Israel, use of ibuprofen (1 week prior to diagnosis or during the course of disease) was **not** associated with increased mortality or the need for respiratory support compared with acetaminophen or no antipyretic drug. [15] **Indomethacin:** In vitro studies and animal models only; [6, 7] currently no published studies evaluating use specifically in COVID-19 patients		**NIH COVID-19 Treatment Guidelines Panel** states that patients who are receiving NSAIAs for an underlying medical condition should not discontinue such therapy unless discontinuation is otherwise warranted by their clinical condition; the panel also states that antipyretic strategy (e.g., use of acetaminophen or NSAIAs) in patients with COVID-19 should remain similar to the approaches used in other patients. [5] The Surviving Sepsis Campaign COVID-19 guidelines state that, for critically ill adults with COVID-19 who develop fever, use of acetaminophen over no treatment for fever control is suggested (weak recommendation) [2] IDSA makes no specific recommendation for or against the use of NSAIAs in patients with COVID-19 [12] **Indomethacin**: Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy in the treatment of COVID-19
Thrombolytic Agents (t-PA [alteplase], tenecteplase) ***Updated 5/13/21***	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), 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	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] There is some evidence suggesting that t-PA (alteplase) may decrease dead-space ventilation in patients with COVID-19-associated ARDS, but whether this leads to improved clinical outcomes is not known. [27, 28] Various case reports or case series describing the use of t-PA in severe COVID-19 patients have been published. [20, 21, 24, 28-30, 31] In one 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	t-PA (alteplase): Various IV dosage regimens of t-PA (alteplase) are being evaluated in patients with COVID-19; the optimum dose, route of administration, and duration of treatment remain to be determined. [1, 9, 12, 14, 20] Tenecteplase: A low-dose IV bolus of tenecteplase (0.25 mg/kg or 0.5 mg/kg) is being evaluated in the registered NCT04505592 trial. [12]	t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who are not responding to or do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). [1, 13, 14, 22, 29] Several institutions (e.g., Beth Israel Deaconess, University of Colorado, Denver Health) are currently testing this approach with t-PA (alteplase). [2, 12] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		microthrombi formation in the alveoli and pulmonary vasculature. [1, 11, 14] Many patients are found to have increased dead-space ventilation, a clinical feature of pulmonary embolism and diffuse pulmonary microemboli. [27, 28] Dysregulation of the clotting system in ARDS is a result of both enhanced activation of coagulation and suppression of fibrinolysis. [12, 19] Fibrinolysis shutdown, as evidenced by complete failure of clot lysis on thromboelastography, has been observed in critically ill patients with COVID-19.[23] Thrombolytic therapy may restore microvascular patency and limit progression of ARDS in patients with COVID-19 [1, 14, 19, 22]	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. [20] In another case series, t-PA (doses varied) was administered concomitantly with heparin anticoagulation in 5 critically ill mechanically ventilated COVID-19 patients with apparent thrombotic coagulopathy and ARDS. Although respiratory status in all 5 patients improved following t-PA administration, sustained improvement was observed in only 3 of the patients. [29] Other case reports or case series have described the use of t-PA in COVID-19 patients with severe respiratory failure or ARDS who were rapidly deteriorating and were either already on mechanical ventilation or likely to require intubation. Following IV infusion of t-PA (dosages varied), the majority of patients responded with rapid improvement in oxygenation. [21, 24, 28, 30] In these case reports, multiple confounding factors (including the use of various other treatments) were present, limiting interpretation of findings. [21, 24, 28, 29] **Multiple clinical trials are ongoing to evaluate thrombolytic agents (alteplase, tenecteplase) in patients with COVID-19; some are registered at clinicaltrials.gov. [12] As of December 16, 2020, there were 6 randomized controlled trials of thrombolytic agents in patients with COVID-19 registered at clinicaltrials.gov or the World Health Organization clinical trials registry. [12, 32] Most of these studies include patients with severe disease (e.g., severe ARDS, elevated troponin levels, elevated D-dimer levels) and are evaluating improvement in PaO_2/FiO_2 ratio or ventilator-free days as the primary efficacy end point. [12, 32] A phase 2 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]		standard of care in patients without COVID-19. [17] The CHEST guideline for the prevention, diagnosis, and treatment of VTE in patients with COVID-19 states that there is a lack of evidence regarding use of thrombolytic therapies in critically ill patients with COVID-19 without objective evidence of VTE or VTE-associated hypotension; based on indirect evidence from other populations, the expert panel recommends against the use of thrombolytic therapy in COVID-19 patients without objectively confirmed PE and PE-induced hypotension. [25] The Anticoagulation Forum recommends against the use of thrombolytic agents in COVID-19 patients outside the setting of a clinical trial unless there is another clinical indication (e.g., STEMI, acute ischemic stroke, high-risk [massive] PE with hemodynamic compromise); in general, thrombolytic therapy is not recommended in the vast majority of patients with PE given limited efficacy data in patients who are hemodynamically stable. [26] The American Society of Hematology states that treatment of the underlying pathology is paramount in COVID-19 patients with coagulopathies; 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.

REFERENCES

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020; 8:e21. PMID 32171062. DOI: 10.1016/S2213-2600(20)30116-8.
2. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. J Card Fail. 2020; 26:370. PMID: 32439095. DOI: 10.1016/j.cardfail.2020.04.013.
3. Position statement of the ESC council on hypertension on ACE-inhibitors and angiotensin receptor blockers. 2020 Mar 13. From European Society of Cardiology website. Accessed 2020 Sep 18. Available from https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.
4. Zheng, Y., Ma, Y., Zhang, J. et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17:259-60. PMID 32139904. DOI: 10.1038/s41569-020-0360-5.
5. Lu R, Li J. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor. Lancet.2020.395:565-74. PMID 32007145. DOI: 10.1016/S0140-6736(20)30251-8.
6. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020; 81:537-40. PMID 32129518. DOI: 10.1002/ddr.21656.
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 2. Available from https://clinicaltrials.gov.
8. Vaduganathan M, Vardeny O, Michel T. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020; 382:1653-9. PMID 32227760. DOI: 10.1056/NEJMsr2005760.
9. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 22. Updates may be available at NIH website.
10. Mehra MR, Desai SS, Kuy S et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. 2020; 382:e102. PMID: 32356626. DOI: 10.1056/NEJMoa2007621.
11. Mehra MR, Desai SS, Kuy S et al. Retraction: Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. N Engl J Med. 2020; 382:2582. PMID: 32501665. DOI: 10.1056/NEJMc2021225.
12. Rubin EJ. Expression of concern: Mehra MR et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. N Engl J Med. 2020; 382:2464. PMID: 32484612. DOI: 10.1056/NEJMe2020822.
13. Reynolds HR, Adhikari S, Pulgarin C et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med. 2020; 382:2441-8. PMID: 32356628. DOI: 10.1056/NEJMoa2008975.
14. Mancia G, Rea F, Ludergnani M et al. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med. 2020; 382:2431-40. PMID: 32356627. DOI: 10.1056/NEJMoa2006923.
15. Hakeam HA, Alsemari M, Al Duhailib Z et al. Association of angiotensin-converting enzyme inhibitors and angiotensin II blockers with severity of COVID-19: a multicenter, prospective study. J Cardiovasc Pharmacol Ther. 2021; 26:244-52. PMID: 33231487. DOI: 10.1177/1074248420976279.
16. COVID-19 Risk and Treatments (CORIST) Collaboration. RAAS inhibitors are not associated with mortality in COVID-19 patients: findings from an observational multicenter study in Italy and a meta-analysis of 19 studies. Vascul Pharmacol. 2020 Dec; 135:106805. PMID: 32992048. DOI: 10.1016/j.vph.2020.106805.
17. Cohen JB, Hanff TC, William P et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respir Med. 2021: 9:275-84. PMID: 33422263. DOI: 10.1016/S2213-2600(20)30558-0.
18. Lopes RD, Macedo AVS, de Barros E Silva PGM et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. JAMA. 2021; 325:254-64. PMID: 33464336. DOI: 10.1001/jama.2020.25864.

Anakinra:

1. Swedish Orphan Biovitrum AB (publ). Kineret® (anakinra) injection, solution prescribing information. Stockholm, Sweden; 2018 Jun.
2. Sobi to initiate a clinical study to evaluate whether anakinra and emapalumab may relieve complications associated with severe COVID-19 disease [press release]. Stockholm, Sweden; Swedish Orphan Biovitrum AB (publ): March 18, 2020. https://www.sobi.com/sites/default/files/pr/202003183346-1.pdf. Accessed 2020 Mar 30.
3. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 5. Available at http://www.clinicaltrials.gov.
4. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033-4. PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0
5. Genentech, Inc, South San Francisco, CA. Actemra use in Coronavirus Disease 2019 (COVID-19) standard reply letter. 2020 Mar 16.
6. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. Available on chinaXiv website. Accessed online 2020 Mar 19.
7. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Mar 5. From National Institutes of Health website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 5. Updates may be available at NIH website.
8. Aouba A, Baldolli A, Geffray L et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020; 79:1381-2. PMID: 32376597 DOI: 10.1136/annrheumdis-2020-217706
9. Huet T, Beaussier H, Voisin O et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020; 2(7):e393-e400. Published online 2020 May 29. DOI: 10.1016/S2665-9913(20)30164-8.
10. Cavalli G, De Luca G, Campochiaro C et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020; 2(6):e325–e331. Published online 2020 May 7. PMID: 32501454 DOI: 10.1016/S2665-9913(20)30127-2.

Anticoagulants

1. Deng Y, Liu W, Liu K. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020 PMID:32209890 DOI:10.1097/CM9.0000000000000824
2. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020; 9: 687-690. PMID: 32208840 DOI: 10.1080/22221751.2020.1741327
3. Wu C, Chen X, Cai Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020. PMID: 32167524 DOI:10.1001/jamainternmed.2020.0994
4. American Society of Hematology. COVID-19 and coagulopathy: frequently asked questions (version 7.0 last updated Jan 29, 2021). From the ASH website. Accessed 2021 Feb 22. Available from https://www.hematology.org/covid-19/covid-19-and-coagulopathy
5. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020; 18:1023-1026. PMID: 32338827 DOI:10.1111/jth.14810
6. Tang N, Li D, Wang X. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18: 844-847. PMID:32073213 DOI: 10.1111/jth.14768
7. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020; 18:1421-1424. PMID: 32271988 DOI:10.1111/jth.14830
8. Middeldorp S, Coppens M, van Haaps TF et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1995-2002. DOI: 10.1111/jth.14888. Epub 2020 Jul 27. PMID: 32369666.
9. Dixon DL, Van Tassell BW, Vecchié A, et al. Cardiovascular considerations in treating patients with coronavirus disease 2019 (COVID-19). J Cardiovasc Pharmacol. 2020; 75:359-367. PMID: 32282502 DOI :10.1097/FJC.0000000000000836
10. Thrombosis UK. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. From the Thrombosis UK website. Accessed 2020 Apr 15. Available from https://thrombosisuk.org/downloads/T&H%20and%20COVID.pdf
11. Klok FA, Kruip MJHA, van der Meer NJM. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Throm Res. 2020. https://doi.org/10.1016/j.thromres.2020.04.013
12. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 April 26. Available at https://www.clinicaltrials.gov
13. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020;50(1):54-67. PMID: 32415579 DOI:10.1007/s11239-020-02134-3
14. Barrett CD, Moore HB, Yaffe MB. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A Comment. J Thromb Haemost. 2020. PMID: 32302462 DOI: 10.1111/jth.14860
15. American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions (version 9.0 last updated Feb 25, 2021). From the ASH website. Accessed 2021 Apr 26. Available from https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation.
16. Ranucci M, Ballotta A, Di Dedda U. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020. PMID: 32302448 DOI: 10.1111/jth.14854
17. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020 PMID: 32239799 DOI: 10.1111/jth.14821
18. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020; 191:148-150. PMID: 32381264 DOI:10.1016/j.thromres.2020.04.041
19. Tang N, Bai H, Chen X. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18: 1094-1099. PMID:32220112 DOI:10.1111/jth.14817
20. Thachil J, Tang N, Gando S. Type and dose of heparin in COVID-19. J Thromb Haemost. 2020. PMID: 32329221 DOI: 10.1111/jth.
21. Cattaneo M, Bertinato EM, Birocchi S. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? Thromb Haemost. 2020. PMID: 32349132 DOI: 10.1055/s-0040-1712097
22. Ranucci M, Ballotta A, Di Dedda U. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020. PMID: 32302448 DOI: 10.1111/jth.14854
23. Llitjos JF, Leclerc M, Chochois C. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020. PMID:32320517 DOI: 10.1111/jth.14869
24. Greenstein YY. Inaccurate conclusions by Tang and colleagues. J Thromb Haemost. 2020. PMID: 32304156 DOI: 10.1111/jth.14857
25. World Health Organization. COVID-19 clinical management living guidance. 2021 Jan 25. From WHO website. Accessed 2021 Feb 22. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.
26. Tang N, Response to 'Inaccurate conclusions by Tang and colleagues. J Thromb Haemost. PMID: 32311835 DOI: 10.1111/jth.14862
27. Bikdeli B, Madhavan MV, Jimenez D et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 16;75(23):2950-2973. DOI: 10.1016/j.jacc.2020.04.031. Epub 2020 Apr 17. PMID: 32311448
28. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated 2021 Apr 21). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 26. Updates may be available at NIH website.
29. US Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) Updated 2020 Dec 8. From CDC website. Accessed 2021 Jan 11. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).
30. American College of Cardiology. Thrombosis and COVID-19: FAQs for current practice (April 22, 2020). From the ACC website. Accessed 2020 May 18. Available from https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice
31. Paranjpe I, Fuster V, Lala A, Russak AJ, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020 Jul 7;76(1):122-124. DOI: 10.1016/j.jacc.2020.05.001. Epub 2020 May 6. PMID: 32387623

32. Barnes GD, Burnett A, Allen A et a;. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2020 Jul;50(1):72-81. PMID: 32440883 DOI: 10.1007/s11239-020-02138-z.
33. Spyropoulos AC, Ageno W, Barnathan ES. Hospital-based use of thromboprophylaxis in patients with COVID-19. Lancet. 2020; 395(10234):e75. PMID: 32330428 DOI:10.1016/S0140-6736(20)30926-0
34. Spyropoulos AC, Levy JH, Ageno W et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1859-1865. PMID: 32459046 DOI: 10.1111/jth.14929.
36. Helms J, Tacquard C, Severac F et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098. doi: 10.1007/s00134-020-06062-x. Epub 2020 May 4. PMID: 32367170
37. Zhai Z, Li C, Chen Y, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A consensus statement before guidelines. Thromb Haemost. 2020; 120:937-948. PMID: 32316065 DOI:10.1055/s-0040-1710019
38. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. J Thromb Thrombolysis. 2020;50(2):298-301. PMID: 32476080 DOI:10.1007/s11239-020-02162-z
39. Hasan SS, Radford S, Kow CS et al. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. J Thromb Thrombolysis. 2020 Nov;50(4):814-821. DOI: 10.1007/s11239-020-02235-z. PMID: 32748122
40. Nadkarni GN, Lala A, Bagiella E et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76(16):1815-26. PMID: 32860872 DOI: 10.1016/j.jacc.2020.08.041. Epub 2020 Aug 26.
41. NIH. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV). From the NIH website. Accessed 2020 Nov 2. Available from https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials
42. Hanif A, Khan S, Mantri N, Hanif S et al. Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience. Ann Hematol. 2020 Oct; 99(10):2323-2328. doi: 10.1007/s00277-020-04216-x. Epub 2020 Aug 17. PMID: 32808105; PMCID: PMC7430929.
43. Tritschler T, Mathieu ME, Skeith L et al. Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. J Thromb Haemost. 2020 Sep 5. DOI: 10.1111/jth.15094. Epub ahead of print. PMID: 32888372.
44. Thachil J, Juffermans NP, Ranucci M et al. ISTH DIC subcommittee communication on anticoagulation in COVID-19. J Thromb Haemost. 2020 Sep;18(9):2138-2144. DOI: 10.1111/jth.15004. PMID: 32881336.
45. Hsu A, Liu Y, Zayac AS, Olszewski AJ et al. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. Thromb Res. 2020 Sep 23;196:375-378. doi: 10.1016/j.thromres.2020.09.030. Epub ahead of print. PMID: 32980620; PMCID: PMC7511207.
46. Ferguson J, Volk S, Vondracek T et al. Empiric Therapeutic Anticoagulation and Mortality in Critically Ill Patients with Respiratory Failure From SARS-CoV-2: A Retrospective Cohort Study. J Clin Pharmacol. 2020 Nov; 60(11):1411-1415. DOI: 10.1002/jcph.1749. Epub 2020 Sep 30. PMID: 32885463.
47. Bikdeli B, Talasaz AH, Rashidi F et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thromb Res. 2020 Sep 24; 196:382-394. DOI: 10.1016/j.thromres.2020.09.027. Epub ahead of print. PMID: 32992075.
48. Gerotziafas GT, Catalano M, Colgan MP et al. Guidance for the Management of Patients with Vascular Disease or Cardiovascular Risk Factors and COVID-19: Position Paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost. 2020 Sep 13. DOI: 10.1055/s-0040-1715798. Epub ahead of print. PMID: 32920811.
49. Bowles L, Platton S, Yartey N et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. N Engl J Med. 2020 Jul 16;383(3):288-290.DOI: 10.1056/NEJMc2013656. Epub 2020 May 5. PMID: 32369280.
50. Ionescu F, Jaiyesimi I, Petrescu I et al. Association of Anticoagulation Dose and Survival in Hospitalized COVID-19 Patients: A Retrospective Propensity Score Weighted Analysis. Eur J Haematol. 2020 Oct 11. DOI: 10.1111/ejh.13533. Epub ahead of print. PMID: 33043484.
51. Bai C, Chotirmall SH, Rello J et al. Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force (29 July 2020). Eur Respir Rev. 2020 Oct 5;29(157):200287. DOI: 10.1183/16000617.0287-2020. PMID: 33020069.
52. Daughety MM, Morgan A, Frost E et al. COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy. Thromb Res. 2020 Oct 15;196:483-485. DOI: 10.1016/j.thromres.2020.10.004. Epub ahead of print. PMID: 33091700.
53. Lemos ACB, do Espírito Santo DA, Salvetti MC et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res. 2020 Sep 21;196:359-366. DOI: 10.1016/j.thromres.2020.09.026. Epub ahead of print. PMID: 32977137.
54. Dobesh PP, Trujillo TC. Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19. Pharmacotherapy. 2020 Oct 1:10.1002/phar.2465. DOI: 10.1002/phar.2465. Epub ahead of print. PMID: 33006163.
55. Lopes RD, Fanaroff AC. Anticoagulation in COVID-19: It Is Time for High-Quality Evidence. J Am Coll Cardiol. 2020 Oct 20;76(16):1827-1829. DOI: 10.1016/j.jacc.2020.09.008. PMID: 33059827.
56. Flaczyk A, Rosovsky RP, Reed CT et al. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Crit Care. 2020;24(1):559. Published 2020 Sep 16. DOI: 10.1186/s13054-020-03273-y
57. Atallah B, Sadik ZG, Salem N et al. The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients. Anaesthesia. 2021 Mar;76(3):327-335. DOI: 10.1111/anae.15300. Epub 2020 Nov 5.PMID: 33047335
58. NIH ACTIV trial of blood thinners pauses enrollment of critically ill COVID-19 patients. News release. NIH: 2020 Dec 22. Available from: https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients
59. McBane RD 2nd, Torres Roldan VD, Niven AS, et al. Anticoagulation in COVID-19: a systematic review, meta-analysis, and rapid guidance from Mayo Clinic. Mayo Clin Proc. 2020 Nov; 95(11):2467-2486. PMID: 33153635 DOI: 10.1016/j.mayocp.2020.08.030. Epub 2020 Aug 31.

60. Chowdhury JF, Moores LK, Connors JM. Anticoagulation in hospitalized p atients with Covid-19. N Engl J Med. 2020 Oct 22;383(17):1675-1678. PMID: 33085867 DOI: 10.1056/NEJMclde2028217.
61. Musoke N, Lo KB, Albano J et al. Anticoagulation and bleeding risk in patients with COVID-19. Thromb Res. 2020 Dec;196:227-230. PMID: 32916565 DOI: 10.1016/j.thromres.2020.08.035. Epub 2020 Aug 24.
62. Lynn L, Reyes JA, Hawkins K et al. The effect of anticoagulation on clinical outcomes in novel Coronavirus (COVID-19) pneumonia in a U.S. cohort. Thromb Res. 2021 Jan;197:65-68. PMID: 33186849 DOI: 10.1016/j.thromres.2020.10.031. Epub 2020 Nov 5.
63. Full-dose blood thinners decreased the need for life support and improved outcome in hospitalized COVID-19 patients. News release. NIH: 2021 Jan 22. Available from: https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients
64. Alhazzani W, Evans L, Alshamsi F et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021 Jan 28. DOI: 10.1097/CCM.0000000000004899. Epub ahead of print. PMID: 33555780.
65. Rentsch CT, Beckman JA, Tomlinson L et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ. 2021;372:n311. DOI: 10.1136/bmj.n311. PMID: 33574135.
66. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021;5(3):872-88. DOI: 10.1182/bloodadvances.2020003763. PMID: 33560401.
67. Talasaz AH, Sadeghipour P, Kakavand H,et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol. 2021 Apr 20;77(15):1903-1921. DOI: 10.1016/j.jacc.2021.02.035. PMID: 33741176.
68. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial. JAMA. 2021 Apr 27;325(16):1620-1630. DOI: 10.1001/jama.2021.4152. PMID: 33734299.
69. Mennuni MG, Renda G, Grisafi L et al. Clinical outcome with different doses of low-molecular-weight heparin in patients hospitalized for COVID-19. J Thromb Thrombolysis. 2021 Mar 1:1–9. doi: 10.1007/s11239-021-02401-x. Epub ahead of print. PMID: 33649979; PMCID: PMC7919624.

Ascorbic acid:

1. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Oct 28. (https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=ascorbic+acid&cntry=&state=&city=&dist=).
2. Hemilä H. Vitamin C and infections. Nutrients. 2017; 9 pii: E339. DOI: 10.3390/nu9040339. PMID: 28353648.
3. Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev. 2013; 8:CD005532. DOI: 10.1002/14651858.CD005532.pub3. PMID: 23925826.
4. Kashiouris MG, L'Heureux M, Cable CA et al. The emerging role of vitamin C as a treatment for sepsis. Nutrients. 2020; 12:292. DOI: 10.3390/nu12020292. PMID: 31978969.
5. Marik PE. Vitamin C: an essential "stress hormone" during sepsis. J Thorac Dis. 2020; 12(Suppl 1):S84-S88. DOI: 10.21037/jtd.2019.12.64. PMID: 32148930.
6. Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med. 2020; 46:315-28. DOI: 10.1007/s00134-020-05943-5. PMID: 32040667.
7. Erol A. High-dose intravenous vitamin C treatment for COVID-19 (a mechanistic approach). Preprint 2020 Feb. (https://www.researchgate.net/publication/339511104). DOI: 10.31219/osf.io/p7ex8.
8. Li J. Evidence is stronger than you think: a meta-analysis of vitamin C use in patients with sepsis. Crit Care. 2018; 22:258. DOI: 10.1186/s13054-018-2191-x. PMID: 30305111.
9. Fowler AA 3rd, Truwit JD, Hite RD et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. JAMA. 2019; 322:1261-1270. DOI: 10.1001/jama.2019.11825. PMID: 31573637.
10. Fujii T, Luethi N, Young PJ et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: The VITAMINS randomized clinical trial. JAMA. 2020; 323:423-31. DOI: 10.1001/jama.2019.22176. PMID: 31950979.
11. McGuff Pharmaceuticals, Inc. Ascor® (ascorbic acid) injection prescribing information. Santa Ana, CA; 2017 Oct.
12. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated 2021 Feb 23). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 26. Updates may be available at NIH website.
13. Chang P, Liao Y, Guan J et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. Chest. 2020; 158:174-82. DOI: 10.1016/j.chest.2020.02.065. PMID: 32243943.
14. Iglesias J, Vassallo AV, Patel VV et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. Chest. 2020; 158:164-73. DOI: 10.1016/j.chest.2020.02.049. PMID: 32194058.
15. Hwang SY, Ryoo SM, Park JE et al. Combination therapy of vitamin C and thiamine for septic shock: a multi‐centre, double‐blinded randomized, controlled study. Intensive Care Med. 2020; 46:2015-25. DOI: 10.1007/s00134-020-06191-3. PMID: 32780166.
16. Moskowitz A, Huang DT, Hou PC et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020; 324:642-50. DOI: 10.1001/jama.2020.11946. PMID: 32809003.
17. Thomas S, Patel D, Bittel B et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open. 2021; Feb 1;4(2):e210369. DOI: 10.1001/jamanetworkopen.2021.0369. PMID: 33576820.
18. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S et al. Safety and effectiveness of high‐dose vitamin C in patients with COVID‐19: a randomized open‐label clinical trial. Eur J Med Res. 2021; Feb 11;26(1):20. DOI: 10.1186/s40001-021-00490-1. PMID: 33573699.

Azithromycin:

1. Tran DH, Sugamata R, Hirose T et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A (H1N1)pdm09 virus infection by interfering with virus internalization process. J Antibiot (Tokyo). 2019; 72:759-768. (PubMed 31300721) (DOI 10.1038/s41429-019-0204-x)

2. Bermejo-Martin JF, Kelvin DJ, Eiros JM et al. Macrolides for the treatment of severe respiratory illness caused by novel H1N1 swine influenza viral strains. J Infect Dev Ctries. 2009; 3:159-161. PMID: 19759469 DOI: 10.3855/jidc.18
3. Retallack H, Di Lullo E, Arias C et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci U S A. 2016; 113:14408-14413. (PubMed 27911847) (DOI 10.1073/ pnas.1618029113)
4. Bosseboeuf E, Aubry M, Nhan T et al. Azithromycin inhibits the replication of Zika virus. J Antivirals Antiretrovirals. 2018; 10:6-11.
5. Li C, Zu S, Deng YQ et al. Azithromycin protects against Zika virus Infection by Upregulating virus-induced Type I and III Interferon Responses. Antimicrob Agents Chemother. 2019; 63:e00394-19. (PubMed 31527024) (DOI 10.1128/ AAC.00394-19)
6. Zhang Y, Dai J, Jian H et al. Effects of macrolides on airway microbiome and cytokine of children with bronchiolitis: A systematic review and meta-analysis of randomized controlled trials. Microbiol Immunol. 2019; 63:343-349. (PubMed 31283028) (DOI 10.1111/1348-0421.12726)
7. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul; 56 (1):105949. (PMID 32205204) (DOI 10.1016/jantimicag.2020.105949)
8. Kawamura K, Ichikado K, Takaki M et al. Adjunctive therapy with azithromycin for moderate and severe acute respiratory distress syndrome: a retrospective, propensity score-matching analysis of prospectively collected data at a single center. Int J Antimicrob Agents. 2018; 51:918-924. (PubMed 29501821) (DOI 10.1016/j. ijantimicag.2018.02.009)
9. Kuo CH, Lee MS, Kuo HF et al. Azithromycin suppresses Th1- and Th2-related chemokines IP-10/MDC in human monocytic cell line. J Microbiol Immunol Infect. 2019; 52:872-879. (PubMed 31759853) (DOI 10.1016/j.jmii.2019.10.001)
10. Lee N, Wong CK, Chan MCW et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: A randomized controlled trial. Antiviral Res. 2017; 144:48-56. (PubMed 28535933) (DOI 10.1016/j.antiviral.2017.05.008)
11. Abrams EM, Raissy HH. Emerging therapies in the treatment of early childhood wheeze. Pediatr Allergy Immunol Pulmonol. 2019; 32:78-80. (PubMed 31508261) (DOI 10.1089/ped.2019.1043)
12. Arabi YM, Deeb AM, Al-Hameed F et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. Int J Infect Dis. 2019; 81:184-190. (PubMed 30690213) (DOI 10.1016/ j.ijid.2019.01.041)
13. Ishaqui AA, Khan AH, Sulaiman SAS et al. Assessment of efficacy of oseltamivir-azithromycin combination therapy in prevention of Influenza-A (H1N1)pdm09 infection complications and rapidity of symptoms relief. Expert Rev Respir Med. 2020; 14:533-541. (PubMed 32053044) (DOI 10.1080/17476348.2020.1730180)
14. Schogler A, Kopf BS, Edwards MR et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. Eur Respir J. 2015; 45:428-39. (PubMed 25359346) (DOI 10.1183/09031936.00102014)
15. Wang D, Hu B, Hu C et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus- Infected Pneumonia in Wuhan, China. JAMA. 2020; 323: 1061-1069. (PubMed 32031570) (DOI 10.1001/jama.2020.1585)
17. Gordon CL. Azithromycin. In: Grayson ML, ed. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs. 7th ed. Boca Raton, FL: CRC Press; 2018: 1122-44.
18. Molina JM, Delaugerre C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020; 50:384. PMID: 32240719 DOI: 10.1016/j.medmal.2020.03.006.
19. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020; 34:101663. PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663.
20. Giudicessi JR, Noseworthy PA, Friedman PA et al. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc. 2020; 95:1213-1221. PMID: 32359771 DOI: 10.1016/j.mayocp.2020.03.024.
21. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Mar 5. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Mar 8. Updates may be available at NIH website.
22. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Mar 5. Accessed 2021 Mar 8. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Updates may be available at IDSA website.
23. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020 May 5; 35:101738. PMID:32387409 DOI: 10.1016/j.tmaid.2020.101738
24. ACTG AIDS Clinical Trials Group. A5395: A randomized, double-blind, placebo-controlled trial to evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalization or death in persons with COVID-19. From ACTG Network website. (https://actgnetwork.org/studies/a5395/)
25. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5:1036-1041. PMID: 32936252 DOI: 10.1001/jamacardio.2020.1834
26. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. Letter. JAMA Cardiol. 2020; 5:1067-1069. PMID: 32936266 DOI: 10.1001/jamacardio.2020.1787
27. Bonow RO, Hernandez AF, Turakhia M. Hydrocychloroquine, coronavirus disease 2019, and QT prolongation. JAMA Cardiol. 2020; 5:986-987. PMID: 32936259 DOI: 10.1001/ jamacardio.2020.1782
28. Ramireddy A, Chugh H, Reinier K, et al. Experience with hydroxychloroquine and azithromycin in the COVID-19 pandemic: implications for QT interval monitoring. J Am Heart Assoc. 2020 Jun 16;19(12):e017144. PMID: 32463348 DOI: 10.1161/JAHA.120.017144.
29. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Mar 8. Available at http://www.clinicaltrials.gov.
30. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydrochloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020; 323:2493-2502. PMID: 32392282 DOI: 10.1001/jama.2020.8630
31. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020; 382:2411-2418. PMID: 32379955 DOI: 10.1056/ NEJMoa2012410

32. Metlay JP, Waterer GW. Treatment of community-acquired pneumonia during the coronavirus disease 2019 (COVID-19) pandemic. Ann Intern Med. 2020; 173:304-305. PMID: 32379883 DOI: 10.7326/M20-2189
33. Sultana J, Cutroneo PM, Crisafulli S et al. Azithromycin in COVID-19 patients: pharmacological mechanism, clinical evidence and prescribing guidelines. Drug Saf. 2020; 43:691-698. PMID: 32696429 DOI: 10.1007/s40264-020-00976-7
34. Furtado RHM, Berwanger O, Fonseca HA et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet. 2020; 396:959-967. PMID: 32896292 DOI: 10.1016/S0140-6736(20)31862-6
35. Oliver ME, Hinks TSC. Azithromycin in viral infections. Rev Med Virol. 2020 Sept 23; e2163 [Epub ahead of print]. PMID: 32969125 DOI: 10.1002/rmv.2163
36. Touret F, Gilles M, Barral K, et al. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Sci Rep. 2020; 10:13093. PMID: 32753646 DOI: 10.1038/s41598-020-70143-6.
37. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Eng J Med. 2020; 383:2041-2052. PMID: 32706953 DOI: 10.1056/NEJMoa2019014.
38. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. Lancet. 2021; 397:605-612. PMID: 33545096 DOI: 10.1016/S0140-6736(21)00149-5.
39. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021 Mar 4;S0140-6736(21)00461-X. [Online ahead of print] PMID: 33676597 DOI: 10.1016/S0140-6736(21)00461-X.

Baloxavir:

1. Lou Y, Liu L, Yao H et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. Eur J Pharm Sci. 2021 Feb 1:105631. PMID: 33115675 DOI: 10.1016/j.ejps.2020.105631
2. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19:149–150. PMID: 32127666 DOI: 10.1038/d41573-020-00016-0
3. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2020 Dec 17. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Jan 6. Updates may be available at NIH website.
4. Choy KT, Wong AY, Kaewpreedee P et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020; 178:104786. PMID: 32251767 DOI: 10.1016/j.antiviral.2020.104786.
5. US Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. From CDC website (https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm). Updated 2020 Nov 30. Accessed 2021 Jan 6.
6. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020 Mar 23;7(4):ofaa105. PMID: 32284951 DOI: 10.1093/ofid/ofaa105
7. World Health Organization. Landscape analysis of therapeutics as 21st March 2020. From WHO website. (https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf)

Baricitinib:

1. Richardson P, Griffin I, Tucker C et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395:e30-e31. PubMed: 32032529 DOI: 10.1016/S0140-6736(20)30304-4.
2. Ceribelli A, Motta F, De Santis M et al. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. J Autoimmun. 2020;109:102442.
3. Lilly Begins Clinical Testing of Therapies for COVID-19. Press release. Lilly: 2020 Apr 10. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-begins-clinical-testing-therapies-covid-19
4. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20:400-402.
5. Zhang W, Zhao Y, Zhang F et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020; 214: 108393. PMID: 32222466. DOI: 10.1016/j.clim.2020.108393.
6. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 15. Available from: https://clinicaltrials.gov/ct2/show/NCT04340232?term= NCT04340232&draw=2&rank=1
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 15. Available from: https://clinicaltrials.gov/ct2/show/NCT04346147?term= NCT04346147&draw=2&rank=1
8. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 15. Available from: https://clinicaltrials.gov/ct2/show/NCT04320277?term= NCT04320277&draw=2&rank=1
9. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 15. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04345289?term= NCT04345289&draw=2&rank=1
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 15. Available from: https://clinicaltrials.gov/ct2/show/NCT04321993?term= NCT04321993&draw=2&rank=1
11. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Feb 11. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 16. Updates may be available at NIH website.
12. National Institutes of Health. NIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins. 2020 May 8. From NIH website (https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins). Accessed 2020 May 11.
13. Cantini F, Niccoli L, Matarrese D et al. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect. 2020 Apr 23 . [Epub ahead of print]. PMID: 32333918 DOI: 10.1016/j.jinf.2020.04.017
14. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 May 12. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04358614?term=baricitinib&cond=covid&draw=2&rank=2
15. Lilly Begins a Phase 3 Clinical Trial with Baricitinib for Hospitalized COVID-19 Patients. Press release. Lilly: 2020 Jun 15. Available from: https://investor.lilly.com/node/43351/pdf
16. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jun 24. Available from: https://clinicaltrials.gov/ct2/show/NCT04421027?term=NCT04421027&draw=2&rank=1
17. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jun 25. Available from: https://clinicaltrials.gov/ct2/show/NCT04401579?term=NCT04401579&draw=2&rank=1

18. US Food and Drug Administration. Letter of authorization: Emergency use authorization (EUA) for emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older, requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Dated 2020 Nov 19. From FDA website. Accessed 2020 Nov 30. (https://www.fda.gov/media/143822/download)
19. US Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of baricitinib. Dated 2020 Nov. From FDA website. Accessed 2020 Nov 23. (https://www.fda.gov/media/143823/download)
20. US Food and Drug Administration. Fact sheet for patients, parents and caregivers: emergency use authorization (EUA) of baricitinib. Dated 2020 Nov. From FDA website. Accessed 2020 Nov 23. (https://www.fda.gov/media/143824/download)
21. Eli Lilly. Baricitinib has significant effect on recovery time, most impactful in COVID-19 patients requiring oxygen. Press release. 2020 Oct 8. Available at https://investor.lilly.com/news-releases/news-release-details/baricitinib-has-significant-effect-recovery-time-most-impactful.
22. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Nov 24. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04373044?term=baricitinib&recrs=ab&cond=Covid19&draw=2&rank=3
23. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Nov 24. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04393051?term=baricitinib&recrs=ab&cond=Covid19&draw=2
24. Kalil AC, Patterson TF, Mehta AK et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med. 2020 Dec 11 [published online ahead of print]. PMID: 33306283 DOI: 10.1056/NEJMoa2031994.
25. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 16. Available at http://www.clinicaltrials.gov.

Chloroquine and Hydroxychloroquine:

1. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269-271. (PubMed 32020029) (DOI 10.1038/s41422- 020-0282-0)
2. Keyaerts E, Vijgen L, Maes P et al. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004; 323:264-8. (PubMed 15351731) (DOI 10.1016/j. bbrc.2004.08.085)
3. Devaux CA, Rolain JM, Colson P et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. Int J Antimicrob Agents. 2020; :105938. (PubMed 32171740) (DOI 10.1016/j. ijantimicag.2020.105938)
4. Cortegiani A, Ingoglia G, Ippolito M et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020; (PubMed 32173110) (DOI 10.1016/j.jcrc.2020.03.005)
5. Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020; :105932. Editorial. (PubMed 32145363) (DOI 10.1016/j. ijantimicag.2020.105932)
6. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020; 14:72-73. (PubMed 32074550) (DOI 10.5582/bst.2020.01047)
7. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agnts. 2020; 56:105949. (PubMed 32205204) (DOI 10.1016/jantimicag.2020.105949)
8. Yao X, Ye F, Zhang M et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020; 71:732-739. (PubMed 32150618) (DOI 10.1093/cid/ciaa237)
9. Vincent MJ, Bergeron E, Benjannet S et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2:69. (PubMed 16115318) (DOI 10.1186/1743-422X-2-69)
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Dec 8. Available at https://www.clinicaltrials.gov/.
11. National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 patients (tentative 8th edition). Updated 2020 Sep 8. English translation available at http://regional.chinadaily.com.cn/pdf/DiagnosisandTreatmentProtocolforCOVID-19Patients(Tentative8thEdition).pdf. Accessed 2020 Nov 13.
12. Liu J, Cao R, Xu M et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020; 6:1-4. (PubMed 32194981) (DOI 10.1038/s41421-020- 0156-0)
13. Barber BE. Chloroquine and Hydroxychloroquine. In: Grayson ML, ed. Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs. 7th ed. Boca Raton, FL: CRC Press; 2018: 3030-48.
14. Rolain MJ, Colson, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30:297-308. (PubMed 17629679) (DOI 10.1016/j.ijantimicag.2007.05.015)
15. Sahraei Z, Shabani M, Shokouhi S et al. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. Int J Antimicrob Agents. 2020; 55:105945. (PubMed 32194152) (DOI 10.1016/j.ijantimicag.2020.105945)
16. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020; 75:1667-70. (PubMed 32196083) (DOI 10.1093/jac/dkaa114)
17. Rising Pharmaceuticals. Chloroquine phosphate tablets prescribing information. Saddle Brook, NJ; 2018 Feb 3.
18. Chen J, Liu D, Liu L et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. J Zhejiang Univ. 2020; 49:215-19. (PubMed 32391667) (DOI 10.3785/j.issn.1008-9292.2020.03.03)
19. CDC 2019-Novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. For emergency use only. Instructions for use. Catalog # 2019-nCoVEUA-01 (https://www.fda.gov/media/134922/download)
20. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. J Mol Cell Biol. 2020 Apr 1. (PubMed 32236562) (DOI 10.1093/jmcb/mjaa014)
21. US Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). From CDC website (https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html). (Accessed May 15, 2020).

22. Pan Y, Zhang D, Yang P et al. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020; 20: 411-12. Letter. (PMID: 32105638) (DOI: 10.1016/S1473-3099(20)30113-4)
23. Zhang W, Du RH, Li B et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020. 9:386-389. (PMID: 32065057) (DOI: 10.1080/22221751.2020.1729071)
24. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 Coronavirus disease. Dated 2020 Mar 28 [Revoked]. From FDA website. Accessed 2020 Mar 30. (https://www.fda.gov/media/136534/download)
25. US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 27 [Revoked]. Accessed 2020 Mar 30. From FDA website. (https://www.fda.gov/media/136535/download)
26. US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 27 [Revoked]. Accessed 2020 Mar 30. From FDA website. (https://www.fda.gov/media/136537/download)
27. US Food and Drug Administration. Fact sheet for patients and parent/caregivers emergency use authorization (EUA) of chloroquine phosphate for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28 (Revoked]. Accessed 2020 Mar 30. (https://www.fda.gov/media/136536/download)
28. US Food and Drug Administration. Fact sheet for patients and parent/caregivers emergency use authorization (EUA) of hydroxychloroquine sulfate for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28 [Revoked]. Accessed 2020 Mar 30. From FDA website. (https://www.fda.gov/media/136538/download)
29. US Department of Health and Human Services (HHS). HHS accepts donations of medicine to strategic national stockpile as possible treatments for COVID-19 patients. March 29, 2020. From HHS website. (https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html)
30. Song Y, Zhang M, Yin L, et al. COVID-19 treatment: Close to a cure ? – a rapid review of pharmacotherapies for the novel coronavirus. 2020. 2020030378. DOI: 10.20944/preprints202003.0378.v1.
31. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. Posted Apr 10, 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2.full.pdf).
32. Chinese Clinical Trial Registry. ChiCTR2000029559. Accessed 2020 Apr 4. Available at http://www.chictr.org/cn.
33. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020; 50:384. Letter. PMID: 32240719 DOI: 10.1016/j.medmal.2020.03.006.
34. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis. 2020; 34:101663. PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663.
35. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Feb 11. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 22. Updates may be available at NIH website.
36. Giudicessi JR, Noseworthy PA, Friedman PA et al. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. Mayo Clin Proc. 2020; 95:1213-1221. PMID: 32359771 DOI: 10.1016/j.mayocp.2020.03.024.
37. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020; 3:e208857. Epub. PMID: 32330277 DOI:10.1001/jamanetworkopen.2020.8857.
38. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Feb 18. From IDSA website (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/). Accessed 2021 Feb 22. Updates may be available at IDSA website.
39. US Food and Drug Administration. FDA drug safety communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. April 24, 2020. Available at https://www.fda.gov/media/137250/download.
40. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med (NY). 2020 Jun 5 [Online ahead of print]. PMID: 32838355 DOI: 10.1016/j.medj.2020.06.001.
41. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5:1036-1041. PMID: 32936252 DOI: 10.1001/jamacardio.2020.1834
42. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. Letter. JAMA Cardiol. 2020; 5:1067-1069. PMID: 32936266 DOI: 10.1001/jamacardio.2020.1787
43. Bonow RO, Hernandez AF, Turakhia M. Hydrocychloroquine, coronavirus disease 2019, and QT prolongation. JAMA Cardiol. 2020; 5:986-987. PMID: 32936259 DOI: 10.1001/jamacardio.2020.1782
44. Ramireddy A, Chugh H, Reinier K, et al. Experience with hydroxychloroquine and azithromycin in the COVID-19 pandemic: implications for QT interval monitoring. J Am Heart Assoc. 2020 Jun 16;19(12):e017144. PMID: 32463348 DOI: 10.1161/JAHA.120.017144.
45. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydrochloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020; 323:2493-2502. PMID: 32392282 DOI: 10.1001/jama.2020.8630
46. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020; 382:2411-2418. PMID: 32379955 DOI: 10.1056/NEJMoa2012410
47. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020 May 5; 35:101738. PMID:32387409 DOI: 10.1016/j.tmaid.2020.101738
48. ACTG AIDS Clinical Trials Group. A5395: A randomized, double-blind, placebo-controlled trial to evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalization or death in persons with COVID-19. From ACTG Network website. (https://actgnetwork.org/studies/a5395/)
49. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ. 2020 May 14; 369:m1849. PMID: 32409561 DOI: 10.1136/bmj.m1849
50. Mehra MR, Desai SS, Ruschitzka F, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020 May 22 [Retracted]. PMID: 32450107 DOI: 10.1016/50140-6736(20)31180-6.

51. Lancet editors. Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020 Jun 2. https://doi.org/10.1016/S0140-6736(20)31290-3.
52. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020 Jun 4. (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext). DOI: 10.1016/S0140-6736(20)31324-6.
53. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020 Oct 8; NEJMoa2022926 [Epub ahead of print]. PMID: 33031652 DOI: 10.1056/NEJMoa2022926.
55. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020; 383:517-525. PMID: 32492293 DOI: 10.1056/NEJMoa2016638.
56. Cohen MS. Hydroxychloroquine for the prevention of COVID-19 – searching for evidence. N Engl J Med. 2020; 383:585-586. PMID: 32492298 DOI: 10.1056/NEJMe2020388.
57. US Food and Drug Administration. Letter regarding revocation of emergency use authorization (EUA) for emergency use of chloroquine phosphate and hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of Coronavirus disease 2019. Dated 2020 Jun 15. Accessed 2020 Jun 15. (https://www.fda.gov/media/138945/download).
58. Arshad S, Kilgore P, Chaudry ZS et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis. 2020 Jul 2; 97:396-403. PMID: 32623082 DOI:10.1016/j.ijid.2020.06.099.
59. Mitja O, Corbacho-Monné M, Ubals M et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clin Infect Dis. 2020 Jul 16; ciaa1009 [Epub ahead of print]. PMID: 32674126 DOI: 10.1093/cid/ciaa1009.
60. Skipper CP, Pastick KA, Engen NW et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med. 2020; 173:623-631. PMID: 32673060 DOI: 10.7326/M20-4207.
61. Cavalcanti AB, Zampieri FG, Rosa RG et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Eng J Med. 2020; 383:2041-2052. PMID: 32706953 DOI: 10.1056/NEJMoa2019014.
62. Abella BS, Jolkovsky EL, Biney BT et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. JAMA Intern Med. 2021; 181:195-202. PMID: 33001138 DOI: 10.1001/jamainternmed.2020.6319.
63. Gentry CA, Humphrey MB, Thind SK et al. Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study. Lancet Rheumatol. 2020; 2:e689-e697. PMID: 32984847 DOI: 10.1016/S2665-9913(20)30305-2.
64. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 – interim WHO Solidarity trial results. N Engl J Med. 2020 Dec 2 [published online ahead of print]. PMID: 33264556 DOI: 10.1056/NEJMoa2023184.
65. World Health Organization. Public health emergency SOLIDARITY trial: World Health Organization COVID-19 core protocol, version 10.0. 2020 Mar 22. From WHO website. Accessed 2020 Dec 7. (https://www.who.int/publications/m/item/an-international-randomised-trial-of-additional-treatments-for-covid-19-in-hospitalised-patients-who-are-all-receiving-the-local-standard-of-care).
66. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA. 2020; 324:2165-2176. PMID: 33165621 DOI: 10.1001/jama.2020.22240
67. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Clin Infect Dis. 2020 Oct 17;ciaa1571 [online ahead of print]. PMID: 33068425 DOI: 10.1093/cid/ciaa1571.
68. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. Ann Intern Med. 2020 Dec 8;M20-6519 [online ahead of print]. PMID: 33284679 DOI: 10.7326/M20-6519.
69. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med. 2020; 383:517-525. PMID: 32492293 DOI: 10.1056/NEJMoa2016638.

Colchicine:

1. U.S. National Library of Medicine. ClinicalTrials.gov. Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19). Accessed 2020 Jun 24. Available from https://clinicaltrials.gov/ct2/show/NCT04322682.
2. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 12. Available from https://clinicaltrials.gov/ct2/results?cond=COVID&term=colchicine&cntry=&state=&city=&dist=.
3. Deftereos SG, Siasos G, Giannopoulos G et al. The GReek study in the Effects of Colchicine in COvid-19 complications prevention (GRECCO-19 study): rationale and study design. Hellenic J Cardiol. 2020; 61:42-5. PMID: 32251729. DOI: 10.1016/j.hjc.2020.03.002.
4. Gandolfini I, Delsante M, Fiaccadori E et al. COVID-19 in kidney transplant recipients. Am J Transplant. 2020; 20:1941-3. PMID: 32233067. DOI: 10.1111/ajt.15891.
5. Takeda Pharmaceuticals. Colcrys® (colchicine) tablets prescribing information. Deerfield, IL; 2015 Dec.
6. Slobodnick A, Shah B, Krasnokutsky S et al. Update on colchicine, 2017. Rheumatology (Oxford). 2018; 57:i4-i11. PMID: 29272515. DOI: 10.1093/rheumatology/kex453.
7. Tardif JC, Kouz S, Waters DD et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019: 381:2497-505. PMID: 31733140 DOI: 10.1056/NEJMoa1912388.
8. Vaidya K, Martínez G, Patel S. The role of colchicine in acute coronary syndromes. Clin Ther. 2019; 41:11-20. PMID: 30185392. DOI: 10.1016/j.clinthera.2018.07.023.
9. Webb CA, Barry AR. Colchicine for secondary cardiovascular prevention: a systematic review. Pharmacotherapy. 2020; 40:575-83. PMID: 32259308. DOI: 10.1002/phar.2401.
10. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. JAMA. 2015; 314:1498-506. PMID: 26461998. DOI:10.1001/jama.2015.12763.
11. Grailer JJ, Canning BA, Kalbitz M et al. Critical role for the NLRP3 inflammasome during acute lung injury. J Immunol. 2014; 192:5974-83. PMID: 24795455. DOI: 10.4049/jimmunol.1400368.
12. Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology. 2015; 485:330-9. PMID: 26331680. DOI: 10.1016/j.virol.2015.08.010.
13. Castaño-Rodriguez C, Honrubia JM, Gutiárrez-Álvarez J et al. Role of severe acute respiratory syndrome coronavirus viroporins E, 3a, and 8a in replication and pathogenesis. mBio. 2018; 9 (3):1-23. PMID: 29789363. DOI: 10.1128/mBio.02325-17.

14. Cure MC, Kucuk A, Cure E. Colchicine may not be effective in COVID-19 infection; it may even be harmful? Clin Rheumatol. 2020; 39:2101-2. Letter. PMID: 32394215. DOI: 10.1007/s10067-020-05144-x.
15. Gendelman O, Amital H, Bragazzi NL et al. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Autoimmun Rev. 2020 Jul;19(7): 102566. [Epub ahead of print]. PMID: 32380315. DOI: 10.1016/j.autrev.2020.102566.
16. Della-Torre E, Della-Torre F, Kusanovic M et al. Treating COVID-19 with colchicine in community healthcare setting. Clin Immunol. 2020 Aug; 217:108490 [Epub ahead of print]. Letter. PMID: 32492478. DOI: 10.1016/j.clim.2020.108490.
17. Deftereos SG, Giannopoulos G, Vrachatis DA et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019; the GRECCO-19 randomized clinical trial. JAMA Network Open. 2020; 3(6):e2013136. PMID: 32579195. DOI: 10.1001/jamanetworkopen.2020.13136.
18. Lopes MIF, Bonjorno LP, Giannini MC et al. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv. Posted 2020 Aug 12. Preprint (not peer reviewed). Available at https://www.medrxiv.org/content/10.1101/2020.08.06.20169573v2.
19. Papadopoulos C, Patoulias D, Teperikidis E et al. Colchicine as a potential therapeutic agent against cardiovascular complications of COVID-19: an exploratory review. SN Compr Clin Med. 2020; Aug 4;1-11. [Epub ahead of print]. PMID: 32838182. DOI: 10.1007/s42399-020-00421-x.
20. Scarsi M, Piantoni S, Colombo E et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020: 79:1286-9. PMID: 32732245. DOI: 10.1136/annrheumdis-2020-217712.
21. Sandhu T, Tieng A, Chilimuri S et al. A case control study to evaluate the impact of colchicine on patients admitted to the hospital with moderate to severe COVID-19 infection. Can J Infect Dis Med Microbiol. 2020 Oct 27; 2020:8865954. eCollection 2020. PMID: 33133323. DOI: 10.1155/2020/8865954.
22. Brunetti L, Diawara O, Tsai A et al. Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. J Clin Med. 2020 Sep 14; 9:2961. PMID: 32937800. DOI: 10.3390/jcm9092961.
23. Pinzón MA, Arango DC, Betancur JF et al. Clinical outcome of patients with COVID-19 pneumonia treated with corticosteroids and colchicine in Colombia. Preprint (not peer reviewed). From Research Square website (https://www.researchsquare.com/article/rs-94922/v1). Accessed 2020 Dec 4. DOI: 10.21203/rs.3.rs-94922/v1.
24. Tardif J-C, Bouabdallaoui N, L´Allier PL et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. medRxiv. Posted 2021 Jan 27. Preprint (not peer reviewed). Available at https://www.medrxiv.org/content/10.1101/2021.01.26.21250494v1.full.pdf.
25. Tardif J-C. ColCorona: answers to frequently asked questions. Available at https://www.colcorona.net/faq. Accessed 2021 Feb 9.
26. Colchicine to be investigated as a possible treatment for COVID-19 in the RECOVERY trial. News release. 2020 Nov 27. From the RECOVERY trial website (https://www.recoverytrial.net/news/colchicine-to-be-investigated-as-a-possible-treatment-for-covid-19-in-the-recovery-trial).
27. RECOVERY trial closes recruitment to colchicine treatment for patients hospitalised with COVID-19. News release. 2021 Mar 5. From the RECOVERY trial website (https://www.recoverytrial.net/news/recovery-trial-closes-recruitment-to-colchicine-treatment-for-patients-hospitalised-with-covid-19.)
28. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 26. Updates may be available at NIH website.

Corticosteroids (systemic) and Corticosteroids (inhaled):

1. World Health Organization. COVID-19 clinical management living guidance. 2021 Jan 25. From WHO website. Accessed 2021 Mar 9. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Updates may be available at WHO website.
2. Centers for Disease Control. Healthcare professionals: Frequently asked questions and answers. Updated 2020 Jun 28. From CDC website. Accessed 2020 Jul 1. https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html.
3. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-CoV lung injury. Lancet. 2020: 395:473-5. DOI: 10.1016/S0140-6736(20)30317-2. PMID: 32043983.
4. Lamontagne F, Rochwerg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ. 2018; 362:1-8. DOI: 10.1136/bmj.k3284. PMID: 30097460.
5. Lewis SR, Pritchard MW, Thomas CM et al. Pharmacological agents for adults with acute respiratory distress syndrome (Review). Cochrane Database Syst Rev. 2019 Jul 23. doi: 10.1002/14651858.CD004477.pub3. PMID: 31334568.
6. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180:934-43. doi: 10.1001/jamainternmed.2020.0994. PMID: 32167524.
7. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020; 395:683-684. doi: 10.1016/S0140-6736(20)30361-5. Epub 2020 Feb 12. PMID: 32122468.
8. Farkas J. Internet Book of Critical Care. From EMCrit Project website. Accessed 2020 Apr 14. https://emcrit.org/ibcc/COVID19/.
9. Villar J, Belda J, Añón JM, et al. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. Trials. 2016; 17:342. doi: 10.1186/s13063-016-1456-4. PMID: 2744964.
11. Sepsis Alliance. The connection between COVID-19, sepsis, and sepsis survivors. From Sepsis Alliance website. Accessed 2020 Mar 20. https://www.sepsis.org/about/our-story/.
12. Alhazzani W, Møller MH, Arabi YM et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020; 48:e440-e469. doi: 10.1097/CCM.0000000000004363. PMID: 32224769.
13. Wang Y, Jiang W, He Q et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther. 2020; 5:57. PMID: 32341331 . DOI: 10.1038/s41392-020-0158-2.
14. Griffiths MJD, McAuley DF, Perkins GD et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Resp Res. 2019; 6:e000420. PMID 31258917 DOI: 10.1136/bmjresp-2019-000420
15. Siemieniuk RA, Meade MO, Alonso-Coello P et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and meta-analysis. Ann Intern Med. 2015; 163(7):519-28. PMID: 26258555 DOI: 10.7326/M15-0715.

16. Lansbury L, Rodrigo C, Leonardi-Bee J et al. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2019 Feb 24. PMID: 30798570. DOI: 10.1002/14651858.CD010406.pub3.
17. Villar J, Ferrando C, Martínez D et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar; 8:267-76. PMID: 32043986 DOI: 10.1016/S2213-2600(19)30417-5.
18. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28; 395:1033-34. PMID:32192578 DOI: 10.1016/S0140-6736 (20)30628-0
19. Kaiser UB, Mirmira RG, Stewart PM. Our response to COVID-19 as endocrinologists and diabetologists. J Clin Endocrinol Metab. 2020 May 1; 105:1-3.PMID: 32232480. DOI: 10.1210/clinem/ dgaa148.
20. Harrison P. Patients on steroids with COVID-19 might need rescue steroids. From Medscape website. Accessed 2020 Apr 15. https://www.medscape.com/viewarticle/928072.
22. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 1. Available at https://clinicaltrials.gov
23. U.S. National Library of Medicine. ClinicalTrials.gov. Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure. Accessed 2020 Nov 2. Available from https://clinicaltrials.gov/ct2/show/NCT04244591.
24. National Institutes of Health. COVID-19 treatment guidelines. Updated 2021 Apr 21. From NIH website. Accessed 2021 Apr 22. Available from https:// www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/. Updates may be available at NIH website.
25. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Updated 2020 Sep 25. Accessed 2020 Dec 10. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Updates may be available at IDSA website.
26. Isidori AM, Pofi R, Hasenmajer V et al. Use of glucocorticoids in patients with adrenal insufficiency and COVID-19 infection. Letter. Lancet Diabetes Endocrinol. 2020; 8:472-3. DOI: 10.1016/ S2213-8587(20)30149-2.
27. Prete A, Taylor AE, Bancos I et al. Prevention of adrenal crisis: cortisol responses to major stress compared to stress dose hydrocortisone delivery. J Clin Endocrinol Metab. 2020; 105:2262-74. PMID: 32170323. DOI: 10.1210/clinem/dgaa133.
28. Misra DP, Agarwal V, Gasparyan AY et al. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol. 2020; 39:2055-62. PMID: 32277367. DOI: 10.1007/s10067-020-05073-9.
29. American College of Rheumatology COVID-19 clinical guidance task force. COVID-19 clinical guidance for adult patients with rheumatic diseases. 2020; Apr 11. Available from https:// www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-Patients-with-Rheumatic-Diseases.pdf.
30. Mikuls TR, Johnson SR, Fraenkel L et al. American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic. Version 3. Arthritis Rheumatol. 2021; 73:e1-e12. PMID: 33277981. DOI: 10.1002/art.41596.
31. University of Oxford. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Press release. 2020 Jun 16. Available at https://www.recoverytrial.net/results.
32. U.S. National Library of Medicine. ClinicalTrials.gov. Randomised evaluation of COVID-19 therapy (RECOVERY). Accessed 2020 Jun 16. Available from https://clinicaltrials.gov/ct2/show/ NCT04381936.
33. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR et al. Dexamethasone in hospitalized patients with COVID-19. 2021; 384:693-704. N Engl J Med. PMID: 32678530. DOI: 10.1056/NEJMoa2021436 .
34. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J. 2020; 55:2001009. Editorial. PMID: 32341100. DOI: 10.1183/13993003.01009-2020.
35. Iwabuchi K, Yoshie K, Kurakami Y, et al. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases. J Infect Chemother. 2020; 26:625-32. PMID: 32362440. DOI: 10.1016/j.jiac.2020.04.007.
36. Keller MJ, Kitsis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. J Hosp Med. 2020; 15:489-93. PMID: 32804611. DOI: 10.12788/jhm.3497.
37. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: A potential strategy to avoid steroid-related Strongyloides hyperinfection. JAMA. [published online ahead of print 2020 Jul 30]. PMID: 32761166. DOI: 10.1001/jama.2020.13170.
38. Liu J, Wang, T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. Hepatol Res. 2020; 50:1211-21. PMID: 32761993. DOI: 10.1111/hepr.13553.
39. Tomazini BM, Maia IS, Cavalcanti AB et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA. 2020; 324:1307-16. PMID: 32876695. DOI: 10.1001/jama.2020.17021.
40. Dequin PF, Heming N, Meziani F et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: arandomized clinical trial. JAMA. 2020; 324:1298-1306. PMID: 32876689. DOI: 10.1001/jama.2020.16761.
41. The Writing Committee for the REMAP-CAP Investigators. Angus DC, Derde L, Al-Beidh F et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA. 2020; 324:1317-29. PMID: 32876697. DOI: 10.1001/jama.2020.17022.
42. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Sterne JAC, Murthy S, Diaz JV et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020; 324:1330-41. PMID: 32876694. DOI: 10.1001/jama.2020.17023.
43. World Health Organization. Corticosteroids for COVID-19. 2020 Sep 2. From WHO website. Accessed 2020 Sep 16. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids -2020.1. Updates may be available at WHO website.
44. Singh D, Halpin DMG. Inhaled corticosteroids and COVID-19-related mortality: confounding or clarifying? Lancet Respir Med. 2020; 8:1065-6. Editorial. PMID: 32979985. DOI: 10.1016/S2213 -2600(20)30447-1.

45. Schultze A, Walker AJ, MacKenna B et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. Lancet Respir Med. 2020; 8:1106-20. PMID: 32979987. DOI: 10.1016/S2213-2600(20)30415-X.
46. Halpin DMG, Faner R, Sibila O et al. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med. 2020; 8:436-438. Editorial. PMID: 32251625. DOI: 10.1016/S2213-2600(20)30167-3.
47. Jeronimo CMP, Farias MEL, Val FFA et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis. [published online ahead of print 2020 Aug 12]. PMID: 32785710. DOI: 10.1093/cid/ciaa1177.
48. Salton F, Confalonieri P, Meduri GU et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. Open Forum Infect Dis. 2020 Sep 12; 7:ofaa421. PMID: 33072814. DOI: 10.1093/ofid/ofaa421.
49. Li Q, Li W, Jin Y et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. Infect Dis Ther. 2020; 9:823-36. PMID: 32880102. DOI: 10.1007/s40121-020-00332-3.
50. Favalli EG, Bugatti S, Klersy C et al. Impact of corticosteroids and immunosuppressive therapies on symptomatic SARS-CoV-2 infection in a large cohort of patients with chronic inflammatory arthritis. Arthritis Res Ther. 2020 Dec 30; 22:290. PMID: 33380344. DOI: 10.1186/s13075-020-02395-6.
51. Fadel R, Morrison AR, Vahia A et al. Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis. 2020; 71:2114-20. PMID: 32427279. DOI: 10.1093/cid/ciaa601.
52. Alhazzani W, Evans L, Alshamsi F et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021; 49:e219-e234. PMID: 33555780. DOI: 10.1097/CCM.0000000000004899.
53. Ramakrishnan S, Nicolau DV, Langford B et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. [published erratum appears in Lancet Respir Med 2021 Apr 14]. Lancet Respir Med. [published online ahead of print 2021 Apr 9]. PMID: 33844996. DOI: 10.1016/S2213-2600(21)00160-0.
54. Yu LM, Bafadhel M, Dorward J et al. Inhaled budesonide in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. medRxiv. Posted Apr 12 2021. Preprint (not peer reviewed). (https://doi.org/10.1101/2021.04.10.21254672).

COVID-19 Convalescent Plasma:

1. Bloch EM, Bailey JA, Tobian AAR. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020; 130:2757-2765. PMID: 32254064 DOI: 10.1172/JCI138745.
2. Tiberghien P, de Lambalarie X, Morel P et al. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. VOX. 2020; 115:488-494. PMID: 32240545 DOI: 10.1111/vox.12926.
3. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. Editorial. JAMA. 2020; 323:1561-1562. PMID: 32219429 DOI: 10.1001/jama.2020.4940.
4. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. J Clin Invest. 2020; 130:1545-8. (https://doi.org/10.1172/JCI138003). PMID 32167489 DOI: 10.1172/JCI138003.
5. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Critical Care. 2020; 24:91. (https://doi.org/10.1186/s13054-020-2818-6). PMID: 32178711 DOI: 10.1186/s13054-020-2818-6
6. Mair-Jenkins J, Saavedra-Compos M, Baillie JK et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015; 211:80-90. PMID: 25030060 DOI: 10.1093/infdis/jiu396.
7. Cheng Y, Wong R, Soo YOY et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005; 24:44-46. PMID: 15616839 DOI 10.1007/s10096-004-1271-9.
8. Soo YOY, Cheng Y, Wong R. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect. 2004; 10:676-8. PMID: 15214887 DOI: 10.1111/j.1469-0691.2004.00956.
9. Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA. 2020; 117:9490-9496 (https://www.pnas.org/cgi/doi/10.1073/pnas.2004168117). PMID: 32253318 DOI: 10.1073/pnas.2004168117.
10. Shen C, Wang Z, Zhao F et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323:1582-1589. PMID: 32219428 DOI: 10.1001/jama.2020.4783.
11. US Department of Health and Human Service, Food and Drug Administration, Center for Biologics Evaluation and Research. Investigational COVID-19 convalescent plasma guidance for industry. 2021 Feb 11. From FDA website. Accessed 2021 Mar 4. (https://www.fda.gov/media/136798/download) Updates may be available at FDA website.
12. Mayo Clinic. Expanded access to convalescent plasma for the treatment of patients with COVID-19. From Mayo Clinic website. (https://www.uscovidplasma.org/)
13. Yeh KM, Chiueh TZ, Siu LK et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother. 2005; 56:919-22. PMID: 16183666 DOI: 10.1093/jac/dki346.
14. AABB. COVID-19 convalescent plasma resources for clinicians. From aabb website. (https://covidplasma.org/resources-for-clinicians/). Accessed 2021 Jan 23.
15. American Red Cross. Coronavirus (COVID-19) convalescent plasma clinician information. From American Red Cross website. Accessed 2021 Jan 23. (https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients/clinician-registration.html).
16. Zeng QL, Yu ZJ, Gou JJ. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. J Infect Dis. 2020; 222:38-43. PMID: 32348485 DOI: 10.1093/infdis/jiaa228
17. Chen L, Xiong J, Bao L. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020; 20: 398-400. PMID: 32113510 DOI: 10.1016/S1473-3099(20)30141-9
18. Ye M, Fu D, Ren Y et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 2020; 92:1890-1901. PMID: 32293713 DOI: 10.1002/jmv.25882
19. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Jan 8. Available at https://clinicaltrials.gov.
20. Rubin R. Testing an old therapy against a new disease: convalescent plasma for COVID-19. JAMA. 2020; 323:214-2117. PMID: 32352484 DOI: 10.1001/jama.2020.7456
21. Rajendran K, Narayanasamy K, Rangarajan J et al. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol. 2020; 92:1475-1483. PMID: 32356910 DOI: 10.1002/jmv.25961
22. Sullivan HC, Roback JD. Convalescent plasma: Therapeutic hope or hopeless strategy in the SARS-CoV-2 pandemic. Transfus Med Rev. 2020; 34:145-150. PMID: 32359788 DOI: 10.1016/j.tmrv.2020.04.001

23. Dzik S. COVID-19 convalescent plasma: Now is the time for better science. Transfus Med Rev. 2020; 34:141-144. PMID: 32359789 DOI: 10.1016/j.tmrv.2020.04.002
24. American Society of Hematology. COVID-19 and convalescent plasma and antibody therapies: frequently asked questions. Updated 2021 Mar 23. From the ASH website. Accessed 2021 Apr 26. (https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma).
25. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 25. Updates may be available at NIH website.
26. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma. Am J Pathol. 2020; 190:1680-1690. PMID: 32473109 DOI:10.1016/j.ajpath.2020.05.014.
27. Valk SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Syst Rev. 2020 May 14;5:CD013600. PMID: 32406927 DOI:10.1002/14651858.CD013600.
28. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA. 2020; 324:460-470. PMID: 32492084 DOI:10.1001/jama.2020.10044.
29. Casadevall A, Joyner MJ, Pirofski LA. A randomized trial of convalescent plasma for COVID-19-potentially hopeful signals. JAMA. 2020; 324:455-457 . PMID: 32492105 DOI:10.1001/jama.2020.10218.
30. Alhazzani W, Møller MH, Arabi YM et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020; 48:e440-e469. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363.
31. Joyner MJ, Bruno KA, Klassen SA et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc. 2020; 95:1888-1897 PMID: 32861333 PMCID: PMC7368917. DOI: 10.1016/j.mayocp.2020.06.028.
32. Liu STH, Lin H, Baine I et al. Convalescent plasma treatment of severe COVID-19: A propensity score–matched control study. Nat Med. 2020; 26:1708-1713. PMID: 32934372. DOI: 10.1038/s41591-020-1088-9.
33. Madariaga MLL, Guthmiller JJ, Schrantz S et al. Clinical predictors of donor antibody titer and correlation with recipient antibody response in a COVID-19 convalescent plasma clinical trial. J Intern Med. 2020 Oct 9 [Epub ahead of print]. PMID: 33034095. DOI: 10.1111/joim.13185.
34. Joyner MJ, Klassen SA, Senefeld JW et al. Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy. medRxiv. Posted July 30 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1).
35. Chen S, Lu C, Li P et al. Effectiveness of convalescent plasma for treatment of COVID-19 patients. medRxiv. Posted Aug 4 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.08.02.20166710v1.full.pdf)
36. Joyner MJ, Senefeld JW, Klassen SA et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience. medRxiv. Posted Aug 12 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1)
37. US Food and Drug Administration. Letter of authorization: Reissuance of emergency use authorization for use of COVID-19 convalescent plasma for the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19). 2021 Feb 4. From FDA website. (https://www.fda.gov/media/141477/download)
38. US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients. 2021 Feb 4. From FDA website. (https://www.fda.gov/media/141478/download)
41. US Food and Drug Administration. Fact sheet for patients and parents/caregivers: Emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients. 2021 Feb 4. From FDA website. (https://www.fda.gov/media/141479/download)
42. Piechotta V, Chai KL, Valk SJ et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2020 Jul 10;7(7): CD013600. PMID: 32648959 DOI: 10.1002/14651858.CD013600.pub2.
43. Rogers R, Shehadeh F, Mylona EK et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. Clin Infect Dis. 2020 Oct 10 [Epub ahead of print]. PMID: 33038227. DOI: 10.1093/cid/ciaa1548.
44. Gharbharan A, Jordans CCE, Geurtsvankessel C et al. Convalescent plasma for COVID-19. A randomized clinical trial. medRxiv. Posted Jul 3 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1.full.pdf)
45. Ibrahim D, Dulipsingh L, Zapatka L et al. Factors associated with good patient outcomes following convalescent plasma in COVID-19: a prospective phase II clinical trial. Infect Dis Ther. 2020; 9:913-926. PMID: 32951151. DOI: 10.1007/s40121-020-00341-2.
46. Agarwal A, Mukherjee A, Kumar G et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: Open-label phase II multicentre randomized controlled trial (PLACID Trial). BMJ. 2020; 371:m3939. PMID: 33093056. DOI: 10.1136/bmj.m3939.
47. Balcells ME, Rojas L, Le Corre N L et al. Early Anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. medRxiv. Posted 2020 Sep 18. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.09.17.20196212v1)
48. Salazar E, Christensen PA, Graviss EA et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. Am J Pathol. 2020; 190:2290-2303. PMID: 32795424. DOI: 10.1016/j.ajpath.2020.08.001.
49. Salazar MR, Gonzalez SE, Regairaz L et al. Effect of convalescent plasma on mortality in patients with COVID-19 pneumonia. medRxiv. Posted 2020 Oct 9. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.10.08.20202606v1)
50. Yoon HA, Bartash R, Gendlina I et al. Treatment of Severe COVID-19 with Convalescent Plasma in the Bronx, NYC. medRxiv. Posted 2020 Dec 4. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.12.02.20242909v1)
51. Libster R, Pérez Marc G, Wappner D et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021 Jan 6 (Epub ahead of print). PMID: 33406353. DOI: 10.1056/NEJMoa2033700.
52. Chai KL, Valk SJ, Piechotta V et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2020 Oct 12; 10:CD013600. PMID: 33044747. DOI: 10.1002/14651858.CD013600.pub3.

53. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med. 2021; 384(11):1015-1027. PMID: 33523609 DOI:10.1056/NEJMoa2031893.
54. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv. Posted 2021 Mar 10. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2021.03.09.21252736v1).
55. REMAP-CAP. International Trial of SARS-CoV-2 Convalescent Plasma Pauses Enrollment of Critically ill COVID-19 Patients. Press release. Accessed 2021 Apr 25. (https://www.recover-europe.eu/press-release-international-trial-of-sars-cov-2-convalescent-plasma-pauses-enrollment-of-critically-ill-covid-19-patients/).

Famotidine:

1. Wu C, Liu Y, Yang Y et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020; 10:766-788. PMID: 32292689. DOI: 10.1016/j.apsb.2020.02.008.
2. Dong S, Sun J, Mao Z et al. A guideline for homology modeling of the proteins from newly discovered betacoronavirus, 2019 novel coronavirus (2019-nCoV). J Med Virol. 2020; 92:1542-8. PMID: 32181901. DOI: 10.1002/jmv.25768.
3. Borrell B. New York clinical trial quietly tests heartburn remedy against coronavirus. Science. 2020 Apr 26. From Science magazine website (https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus).
4. Pillaiyar T, Manickam M, Namasivayam V et al. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem. 2016; 59:6595-628. PMID: 26878082. DOI: 10.1021/acs.jmedchem.5b01461.
5. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 16. Available at https://clinicaltrials.gov.
6. Fresenius Kabi. Famotidine injection prescribing information. Lake Zurich, IL; 2019 Sep.
7. Freedberg DE, Conigliaro J, Wang TC et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. Gastroenterology. 2020; 159:1129-31.e3. PMID: 32446698. DOI: 10.1053/j.gastro.2020.05.053.
8. Janowitz T, Gablenz E, Pattinson D et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. Gut. 2020; 69:1592-7. PMID: 32499303. DOI: 10.1136/gutjnl-2020-321852.
9. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Apr 14. From IDSA website. Accessed 2021 Apr 16. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Updates may be available at the IDSA website.
10. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. Am J Gastroenterol. 2020; 115:1617-23. PMID: 32852338. DOI: 10.14309/ajg.0000000000000832.
11. Malone RW, Tisdall P, Fremont-Smith P et al. COVID-19: famotidine, histamine, mast cells, and mechanisms. Preprint [not peer reviewed]. Res Sq. 2020; Jun 22;rs.3.rs-30934. PMID: 32702719. DOI: 10.21203/rs.3.rs-30934/v2.
12. Anson BJ, Chapman ME, Lendy EK et al. Broad-spectrum inhibition of coronavirus main and papain-like 2 proteases by HCV drugs. Preprint [not peer reviewed]. Res Sq. 2020; DOI: 10.21203/rs.3.rs-26344/v1.
13. Hogan RB II, Hogan RB III, Cannon T et al. Dual-histamine receptor blockade with cetirizine - famotidine reduces pulmonary symptoms in COVID-19 patients. Pulm Pharmacol Ther. 2020 Aug; 63:101942. [Epub ahead of print]. PMID: 32871242. DOI: 10.1016/j.pupt.2020.101942.
14. Ortega JT, Serrano ML, Jastrzebska B. Class A G protein-coupled receptor antagonist famotidine as a therapeutic alternative against SARS-CoV2: an in silico analysis. Biomolecules. 2020 10:954. PMID: 32599963. DOI: 10.3390/biom10060954.
15. Cheung KS, Hung IF, Leung WK. Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study. Gastroenterology. 2021; 160:1898-9. PMID: 32682763. DOI: 10.1053/j.gastro.2020.05.098.
16. Yeramaneni S, Doshi P, Sands K et al. Famotidine use is not associated with 30-day mortality: a coarsened exact match study in 7158 hospitalized COVID-19 patients from a large healthcare system. Gastroenterology. 2021; 160:919-21.e3. PMID: 33058865. DOI: 10.1053/j.gastro.2020.10.011.
17. Shoaibi A, Fortin SP, Weinstein R et al. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. Am J Gastroenterol. 2021 Jan 28. [Epub ahead of print]. PMID: 33560648. DOI: 10.14309/ajg.0000000000001153.
18. Sun C, Chen Y, Hu L et al. Does famotidine reduce the risk of progression to severe disease, death, and intubation for COVID-19 patients? A systemic review and meta-analysis. Dig Dis Sci. 2021; Feb 24;1-9. [Epub ahead of print]. PMID: 33625613. DOI: 10.1007/s10620-021-06872-z.

Favipiravir

1. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269–271. PMID: 32020029 DOI: 10.1038/s41422-020-0282-0
2. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14:58–60. PMID: 32147628 DOI: 10.5582/ddt.2020.01012
3. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19:14–150. PMID: 32127666 DOI: 10.1038/d41573-020-00016-0
4. De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J. 2019;14:3962–3968. PMID: 31389664 DOI: 10.1002/asia.201900841
5. McCreary EK, Pogue M, on behalf of the Society of Infectious Diseases Pharmacists. COVID-19 Treatment: a review of early and emerging options. Open Forum Infectious Diseases. 2020; 7:ofaa105. PMID: 32284951 DOI: 10.1093/ofid/ofaa105
6. Chen C, Zhang Y, Huang J et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. Posted April 15, 2020. Preprint (not peer reviewed). DOI: 10.1101/2020.03.17.20037432
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Mar 1. Available at http://www.clinicaltrials.gov.
8. Chinese Clinical Trial Registry. Accessed 2021 Mar 2. Available at http://www.chictr.org/cn.
9. NIPH Clinical Trials Search: NIPH Clinical Trials Search of Japan. Accessed 2021 Mar 2. Available at https://rctportal.niph.go.jp/en.

10. McGrane V. Massachusetts to launch first US trial of Japanese coronavirus drug. Boston Globe. Updated 2020 Apr 15. Accessed 2020 Apr 14. Available at: https://www.bostonglobe.com/2020/04/07/metro/massachusetts-launch-first-trial-japanese-covid-drug
11. Sanders JM, Monogue ML, Jodlowski TZ et al. Pharmacologic treatments for Coronavirus disease 2019 (COVID-19): a review. JAMA. 2020; 323:1824-1836. PMID: 32282022 DOI: 10.1001/jama.2020.6019
12. Mentré F, Taburet AM, Guedj J et al. Dose regimen of favipiravir for Ebola virus disease. Lancet Infect Dis. 2015; 15: 150-1. PMID: 25435054 DOI: 10.1016/S1473-3099(14)71047-3
13. Sissoko D, Laouenan C, Folkesson E et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med. 2016; 13: e1001967. PMID: 26930627 DOI: 10.1371/journal.pmed.1001967
14. Taisho Toyama Pharmaceutical Co., Ltd. Avigan® (favipiravir) tablets prescribing information [English translation]. Tokyo, Japan; 2017 Nov. Accessed 2020 Apr 14. Available at: https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw
15. Cai Q, Yang M, Liu D et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). 2020; 6:1192-1198. PMID: 32346491 DOI: 10.1016/j.eng.2020.03.007
16. Choy KT, Wong AY, Kaewpreedee P et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020; 178: 104786. PMID: 32251767 DOI: 10.1016/j.antiviral.2020.104786
17. Du YX, Chen XP. Favipiravir: Pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020; 108:242-247. PMID: 32246834 DOI: 10.1002/cpt.1844
18. Zhao Y, Harmatz JS, Epstein CR et al. Favipiravir inhibits acetaminophen sulfate formation but minimally affects systemic pharmacokinetics of acetaminophen. Br J Clin Pharmacol. 2015. 80:1076-85. PMID: 25808818 DOI: 10.1111/bcp.12644
19. Eloy P, Solas C, Touret F et al. Dose rationale for favipiravir use in patients infected with SARS-CoV-2. Clin Pharmacol Ther. 2020; 108:188. PMID: 32350860 DOI: 10.1002/cpt.1877.
20. Du YX, Chen XP. Response to "Dose rationale for favipiravir use in patients infected with SARS-CoV-2". Clin Pharmacol Ther. 2020; 108:190. PMID: 32353191 DOI: 10.1002/cpt.1878.
21. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur Heart J Acute Cardiovasc Care. 2020; 9;215-221. PMID: 32372695 DOI: 10.1177/2048872620922784
22. Irie K, Nakagawa A, Fujita H et al. Pharmacokinetics of favipiravir in critically ill patients with COVID-19. Clin Transl Sci. 2020; 13:880-885. PMID: 32475019 DOI: 10.1111/cts.12827
23. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K et al. Real-world experience with favipiravir for treatment of COVID-19 in Thailand: results from a multicenter observational study. medRxiv. Posted July 13, 2020. Preprint (not peer reviewed). DOI: 10.1101/2020.06.24.20133249
24. Ivashchenko AA, Dmitriev KA, Vostokova NV et al. Avifavir for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis. 2020 Aug 9 [Online ahead of print]. PMID: 32770240 DOI: 10.1093/cid/ciaa1176
25. Doi K, Ikeda M, Hayase N et al. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with COVID-19: a case series. Crit Care. 2020; 24:392. PMID: 32620147 DOI: 10.1186/s13054-020-03078-z
26. Takahashi H, Iwasaki Y, Watanabe T et al. Case studies of SARS-CoV-2 treated with favipiravir among patients in critical or severe condition. Int J Infect Dis. 2020; 100:283-285. PMID: 32829044 DOI: 10.1016/j.ijid.2020.08.047
27. Inoue H, Jinno M, Ohta S et al. Combination treatment of short-course systemic corticosteroid and favipiravir in a successfully treated case of critically ill COVID-19 pneumonia with COPD. Respir Med Case Rep. 2020 Aug 27 [Epub ahead of print]. PMID: 32868989 DOI: 10.1016/j.rmcr.2020.101200
28. Murohashi K, Hagiwara E, Kitayama T et al. Outcome of early-stage combination treatment with favipiravir and methylprednisolone for severe COVID-19 pneumonia: a report of 11 cases. Respir Investig. 2020; 58:430-434. PMID: 32893160 DOI: 10.1016/j.resinv.2020.08.001
29. Doi Y, Hibino M, Hase R et al. A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19. Antimicrob Agents Chemother. 2020; 64:e01897-20. PMID: 32958718 DOI: 10.1128/AAC.01897-20
30. Fu D, Cao R, Lei Z et al. Oral favipiravir for patients with delayed SARS-CoV-2 viral RNA clearance: a case series. Crit Care. 2020; 24:578. PMID: 32977854 DOI: 10.1186/s13054-020-03288-5
31. Çalik BaŞaran N, Uyaroğlu OA, Telli Dizman G et al. Outcome of non-critical COVID-19 patients with early hospitalization and early antiviral treatment outside the ICU. Turk J Med Sci. 2020 Jul 28 [Online ahead of print]. PMID: 32718127 DOI: 10.3906/sag-2006-173
32. Yamamura H, Matsuura H, Nakagawa J et al. Effect of favipiravir and an anti-inflammatory strategy for COVID-19. Crit Care. 2020; 24:413. PMID: 32646499 DOI: 10.1186/s13054-020-03137-5
33. Shrestha DB, Budhathoki P, Khadka S et al. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virol J. 2020; 17:141. PMID: 32972430 DOI: 10.1186/s12985-020-01412-z
34. Koba H, Yoneda T, Kaneda T et al. Severe coronavirus disease 2019 (COVID-19) pneumonia patients treated successfully with a combination of lopinavir/ritonavir plus favipiravir: case series. Clin Case Rep. 2020; 8:3143-3148. PMID: 33042544 DOI: 10.1002/ccr3.3358
35. Hirai D, Yamashita D, Seta K. Favipiravir for COVID-19 in a patient on hemodialysis. Am J Kidney Dis. 2020; 77:153-154. PMID: 33011311 DOI: 10.1053/j.ajkd.2020.09.007
36. Takoi H, Togashi Y, Fujimori D et al. Favipiravir-induced fever in coronavirus disease 2019: a report of two cases. Int J Infect Dis. 2020; 101:188-190. PMID: 32992014 DOI: 10.1016/j.ijid.2020.09.1450
37. Koshi E, Saito S, Okazaki M et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease 2019. CEN Case Rep. 2021;10:126-131. PMID: 32940880 DOI: 10.1007/s13730-020-00534-1
38. Sano T, Kimizuka Y, Fujikura Y et al. COVID-19 in older adults: retrospective cohort study in a tertiary hospital in Japan. Geriatr Gerontol Int. 2020; 20:1044-1049. PMID: 32924229 DOI: 10.111/ggi.14034
39. Dauby N, Van Praet S, Vanhomwegen C et al. Tolerability of favipiravir therapy in critically ill patients with COVID-19: a report of four cases. J Med Virol. 2020; 93:689-691. PMID: 32886358 DOI: 10.1002/jmv.26488
40. Kurita T, Ishida K, Muranaka E et al. A favipiravir-induced fever in a patient with COVID-19. Intern Med. 2020;59:2951-2953. PMID: 33191372 DOI: 10.2169/internalmedicine.5394-20
41. Çap M, Bilge Ö, Işık F et al. The effect of favipiravir on QTc interval in patients hospitalized with coronavirus disease 2019. J Electrocardiol. 2020;63:115-119. PMID: 33181454 DOI: 10.1016/j.electrocard.2020.10.015

42. Kocayiğit H, Özmen Süner K, Tomak Y et al. Observational study of the effects of favipiravir vs lopinavir/ritonavir on clinical outcomes in critically ill patients with COVID-19. J Clin Pharm Ther. 2020 Oct 31 [Online ahead of print]. PMID: 33128482 DOI: 10.1111/jcpt.13305
43. Khamis F, Al Naabi H, Al Lawati et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis. 2020; 102:538-543. PMID: 33181328 DOI:10.1016/j.ijid.2020.11.008
44. Szabo BG, Lenart KS, Petrik B et al. Role of favipiravir in the treatment of adult patients with moderate to severe COVID-19: a single-center, prospective, observational, sequential cohort study from Hungary. medRxiv. Posted December 9, 2020. Preprint (not peer reviewed). DOI: 10.1101/2020.11.26.20238014
45. Modrák M, Bürkner PC, Siegar T et al. Detailed disease progression of 213 patients hospitalized with COVID-19 in the Czech Republic: an exploratory analysis. medRxiv. Posted December 22, 2020. Preprint (not peer reviewed). DOI: 10.1101/2020.12.03.20239863
46. Pertinez H, Rajoli RKR, Khoo SH et al. Pharmacokinetic modelling to estimate intracellular favipiravir ribofuranosyl-5′-triphosphate exposure to support posology for SARS-CoV-2. medRxiv. Posted January 5, 2021. Preprint (not peer reviewed). DOI: 10.1101/2021.01.03.21249159
47. Udwadia ZF, Singh P, Barkate H et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021;103:62-71. PMID: 33212256 DOI: 10.1016/j.ijid.2020.11.142
48. Dabbous HM, Abd-Elsalam S, El-Sayed MH et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Arch Virol. 2021;166:949-954. PMID: 33492523 DOI: 10.1007/s00705-021-04956-9

Fluvoxamine:

1. Hashimoto K. Repurposing of CNS drugs to treat COVID-19 infection: targeting the sigma-1 receptor. Eur Arch Psychiatry Clin Neurosci. 2021; 271:249-58. (PubMed: 33403480) (DOI: 10.1007/s00406-020-01231-x)
2. Rosen DA, Seki SM, Fernández-Castañeda A et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019; 11:eaau5266. (PubMed: 30728287) (DOI 10.1126/scitranslmed.aau5266).
3. Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020; 324:2292-2300. (PubMed 33180097) (DOI 10.1001/jama.2020.22760)
4. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 25. Available at https://clinicaltrials.gov.
5. Seftel D, Boulware DR. Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19. Open Forum Infect Dis. 2021 Feb 1; 8:ofab050. (PubMed 33623808) (DOI 10.1093/ofid/ofab050)
6. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 23. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 25. Updates may be available at NIH website.

HIV Protease Inhibitors:

1. Chu CM, Cheng VC, Hung IF et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59:252-6. (PubMed 14985565) (DOI 10.1136/thorax.2003.012658)
2. Chen F, Chan KH, Jiang Y et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004; 31:69-75. (PubMed 15288617) (DOI 10.1016/j.jcv.2004.03.003)
3. Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7; 382:1787-99. (PubMed 32187464) (DOI 10.1056/NEJMoa2001282)
4. Arabi YM, Alothman A, Balkhy HH et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials. 2018; 19:81. (PubMed 29382391) (DOI 10.1186/s13063-017-2427-0)
5. Liu F, Xu A, Zhang Y et al. Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis. 2020; 95: 183-91. (PubMed 32173576) (DOI 10.1016/j.ijid.2020.03.013)
6. Deng L, Li C, Zeng Q et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019:a retrospective cohort study. J Infect. 2020; 81:e1-e5. (PubMed 32171872) (DOI 10.1016/j.jinf.2020.03.002)
7. Chan JF, Yao Y, Yeung ML et al. Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis. 2015; 212:1904-13. (PubMed 26198719) (DOI 10.1093/infdis/jiv392)
8. Kim UJ, Won EJ, Kee SJ et al. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-α for Middle East respiratory syndrome. Antivir Ther. 2016; 21:455-9. (PubMed 26492219) (DOI 10.3851/IMP3002)
9. Yao TT, Qian JD, Zhu WY et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020; 92:556-563. (PubMed 32104907) (DOI 10.1002/jmv.25729)
10. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020; 14:69-71. (PubMed 31996494) (DOI 10.5582/bst.2020.01020)
11. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020; 64:e00399-20. (PubMed 32152082) (DOI 10.1128/AAC.00399-20)
12. Young BE, Ong SWX, Kalimuddin S et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020; 323:1488-1494. (PubMed 32125362) (DOI 10.1001/jama.2020.3204)
13. National Health Commission & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf)

14. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-62. (PubMed 32171076) (DOI 10.1016/S0140-6736 (20)30566-3)
15. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 22. Available at https://clinicaltrials.gov.
16. Lim J, Jeon S, Shin HY, et al. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020; 35:e79. DOI: 10.3346/jkms.2020.35.e79.
17. Fintelman-Rodrigues N, Sacramento CQ, Lima CR, et al. Atazanavir, alone or in combination with ritonavir, inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. Antimicrob Agents Chemother. 2020 Sep 21; 64(10):e00825-20. PMID: 32759267 DOI: 10.1128/AAC.00825-20.
18. De Meyer S, Bojkova D, Cinati J, et al. Lack of antiviral activity of darunavir against SARS-CoV-2. Int J Infect Dis. 2020; 97:7-10. PMID: 32479865. DOI: 10.1016/j.ijid.2020.05.085.
19. Yamamoto N, Matsuyam S, Hoshino T, et al. Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro. bioRxiv. Posted Apr 8, 2020. Preprint (not peer reviewed). DOI: 10.1101/2020.04.06.026476. (https://www.biorxiv.org/content/10.1101/2020.04.06.026476v1.full.pdf)
20. Chinese Clinical Trial Registry. ChiCTR2000029541. Accessed 2020 Apr 14. Available at http://www.chictr.org/cn.
21. Johnson & Johnson. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. From Johnson & Johnson website. Accessed 2020 Jul 7. Available at https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus.
22. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Feb 11. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 22. Updates may be available at NIH website.
23. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Feb 18. From IDSA website (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/). Accessed 2021 Feb 22. Updates may be available at IDSA website.
24. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. J Mol Cell Biol. 2020; 12:322-325. (PubMed 32236562) (DOI 10.1093/jmcb/mjaa014)
25. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomized, phase 2 trial. Lancet. 2020; 395:1695-1704. (Pubmed 32401715) (DOI 10.1016/S0140-6736(20)31042-4)
26. Chen J, Xia L, Liu L et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infect Dis. 2020 Jun 21; 7(7):ofaa241. (Pubmed 32671131) (DOI 10.1093/ofid/ofaa241)
27. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. Lancet. 2020 Oct 5; 396:1345-1352. PMID: 33031764 DOI: 10.1016/S0140-6736(20)32013-4
28. Musarrat F, Chouljenko V, Dahal A et al. The anti-HIV drug nelfinavir mesylate (Viracept) is a potent inhibitor of cell fusion caused by the SARS-CoV-2 spike (S) glycoprotein warranting further evaluation as an antiviral against COVID-19 infections. J Med Virol. 2020 May 6;10.1002/jmv.25985. PMID 32374457 DOI: 10.1002/jmv.25985
29. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 – interim WHO Solidarity trial results. N Engl J Med. 2020 Dec 2 [published online ahead of print]. PMID: 33264556 DOI: 10.1056/NEJMoa2023184.
30. World Health Organization. Public health emergency SOLIDARITY trial: World Health Organization COVID-19 core protocol, version 10.0. 2020 Mar 22. From WHO website. Accessed 2020 Dec 7. (https://www.who.int/publications/m/item/an-international-randomised-trial-of-additional-treatments-for-covid-19-in-hospitalised-patients-who-are-all-receiving-the-local-standard-of-care).

HMG-CoA Reductase Inhibitors (statins)

1. Phadke M, Saunik S. COVID-19 treatment by repurposing drugs until the vaccine is in sight. Drug Dev Res. 2020;81(5):541-543. PMID: 32227357 DOI: 10.1002/ddr.21666
2. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 21. Updates may be available at NIH website.
3. Is there a role for statin therapy in acute viral infections? From ACC website. Accessed 2020 Apr 21. Available from https://www.acc.org/latest-in-cardiology/articles/2020/03/18/15/09/is-there-a-role-for-statin-therapy-in-acute-viral-infections-covid-19
4. Frost FJ, Petersen H, Tollestrup K et al. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007; 131:1006-12. PMID: 17426203 DOI: 10.1378/chest.06-1997
5. Douglas I, Evans S, Smeeth L. Effect of statin treatment on short term mortality after pneumonia episode: cohort study. BMJ. 2011; 342:d1642. PMID: 21471172 DOI: 10.1136/bmj.d1642
6. Vandermeer ML, Thomas AR, Kamimoto L et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis. 2012; 205:13-9. PMID: 22170954 DOI: 10.1093/infdis/jir695
7. Dashti-Khavidaki S, Khalili H. Considerations for statin therapy in patients with COVID-19. Pharmacotherapy. 2020; 40:484-6. PMID: 32267560 DOI: 10.1002/phar.2397
8. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. mBio. 2020; 11:e00398-20. PMID: 32198163 DOI: 10.1128/mBio.00398-20
9. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Jan 11. Available at https://www.clinicaltrials.gov.
10. De Spiegeleer A, Bronselaer A, Teo JT et al. The effects of ARBs, ACEIs and statins on clinical outcomes of COVID-19 infection among nursing home residents. J Am Med Dir Assoc. 2020; 21(7) 909-914.e2. PMCID: PMC7294267 DOI: 10.1016/j.jamda.2020.06.018
11. Zhang XJ, Qin JJ, Cheng X et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metab. 2020;32(2):176-187.e4. PMID: 32592657 DOI: 10.1016/j.cmet.2020.06.015
12. Daniels LB, Sitapati AM, Zhang J et al. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. Am J Cardiol. 2020; 136:149-55. PMID: 32946859 DOI: 10.1016/j.amjcard.2020.09.012
13. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, et al. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care. 2020; 24:429. PMID: 32664990; PMCID: PMC7358561 DOI: 10.1186/s13054-020-03154-4
14. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. Am J Cardiol. 2020; 134:153-5. PMID: 32891399 PMCID: PMC7419280 DOI: 10.1016/j.amjcard.2020.08.004

15. Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020; 14:1613-5. PMID: 32882643 DOI: 10.1016/j.dsx.2020.08.023
16. Song SL, Hays SB, Panton CE et al. Statin use is associated with decreased risk of invasive mechanical ventilation in COVID-19 patients: a preliminary study. Pathogens. 2020; 9:E759. PMID: 32957539 DOI: 10.3390/pathogens9090759
17. Holman N, Knighton P, Kar P et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020 Oct;8: 823-833. PMID: 32798471; PMCID: PMC7426091 DOI: 10.1016/S2213-8587(20)30271-0
18. Cariou B, Goronflot T, Rimbert A et al. Routine use of statins and increased mortality related to COVID-19 in inpatients with type 2 diabetes: Results from the CORONADO study. Diabetes Metab. 2021; 47:101202. PMID: 33091555; PMCID: PMC7572108 DOI: 10.1016/j.diabet.2020.10.001.
19. Saeed O, Castagna F, Agalliu I et al. Statin use and in-hospital mortality in diabetics with COVID-19. J Am Heart Assoc. 2020; 9:e018475. PMID: 33092446 DOI: 10.1161/JAHA.120.018475
20. Masana L, Correig E, Rodríguez-Borjabad C, et al. Effect of statin therapy on SARS-CoV-2 infection-related mortality in hospitalized patients. Eur Heart J Cardiovasc Pharmacother. 2020 Nov 2 [Online ahead of print]. PMID: 33135047 DOI:10.1093/ehjcvp/pvaa128
21. Bifulco M, Ciccarelli M, Bruzzese D, et al. The benefit of statins in SARS-CoV-2 patients: further metabolic and prospective clinical studies are needed. Endocrine. 2021; 71:270-272. PMID: 33219496 DOI:10.1007/s12020-020-02550-8
22. Scheen AJ. Statins and clinical outcomes with COVID-19: meta-analyses of observational studies. Diabetes Metab. 2020; 47:101220. PMID: 33359486 PMCID: PMC7757378 DOI:10.1016/j.diabet.2020.101220.
23. Butt JH, Gerds TA, Schou M, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. BMJ Open. 2020; 10 (12):e044421. PMID: 33277291 DOI:10.1136/bmjopen-2020-044421
24. Fan Y, Guo T, Yan F, et al. Association of statin use with the in-hospital outcomes of 2019-coronavirus disease patients: a retrospective study. Front Med (Lausanne). 2020; 7:584870. PMID: 33330541 PMCID: PMC7717990 DOI:10.3389/fmed.2020.584870
25. Mitacchione G, Schiavone M, Curnis A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. J Clin Lipidol. 2020 [Online ahead of print];S1933-2874(20)30345-7. PMID: 33390341 DOI:10.1016/j.jacl.2020.12.008
26. Pal R, Banerjee M, Yadav U, et al. Statin use and clinical outcomes in patients with COVID-19: an updated systematic review and meta-analysis. Postgrad Med J. 2021 Feb 4 [Online ahead of print];postgradmedj-2020-139172. PMID: 33541927 DOI:10.1136/postgradmedj-2020-139172
27. Permana H, Huang I, Purwiga A, et al. In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): systematic review and meta-analysis. Pharmacol Rep. 2021 Feb 20 [Online ahead of print];1-12. PMID: 33608850 DOI:10.1007/s43440-021-00233-3
28. Oh TK, Song IA, Jeon YT. Statin therapy and the risk of COVID-19: a cohort study of the National Health Insurance Service in South Korea. J Pers Med. 2021;11(2):116. PMID: 33578937 DOI:10.3390/jpm11020116
29. Lee HY, Ahn J, Park J, et al. Beneficial effect of statins in COVID-19-related outcomes-Brief Report: a national population-based cohort study. Arterioscler Thromb Vasc Biol. 2021;41(3):e175-e182. PMID: 33535790 DOI:10.1161/ATVBAHA.120.315551
30. Marić I, Oskotsky T, Kosti I, et al. Decreased mortality rate among COVID-19 patients prescribed statins: data from electronic health records in the US. Front Med (Lausanne). 2021 Feb 3;8:639804. PMID: 33614688 DOI:10.3389/fmed.2021.639804
31. Gupta A, Madhavan MV, Poterucha TJ, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun. 2021;12(1):1325. PMID: 33637713 DOI:10.1038/s41467-021-21553-1

Immune Globulin:

1. AHFS drug information 2020. Snow EK, ed. Immune Globulin. Bethesda, MD. American Society of Health-System Pharmacists; 2020: 3433-53. (https://www.ahfscdi.com/drugs/382815)
2. Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? Int J Mol Sci. 2020; 21. (http://dx.doi.org/10.3390/ijms21072272). PMID: 32218340 DOI: 10.3390/ijms21072272
3. Sanders JM, Monogue ML, Jodlowski et al. Pharmacologic treatments for coronavirus diseases 2019 (COVID-19): a review. JAMA. 2020. Epub. PMID: 32282022 DOI: 10.1001/jama.2020.6019
4. Chiang CH, Chen HM< Shih JF et al. Management of hospital-acquired severe acute respiratory syndrome with difference disease spectrum. J Chin Med Assoc. 2003; 66:328-38. PMID: 12889501
5. Stockman LJ, Bellamy R, Garner P. SARS: Systemic review of treatment effects. PLoS Med. 2006; 3:e343. PMID: 16968120 DOI: 10.1371/journal.pmed.0030343.
6. Umapathi T, Kor AC, Venketasubramanian N et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004; 251:1227-31. PMID: 26811110 DOI: 10.1007/s00415-004-0519-9.
7. Ng KHL, Wu AKL, Cheng VCC et al. Pulmonary artery thrombosis in a patient with severe acute respiratory syndrome. Postgrad Med J. 2005; 81: e3. PMID: 15937197.
8. Cao W, Liu X, Bai T et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infectious Diseases. 2020. PMID: 32258207 DOI: 10.1093/ofid/ofaa102.
9. Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395:507-13. PMID:32007143 DOI: 10.1016/S0140-6736(20)30211-7
10. Yang X, Yuan Y, Zu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Epub. https://doi.org/10.1016/S2213-2600(20)30079-5. PMID: 32105632
11. Guan W, Ni Z, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. Epub. PMID: 32109013 DOI: 10.1056/NEJMoa2002032.
12. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Oct 23. Available from https://www.clinicaltrials.gov.
13. Alhazzani W, Møller MH, Arabi YM et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020; 48:e440-e469. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363.
14. National Health Commission & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf)

15. Wang JT, Sheng WH, Fang CT. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis. 2004; 10: 818-24. PMID: 15200814 DOI:10.3201/eid1005.030640
16. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2020 Oct 22. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Oct 23. Updates may be available at NIH website.
17. Xie Y, Cao S, Dong H, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. Letter. J Infect. 2020 Apr 10 [Epub ahead of print];S0163-4453(20)30172-9. PMID: 32283154 DOI:10.1016/j.jinf.2020.03.044.
18. Díez JM, Romero C, Gajardo R. Currently available intravenous immunoglobulin contains antibodies reacting against severe acute respiratory syndrome coronavirus 2 antigens. Immunotherapy. 2020; 12:571-576. PMID: 32397847 DOI:10.2217/imt-2020-0095.
19. Shao Z, Feng Y, Zhong L, et al.Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: a multicenter retrospective cohort study. MedRxiv. Posted Apr 20, 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v2.full.pdf).
20. Sakoulas G, Geriak M, Kullar R et al. Intravenous immunoglobulin (IVIG) significantly reduces respiratory morbidity in COVID-19 pneumonia: a prospective randomized trial. medRxiv. Posted Jul 25, 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.07.20.20157891v1).
21. Nguyen AA, Habiballah SB, Platt CD et al. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! Clin Immunol. 2020; 216:108459. PMID: 32418917 DOI:10.1016/j.clim.2020.108459.
22. Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005; 142(1):1-11. PMID: 16178850 DOI:10.1111/j.1365-2249.2005.02834.x.
23. de Alwis R, Chen S, Gan ES. Impact of immune enhancement on Covid-19 polyclonal hyperimmune globulin therapy and vaccine development. EBioMedicine. 2020; 55:102768. PMID: 32344202 DOI:10.1016/j.ebiom.2020.102768.
24. CoVIg-19 Plasma Alliance. Questions & answers. Accessed 2020 Oct 23. Available at https://www.covig-19plasmaalliance.org.
25. Takeda Pharmaceuticals. First patient enrolled in NIH phase 3 trial to evaluate potential COVID-19 hyperimmune medicine. Press release. Accessed 2020 Oct 23. Available at https://www.takeda.com/newsroom/newsreleases/2020/first-patient-enrolled-in-nih-phase-3-trial-to-evaluate-potential-covid-19-hyperimmune-medicine/.

Inhaled Prostacyclins:

1. Alessandri F, Pugliese F, Ranieri VM. The Role of Rescue Therapies in the Treatment of Severe ARDS. Respir Care. 2018; 63: 92-101. Pubmed: 29066591 DOI: 10.4187/respcare.05752
2. Cherian SV, Kumar A, Akasapu K. Salvage therapies for refractory hypoxemia in ARDS. Respir Med. 2018; 141: 150-158. Pubmed 30053961 DOI: 10.1016/j.rmed.2018.06.030
3. Tamburro RF, Kneyber MC. Pediatric Acute Lung Injury Consensus Conference Group. Pulmonary specific ancillary treatment for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015; 16 (Suppl 1): S61-72. Pubmed: 26035366 DOI: 10.1097/PCC.0000000000000434
4. Walmrath D, Schneider T, Pilch J. Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet. 1993; 342: 961-2. Pubmed: 8105216 DOI: 10.1016/0140-6736(93)92004-d
5. Ammar MA, Bauer SR, Bass SN. Noninferiority of Inhaled Epoprostenol to Inhaled Nitric Oxide for the Treatment of ARDS. Ann Pharmacother. 2015; 49: 1105-12. Pubmed: 26187741 DOI: 10.1177/1060028015595642
6. Afshari A, Bastholm Bille A, Allingstrup M. Aerosolized prostacyclins for acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev. 2017; 7: CD007733. Pubmed: 28806480 DOI: 10.1002/14651858.CD007733.pub3
7. Dahlem P, van Aalderen WM, de Neef M. Randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury. Crit Care Med. 2004; 32: 1055-60. Pubmed: 15071401 DOI: 10.1097/01.ccm.0000120055.52377.bf
8. Fuller BM, Mohr NM, Skrupky L. The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. Chest. 2015; 147: 1510-1522. Pubmed: 25742022 DOI: 10.1378/chest.14-3161
9. Searcy RJ, Morales JR, Ferreira JA et al. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis. 2015; 9: 302-12. Pubmed: 26294418 DOI: 10.1177/1753465815599345
10. Alhazzani W, Moller MH, Arabi YM et al. Surviving Sepsis Campaign: Guidelines on the management of critically Ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020; 48:e440-e469. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363
12. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Jan 14. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Jan 23. Updates may be available at the NIH website.
13. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Nov 16. Available at https://clinicaltrials.gov.
14. DeGrado JR, Szumita PM, Schuler BR et al. Evaluation of the Efficacy and Safety of Inhaled Epoprostenol and Inhaled Nitric Oxide for Refractory Hypoxemia in Patients With Coronavirus Disease 2019. Crit Care Explor. 2020 Oct 19;2(10):e0259. DOI: 10.1097/CCE.0000000000000259. PMID: 33134949.
15. Sonti R, Pike CW, Cobb N. Responsiveness of inhaled epoprostenol in respiratory failure due to COVID-19. J Intensive Care Med. 2020 Nov 25:885066620976525. DOI: 10.1177/0885066620976525. Epub ahead of print. PMID: 33234007
16. Gattinoni L, Coppola S, Cressoni M et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020 May 15;201(10):1299-1300. DOI: 10.1164/rccm.202003-0817LE. PMID: 32228035.

Interferons:

1. Mantlo E, Bukreyeva N, Maruyama J et al. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Res. 2020 Apr 29; 179:104811. DOI: 10.1016/j.antiviral.2020.104811. PMID: 32360182.
2. Sallard E, Lescure FX, Yazdanpanah Y et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020 Apr 7; 178:104791. DOI: 10.1016/j.antiviral.2020.104791. PMID: 32275914.

3. Lokugamage KG, Hage A, Schindewolf C et al. SARS-CoV-2 is sensitive to type I interferon pretreatment. Preprint (not peer reviewed). bioRxiv. 2020 Apr 9;2020.03.07.982264. DOI: 10.1101/2020.03.07.982264. PMID: 32511335.
4. Prokunina-Olsson L, Alphonse N, Dickenson RE et al. COVID-19 and emerging viral infections: the case for interferon lambda. J Exp Med. 2020; 217:e20200653. DOI: 10.1084/jem.20200653. PMID: 32289152.
5. U.S. National Library of Medicine. ClinicalTrials website. (https://www.clinicaltrials.gov/ct2/results?cond=COVID&term=interferon+lambda&cntry=&state=&city=&dist=). Accessed 2020 Dec 9.
6. Mordstein M, Neugebauer E, Ditt V et al. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. J Virol. 2010; 84:5670-7. DOI: 10.1128/JVI.00272-10. PMID: 20335250.
7. O'Brien TR, Thomas DL, Jackson SS et al. Weak induction of interferon expression by SARS-CoV-2 supports clinical trials of interferon lambda to treat early COVID-19. Clin Infect Dis. 2020; 71:1410-2. DOI: 10.1093/cid/ciaa453. PMID: 32301957.
8. Stockman LJ, Bellamy R, Garner P et al. SARS: systematic review of treatment effects. PLoS Med. 2006; 3:e343. DOI: 10.1371/journal.pmed.0030343. PMID: 16968120.
9. Arabi YM, Shalhoub S, Mandourah Y et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. Clin Infect Dis. 2020; 70:1837-1844. DOI: 10.1093/cid/ciz544. PMID: 31925415.
10. Hung IF, Lung KC, Tso EY et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020; 395:1695-704. DOI: 10.1016/S0140-6736(20)31042-4. PMID: 32401715.
11. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Feb 23. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 26. Updates may be available at NIH website.
13. National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 patients (tentative 8th edition). Updated 2020 Sep 8. English translation available at http://regional.chinadaily.com.cn/pdf/DiagnosisandTreatmentProtocolforCOVID-19Patients(Tentative8thEdition).pdf. Accessed 2020 Nov 13.
14. Qiu H, Wu J, Hong L et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020; 20:689-96. DOI: 10.1016/S1473-3099(20)30198-5. PMID: 32220650.
15. Zhou Q, Chen V, Shannon CP et al. Interferon-α2b treatment for COVID-19. Front Immunol. 2020; May 15; 11:1061. DOI: 10.3389/fimmu.2020.01061. PMID: 32574262.
16. U.S. National Library of Medicine. ClinicalTrials website (https://www.clinicaltrials.gov/ct2/results?cond=COVID&term=interferon+beta&cntry=&state=&city=&dist=). Accessed 2020 Dec 9.
17. Ranieri VM, Pettilä V, Karvonen MK et al. Effect of intravenous interferon β-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2020; 323:725-33. DOI: 10.1001/jama.2019.22525. PMID: 32065831.
18. Chu H, Chan JFW, Wang Y et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. Clin Infect Dis. 2020; 71:1400-9. DOI: 10.1093/cid/ciaa410. PMID: 32270184.
19. Andreakos E, Salagianni M, Galani IE et al. Interferon-λs: front-line guardians of immunity and homeostasis in the respiratory tract. Front Immunol. 2017; 8:1232. DOI: 10.3389/fimmu.2017.01232. PMID: 29033947.
20. Davoudi-Monfared E, Rahmani H, Khalili H et al. A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. Antimicrob Agents Chemother. 2020: 20;64(9):e01061-20. [Epub ahead of print.] PMID: 32661006. DOI: 10.1128/AAC.01061-20.
21. Dastan F, Nadji SA, Saffaei A et al. Subcutaneous administration of interferon beta-1a for COVID-19: A noncontrolled prospective trial. Int Immunopharmacol. 2020 Aug; 85:106688. [Epub posted 2020 Jun 7.] PMID: 32544867. DOI: 10.1016/j.intimp.2020.106688.
22. Synairgen. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients. Southampton, UK; 2020 Jul 20. Press release.
23. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 – interim WHO Solidarity trial results. N Engl J Med. 2020 Dec 2. [Epub ahead of print.] DOI: 10.1056/NEJMoa2023184. PMID: 33264556.
24. Jalkanen J, Hollmén M, Jalkanen S. Interferon beta-1a for COVID-19: critical importance of the administration route. Crit Care. 2020; 24:335. DOI: 10.1186/s13054-020-03048-5. PMID: 32532353.
25. Rahmani H, Davoudi-Monfared E, Nourian A et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. Int Immunopharmacol. 2020 Aug 24;88:106903. [Epub ahead of print.] DOI: 10.1016/j.intimp.2020.106903. PMID: 32862111.
26. Clementi N, Ferrarese R, Criscuolo E et al. Interferon-β-1a inhibition of severe acute respiratory syndrome–coronavirus 2 in vitro when administered after virus infection. J Infect Dis. 2020; 222:722-5. DOI: 10.1093/infdis/jiaa350. PMID: 32559285.
27. Synairgen. Interim results for the six months ended 30 June 2020. Southampton, UK; 2020 Sep 29. Press release.
28. World Health Organization. Public health emergency SOLIDARITY trial: World Health Organization COVID-19 core protocol, version 10.0. 2020 Mar 22. From WHO website. Accessed 2020 Oct 26. (https://www.who.int/publications/m/item/an-international-randomised-trial-of-additional-treatments-for-covid-19-in-hospitalised-patients-who-are-all-receiving-the-local-standard-of-care).
29. Monk PD, Marsden RJ, Tear VJ et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021; 9:196-206. DOI: 10.1016/ S2213-2600(20)30511-7. PMID: 33189161.
30. Wang N, Zhan Y, Zhu L et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host Microbe. 2020; 28:455-64.e2. DOI: 10.1016/j.chom.2020.07.005. PMID: 32707096.
31. Hao S-R, Yan R, Zhang S-Y et al. Interferon-α2b spray inhalation did not shorten virus shedding time of SARS-CoV-2 in hospitalized patients: a preliminary matched case-control study. J Zhejiang Univ Sci B. 2020; 21:628-36. DOI: 10.1631/jzus.B2000211. PMID: 32748578.
32. Feld JJ, Kandel C, Biondi MJ et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med. 2021 Feb 5;S2213-2600(20)30566-X. [Epub ahead of print.] DOI: 10.1016/S2213-2600(20)30566-X. PMID: 33556319.

Ivermectin:

1. Caly L, Druce JD, Catton MG et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020; 178:104787 [Epub]. PMID: 32251768 DOI: 10.1016/j.antiviral.2020.104787.
2. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother. 2012; 67:1884-94. PMID: 22535622 DOI:10.1093/jac/dks147.
3. Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020 May; 177:104760. PMID: 32134219 DOI: 10.1016/j.antiviral.2020.104760.
4. Varghese FS, Kaukinen P, Glasker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016. 126:117-24. PMID: 26752081 DOI: 10.1016/j.antiviral.2015.12.012.
5. Azeem S, Ashraf M, Rasheed MA, et al. Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus. Pak J Pharm Sci. 2015; 28:597-602. PMID: 25730813.
6. Tay MY, Fraser JE, Chan WK, et al. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor ivermectin. Antiviral Res. 2013; 99:301-6. PMID: 23769930 DOI: 10.1016/j.antiviral.2013.06.002.
7. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. Biotechnol, Biotechnol Equip. 2020; 34:469-74. DOI: 10.1080/13102818.2020.1775118.
8. US Food and Drug Administration. FDA letter to stakeholders: do not use ivermectin intended for animals as treatment for COVID-19 in humans. April 10, 2020. From FDA website. (https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans).
9. Schmith VD, Zhou JJ, Lohmer LR. The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19. Clin Pharmacol Ther. 2020; 108:762-765. PMID: 32378737 DOI: 10.1002/cpt.1889
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 23. Available at https://clinicaltrials.gov.
11. Gorial FI, Mashhadani S, Sayaly HM, et al. Effectiveness of ivermectin as add-on therapy in COVID-19 management (pilot trial). medRxiv. Posted July 8, 2020. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.07.07.20145979v1).
12. Rajter JC, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in COVID nineteen study. Chest; 159:85-92. PMID: 33065103 DOI: 10.1016/j.chest.2020.10.009.
13. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 23. Updates may be available at NIH website.
14. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020 Dec 2; 103:214-16. PMID: 33278625 DOI: 10.1016/j.ijid.2020.11.191.
15. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021 Jan 14.
16. Merck. Merck statement on ivermectin use during the COVID-19 pandemic. Press release. 2021 Feb 4. Available at https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/.
17. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Apr 14. From IDSA website (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/). Accessed 2021 Apr 23. Updates may be available at IDSA website.
18. Behera P, Patro BK, Singh AK, et al. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: a matched case-control study. PLoS One. 2021 Feb 16;16 (2):e0247163. PMID: 33592050 DOI: 10.1371/journal.pone.0247163.
19. Aguirre-Chang G, Figueredo AT. COVID-19: post-exposure prophylaxis with ivermectin in contacts. At homes, places of work, nursing homes, prisons, and others. ResearchGate. 2020 (English translation; preprint not peer reviewed). Available at https://www.researchgate.net/publication/344781515_COVID-19_post-exposure _prophylaxis_with_ivermectin_in_contacts.
20. Elgazzar A, Eltaweel A, Youssef SA, et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. Reseach Square. 2020 (preprint not peer reviewed). Available at https://www.researchsquare.com/article/rs-100956/v3.
21. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA. 2021; 325:1426-35. PMID: 33662102 DOI: 10.1001/jama.2021.3071.

Nebulized drugs:

1. American College of Allergy, Asthma & Immunology. Important COVID-19 information for those with asthma and/or allergies. From ACAAI website. Accessed 2021 Feb 8. Available from https://acaai.org/news/important-covid-19-information-those-asthma-andor-allergies.
2. American College of Allergy, Asthma & Immunology. ACAAI announces U.S. albuterol inhaler shortage: a message to asthma sufferers about a shortage of albuterol metered-dose inhalers. From Allergic Living website. Accessed 2021 Feb 8. Available from https://www.allergicliving.com/2020/03/20/acaai-announces-u-s-albuterol-inhaler-shortage/.
3. Simonds AK, Hanak A, Chatwin M et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess. 2010; 14(46):131-72. PMID: 20923611 DOI: 10.3310/hta14460-02.
4. Ari A. Use of aerosolised medications at home for COVID-19. Lancet Respir Med. 2020 Aug; 8:754-6. PMID: 32585138. DOI: 10.1016/S2213-2600(20)30270-8.
5. Ari A. Practical strategies for a safe and effective delivery of aerosolized medications to patients with COVID-19. Respir Med. 2020; 167: 105987. PMID: 32421541. DOI: 10.1016/j.rmed.2020.105987.
6. World Health Organization. Clinical management of COVID-19. Interim guidance. Updated 2020 May 27. From WHO website. Accessed 2020 Jul 13. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

7. Sethi S, Barjaktarevic IZ, Tashkin DP. The use of nebulized pharmacotherapies during the COVID-19 pandemic. Ther Adv Respir Dis. 2020; 14:1-9. PMID: 33167796. DOI:10.1177/1753466620954366.
8. Centers for Disease Control and Prevention. Clinical questions about COVID-19: questions and answers. Updated 2021 Jan 25. From CDC website. Accessed 2021 Feb 8. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html. Updates may be available at CDC website.

Neuraminidase Inhibitors (e.g., oseltamivir):

1. Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–513. PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7
2. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020;14:69–71. PMID: 31996494 DOI: 10.5582/bst.2020.01020
3. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87:281-286. PMID: 32166607 DOI: 10.1007/s12098-020-03263-6
4. Tan EL, Ooi EE, Lin CY et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. Emerg Infect Dis. 2004;10:58–6. PMID: 15200845 DOI: 10.3201/eid1004.030458
5. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Jan 7. Available at https://clinicaltrials.gov.
6. Tan Q, Duan L, Ma Y et al. Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study. Bioorg Chem. 2020; 104:104257. PMID: 32927129 DOI: 10.1016/j.bioorg.2020.104257
7. Liu J, Zhang S, Wu Z et al. Clinical outcomes of COVID-19 in Wuhan, China: a large cohort study. Ann Intensive Care. 2020;10:99. PMID: 32737627 DOI: 10.1186/s13613-020-00706-3
8. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2020 Dec 17. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Jan 6. Updates may be available at NIH website.
9. Choy KT, Wong AY, Kaewpreedee P et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020; 178:104786. PMID: 32251767 DOI: 10.1016/j.antiviral.2020.104786.
10. US Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. From CDC website (https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm). Updated 2020 Nov 30. Accessed 2021 Jan 6.
11. McCreary EK, Pogue JM. Coronavirus disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020 Mar 23;7(4):ofaa105. PMID: 32284951 DOI: 10.1093/ofid/ofaa105

Niclosamide:

1. Wu CJ, Jan JT, Chen CM et al. Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother. 2004; 48:2693–6. PMID: 15215127 DOI: 10.1128/AAC.48.7.2693-2696.2004
2. Xu J, Shi PY, Li H et al. Broad spectrum antiviral agent niclosamide and its therapeutic potential. ACS Infect Dis. 2020; 6:909-15. PMID: 32125140 DOI: 10.1021/acsinfectdis.0c00052
3. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Mar 15. Available at http://www.clinicaltrials.gov.
4. Mostafa A, Kandeil A, Elshaier YAM et al. FDA-approved drugs with potent in vitro antiviral activity against severe acute respiratory syndrome coronavirus 2. Pharmaceuticals (Basel). 2020;13(12):443. PMID: 33291642 DOI: 10.3390/ph13120443
5. Jeon S, Ko M, Lee J et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother. 2020; 64(7):e00819-20. PMID: 32366720 DOI: 10.1128/AAC.00819-20

Nitazoxanide:

1. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269–271. PMID: 32020029 DOI: 10.1038/s41422-020-0282-0
2. Beigel JH, Nam HH, Adams PL et al. Advances in respiratory virus therapeutics - A meeting report from the 6th isirv antiviral group conference. Antiviral Res. 2019; 167:45–67. PMID: 30974127 DOI: 10.1016/j.antiviral.2019.04.006
3. Xu J, Shi PY, Li H et al. Broad spectrum antiviral agent niclosamide and its therapeutic potential. ACS Infect Dis. 2020; 6:909-15. PMID: 32125140 DOI: 10.1021/acsinfectdis.0c00052
4. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health. 2016 May–Jun; 9:227–30. PMID: 27095301 DOI: 10.1016/j.jiph.2016.04.001
5. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Res. 201; 110: 94–103. PMID: 25108173 DOI: 10.1016/j.antiviral.2014.07.014
6. Haffizulla J, Hartman A, Hoppers M et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. Lancet Infect Dis. 2014; 14:609–18. PMID: 24852376 DOI: 10.1016/S1473-3099(14)70717-0
7. Gamiño-Arroyo AE, Guerrero ML, McCarthy S et al. Efficacy and safety of nitazoxanide in addition to standard of care for the treatment of severe acute respiratory illness. Clin Infect Dis. 2019; 69:1903–1911. PMID: 30753384 DOI: 10.1093/cid/ciz100
8. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 22. Available at https://clinicaltrials.gov.
9. Rajoli RKR, Pertinez H, Arshad U et al. Dose prediction for repurposing nitazoxanide in SARS-CoV-2 treatment or chemoprophylaxis. Br J Clin Pharmacol. 2020 Oct 21 [Online ahead of print]. PMID: 33085781 DOI: 10.1111/bcp.14619
10. Bobrowski T, Chen L, Eastman RT et al. Synergistic and antagonistic drug combinations against SARS-CoV-2. Mol Ther. 2021; 29:873-885. PMID: 33333292 DOI: 10.1016/j.ymthe.2020.12.016
11. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2020 Feb 11. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Feb 22. Updates may be available at NIH website.
12. Meneses Calderón J, Figueroa Flores MDR, Paniagua Coria L et al. Nitazoxanide against COVID-19 in three explorative scenarios. J Infect Dev Ctries. 2020; 14:982-986. PMID: 33031085 DOI: 10.3855/jidc.13274

13. Rocco PRM, Silva PL, Cruz FF et al. Early use of nitazoxanide in mild Covid-19 disease: randomized, placebo-controlled trial. Eur Respir J. 2020 Dec 24;2003725 [Online ahead of print]. PMID: 33361100 DOI: 10.1183/13993003.03725-2020
14. Mostafa A, Kandeil A, Elshaier YAM et al. FDA-approved drugs with potent in vitro antiviral activity against severe acute respiratory syndrome coronavirus 2. Pharmaceuticals (Basel). 2020; 13:443. PMID: 33291642 DOI: 10.3390/ph13120443.

Nitric Oxide (inhaled):

1. Akerstrom S, Mousavi-Jazi M, Klingstom J et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. J Virol. 2005; 79(3):1966-9. PMID: 15650225 DOI:10.1128/JVI.79.3.1966-1969.2005
2. Chen L, Liu P, Gao H et al. Inhalation of nitric oxide in the treatment of severely acute respiratory syndrome: a rescue trial in Beijing. Clin Infect Dis. 2004; 39(10):1531-5. PMID:15546092 DOI: 10.1086/425357
3. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Nov 16. Available at https://clinicaltrials.gov.
4. Fuller BM, Mohr NM, Skrupky L et al. The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. Chest. 2015; 147(6):1510-22. PMID: 25742022 DOI: 10.1378/chest.14-3161
5. Griffiths MJD, McAuley DF, Perkins GD et al. Guidelines on the management of acute respiratory distress syndrome. BMJ Open Resp Res. 2019; 6:e000420. PMID 31258917 DOI: 10.1136/bmjresp-2019-000420
6. Papazian L, Aubron C, Brochard L et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019; 9(1): 69. PMID: 31197492 DOI: 10.1186/s13613-019-0540-9.
9. Gebistorf F, Karam O, Wetterslev J et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. 2016; Jun 27 (6): 1-98. PMID: 27347773 DOI: 10.1002/14651858.CD002787.pub3.
10. Alhazzani W, Moller MH, Arabi YM et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020; 48:e440-e469. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363
11. Kobayashi J, Murata I. Nitric oxide inhalation as an interventional rescue therapy for COVID-19-induced acute respiratory distress syndrome. Ann Intensive Care. 2020;10(1):61. Published 2020 May 20. PMID: 32436029 DOI:10.1186/s13613-020-00681-9
12. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Jan 14. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Jan 23. Updates may be available at the NIH website.
13. Zamanian RT, Pollack CV Jr, Gentile MA, et al. Outpatient inhaled nitric oxide in a patient with vasoreactive idiopathic pulmonary arterial hypertension and COVID-19 infection. Am J Respir Crit Care Med. 2020; 202(1):130-132. PMID: 32369396 DOI:10.1164/rccm.202004-0937LE.
14. Ignarro LJ. Inhaled NO and COVID-19. Br J Pharmacol. 2020; 117 (16):3848-9. PMID: 32346862 DOI:10.1111/bph.15085
15. Ferrari M, Santini A, Protti A et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. J Crit Care. 2020 Dec; 60:159-160. DOI: 10.1016/j.jcrc.2020.08.007. Epub 2020 Aug 11. PMID: 32814271.
16. Tavazzi G, Marco P, Mongodi S et al. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. Crit Care. 2020; 24(1):508. Published 2020 Aug 17. PMID: 32807220 DOI:10.1186/s13054-020-03222-9
17. Patel PA, Chandrakasan S, Mickells GE, et al. Severe pediatric COVID-19 presenting with respiratory failure and severe thrombocytopenia. Pediatrics. 2020 Jul;146(1):e20201437. PMID: 32366611 DOI: 10.1542/peds.2020-1437. Epub 2020 May 4.
18. DeGrado JR, Szumita PM, Schuler BR et al. Evaluation of the efficacy and safety of inhaled epoprostenol and inhaled nitric oxide for refractory hypoxemia in patients with coronavirus disease 2019. Crit Care Explor. 2020 Oct 19;2(10):e0259. DOI: 10.1097/CCE.0000000000000259. PMID: 33134949.
19. Safaee Fakhr B, Wiegand SB, Pinciroli R et al. High concentrations of nitric oxide inhalation therapy in pregnantpPatients with severe coronavirus disease 2019 (COVID-19), Obstet Gynecol. 2020; 136:1109-1113. PMID: 32852324 DOI: 10.1097/AOG.0000000000004128.
20. Gattinoni L, Coppola S, Cressoni M et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020 May 15;201(10):1299-1300. DOI: 10.1164/rccm.202003-0817LE. PMID: 32228035.
21. Parikh R, Wilson C, Weinberg J et al. Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients. Ther Adv Respir Dis. 2020 Jan-Dec;14:. DOI: 10.1177/1753466620933510. PMID: 32539647.
22. Abou-Arab O, Huette P, Debouvries F et al. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. Crit Care. 2020 Nov 12;24(1):645. DOI: 10.1186/s13054-020-03371-x. PMID: 33183348.
23. Lotz C, Muellenbach RM, Meybohm P et al. Effects of inhaled nitric oxide in COVID-19-induced ARDS - Is it worthwhile? Acta Anaesthesiol Scand. 2020 Dec 9. DOI: 10.1111/aas.13757. Epub ahead of print.
24. Longobardo A, Montanari C, Shulman R et al. Inhaled nitric oxide minimally improves oxygenation in COVID-19 related acute respiratory distress syndrome. Br J Anaesth. 2021 Jan;126(1):e44-e46. DOI: 10.1016/j.bja.2020.10.011. Epub 2020 Oct 14.
25. Garfield B, McFadyen C, Briar C et al. Potential for personalised application of inhaled nitric oxide in COVID-19 pneumonia. Br J Anaesth. 2021 Feb;126(2):e72-e75. DOI: 10.1016/j.bja.2020.11.006. Epub 2020 Nov 14.

NSAIAs, including ibuprofen:

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020; 8:e21. PMID: 32171062 DOI: 10.1016/S2213-2600(20)30116-8

2. Alhazzani W, Evans L, Alshamsi F, et al. Surviving Sepsis Campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021; 49:e219-34. PMID: 33555780 DOI:10.1097/CCM.0000000000004899.
3. Sodhi M, Etminan M, Safety of Ibuprofen in Patients with COVID-19; Causal or Confounded? Chest. 2020;158(1):55-56. PMID: 32243944 DOI: https://doi.org/10.1016/j.chest.2020.03.040
4. Gupta R, Misra. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in co-morbid diseases (hypertension, diabetes etc). Diabetes Metab Syndr. 2020; 14:251-254. PMID: 32247213 DOI: 10.1016/j.dsx.2020.03.012
5. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 April 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 April 21. Updates may be available at NIH website.
6. Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther. 2006; 11:1021-30. PMID: 17302372
7. Xu T, Gao X, Wu Z, et al. Indomethacin has a potent antiviral activity against SARS CoV-2 in vitro and canine coronavirus in vivo. Preprint. (not peer reviewed). (DOI: https://doi.org/10.1101/2020.04.01.017624)
8. Clark C. Indomethacin in Covid-19. From MedicalUpdateOnline website. Available at https://medicalupdateonline.com/2020/05/indomethacincovid19/. May 4, 2020. Accessed May 14, 2020.
9. World Health Organization. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19: Scientific brief, 2020 April 19. Accessed 2020 Jun 15. Available at https://apps.who.int/iris/handle/10665/331796.
10. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ. 2020;368:m1086. Published 2020 Mar 17. PMID: 32184201 DOI:10.1136/bmj.m1086.
11. US Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020 Mar 19. Accessed 2020 Sep 8. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.
12. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Updated 2020 Sep 4. Accessed 2020 Sep 8. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Updates may be available at IDSA website.
13. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Sep 1. Available at http://www.clinicaltrials.gov.
14. Lund LC, Kristensen KB, Reilev M, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study. PLoS Med. 2020;17(9):e1003308. Published 2020 Sep 8. PMID: 32898149 DOI:10.1371/journal.pmed.1003308.
15. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. 2020 Jun 12 [epub ahead of print]. Clin Microbiol Infect. 2020;26(9):1259.e5-1259.e7. PMID: 32535147 DOI:10.1016/j.cmi.2020.06.003.
16. Chandan JS, Zemedikun DT, Thayakaran R, et al. Non-steroidal anti-inflammatory drugs and susceptibility to COVID-19. 2020 Nov 13 [Epub ahead of print]. Arthritis Rheumatol. 2020;10.1002/art.41593. PMID: 33185016 DOIi:10.1002/art.41593.
17. Wong AY, MacKenna B, Morton CE, et al. Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts [published online ahead of print, 2021 Jan 21]. Ann Rheum Dis. 2021;annrheumdis-2020-219517. PMID: 33478953 DOI:10.1136/annrheumdis-2020-219517.

Remdesivir:

1. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269-271. (PubMed 32020029) (DOI 10.1038/s41422-020-0282-0)
2. Agostini ML, Andres EL, Sims AC et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 2018; 9. (PubMed 29511076) (DOI 10.1128/mBio.00221-18)
3. Brown AJ, Won JJ, Graham RL et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019; 169:104541. (PubMed 31233808) (DOI 10.1016/j.antiviral.2019.104541)
4. Sheahan TP, Sims AC, Graham RL et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017; 9. (PubMed 28659436) (DOI 10.1126/scitranslmed.aal3653)
5. de Wit E, Feldmann F, Cronin J et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020; 117:6771-6776. (PubMed 32054787) (DOI 10.1073/pnas.1922083117)
6. Gordon CJ, Tchesnokov EP, Feng JY et al. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020; 295:4773-4779. (PubMed 32094225) (DOI 10.1074/jbc.AC120.013056)
7. Sheahan TP, Sims AC, Leist SR et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020; 11:222. (PubMed 31924756) (DOI 10.1038/s41467-019-13940-6)
8. Ko WC, Rolain JM, Lee NY et al. Arguments in favor of remdesivir for treating SARS-CoV-2 infections. Int J Antimicrob Agents. 2020; 55:105933. Editorial. (PubMed 32147516) (DOI 10.1016/j.ijantimicag.2020.105933)
9. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020; 64:e00399-20. (PubMed 32152082) (DOI 10.1128/AAC.00399-20)
10. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with severe coronavirus disease (COVID-19). NCT04292899. (https://www.clinicaltrials.gov/ct2/show/NCT04292899)
11. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment. NCT04292730. (https://www.clinicaltrials.gov/ct2/show/NCT04292730)
12. Expanded access remdesivir (RDV; GS-5734). (https://www.clinicaltrials.gov/ct2/show/NCT04302766)
13. Adaptive COVID-19 treatment trial (ACTT). NCT04280705. (https://clinicaltrials.gov/ct2/show/NCT04280705).
14. Lai CC, Liu YH, Wang CY et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect. 2020; 53:404-412. (PubMed 32173241) (DOI 10.1016/j.jmii.2020.02.012)

16. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020; 382:2327-2336. PMID: 32275812 DOI: 10.1056/NEJMoa2007016.
18. Choy KT, Wong AYL, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antivir Res. 2020 Apr 3; 178 [Epub ahead of print]. (https://doi.org/10.1016/j.antiviral.2020.104786). PMID: 32251767 DOI: 10.1016/j.antiviral.2020.104786.
19. Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature. 2020; 585:273-276. PMID: 32516797 DOI: 10.1038/s41586-020-2423-5.
20. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 21. Updates may be available at NIH website.
21. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395: 1569-78. PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9. (https://doi.org/10.1016/S0140-6736(20)31022-9)
22. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19–preliminary report. N Engl J Med. 2020 May 22 [Epub ahead of print]. PMID: 32445440 DOI: 10.1056/NEJMoa2007764
23. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe covid-19. N Engl J Med. 2020; 383:1827-1837. PMID: 32459919 DOI: 10.1056/NEJMoa2015301
24. Gordon CJ, Tshesnokov EP, Woolner E et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020; 295:6785-6797. PMID: 32284326 DOI: 10.1074/jbc.RA120.013679
25. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients. 2020 May 1. From FDA website. Accessed 2020 May 1.
26. US Food and Drug Administration. Fact sheet for healthcare providers: Emergency use authorization (EUA) of Veklury® (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. Revised 2020 Oct. From FDA website. (https://www.fda.gov/media/137566/download)
27. US Food and Drug Administration. Fact sheet for parents and caregivers: Emergency use authorization (EUA) of Veklury® (remdesivir) for hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children less than 12 years of age weighing at least 8 pounds (3.5 kg) with coronavirus disease 2019 (COVID-19). Revised 2020 Oct. From FDA website. (https://www.fda.gov/media/137565/download)
29. Kalil AC, Patterson TF, Mehta AK et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med. 2021; 384:795-807. PMID: 33306283 DOI: 10.1056/NEJMoa2031994.
30. Spinner CD, Gottlieb RL, Criner GJ et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020; 324:1048-1057. PMID: 32821939 DOI: 10.1001/jama.2020.16349.
31. Adaptive COVID-19 treatment trial 2 (ACTT-II). NCT04401579. (https://www.clinicaltrials.gov/ct2/show/NCT04401579).
32. A study to evaluate the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized participants with severe COVID-19 pneumonia (REMDACTA). NCT04409262. Update posted 2020 Nov 20. (https://www.clinicaltrials.gov/ct2/show/NCT04409262).
33. US Food and Drug Administration. Communication regarding remdesivir and newly discovered potential drug interactions that may reduce effectiveness of treatment. 2020 Jun 15. Available at FDA website (https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce).
34. Gilead Sciences. Gilead presents additional data on investigational remdesivir for the treatment of COVID-19. Press release. 2020 Jul 10. Available at https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19.
35. Study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir (GS-5734) in participants from birth to <18 years of age with coronavirus disease 2019 (COVID-19) (CARAVAN). NCT04431453. Update posted 2020 Nov 26. (https://clinicaltrials.gov/ct2/show/NCT04431453).
36. National Institutes of Health. NIH clinical trial testing remdesivr plus interferon beta-1a for COVID-19 treatment begins. 2020 Aug 5. From NIH website. (https://www.niaid.nih.gov/news-events/nih-clinical-trial-testing-remdesivir-plus-interferon-beta-1a-covid-19-treatment-begins). Accessed 2020 Aug 10.
37. Adaptive COVID-19 treatment trial 3 (ACTT-3). NCT04492475. Update posted 2020 Nov 13. (https://clinicaltrials.gov/ct2/show/NCT04492475).
38. US Food and Drug Administration. Letter of authorization: Reissuance of emergency use authorization for use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients. 2020 Aug 28. From FDA website. Accessed 2020 Aug 31.
39. US Food and Drug Administration. Letter of authorization: Reissuance of emergency use authorization for use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients. 2020 Oct 22. From FDA website. Accessed 2020 Oct 23. (https://www.fda.gov/media/137564/download)
40. Gilead Sciences. Update on supply and distribution of Veklury® (remdesivir) in the United States. Press release. 2020 Oct 1. From Gilead website. (https://www.gilead.com/news-and-press/press-room/press-releases/2020/10/gilead-sciences-update-on-supply-and-distribution-of-veklury-remdesivir-in-the-united-states)
41. Study to evaluate the safety and efficacy of remdesivir (GS-5734) treatment of coronavirus disease 2019 (COVID-19) in an outpatient setting. NCT04501952. Update posted 2020 Nov 4. (https://clinicaltrials.gov/ct2/show/NCT04501952).
42. Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the treatment of COVID-19 – final report. N Engl J Med. 2020 Nov 5; 383:1813-1826. PMID: 32445440 DOI: 10.1056/NEJMoa2007764.
43. Eli Lilly. Baricitinib has significant effect on recovery time, most impactful in COVID-19 patients requiring oxygen. Press release. 2020 Oct 8. Available at https://investor.lilly.com/news-releases/news-release-details/baricitinib-has-significant-effect-recovery-time-most-impactful.
44. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 – interim WHO Solidarity trial results. N Engl J Med. 2021; 384:497-511. PMID: 33264556 DOI: 10.1056/NEJMoa2023184.
45. National Institutes of Health. NIH clinical trial testing hyperimmune intravenous immunoglobulin plus remdesivir to treat COVID-19 begins. 2020 Oct 8. From NIH website. (https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-hyperimmune-intravenous-immunoglobulin-plus-remdesivir-treat-covid-19-begins). Accessed 2020 Oct 21.
46. Gilead Sciences. Veklury® (remdesivir) for injection and injection prescribing information. Foster City, CA; 2021 Feb.
47. Gilead. Veklury® (remdesivir) distribution and access. From Gilead website (https://www.vekluryhcp.com/product-access/). Accessed 2020 Oct 24.
48. U.S. Food and Drug Administration. Frequently asked questions for Veklury (remdesivir). Updated 2021 Feb 4. From FDA website (https://www.fda.gov/media/137574/download). Accessed 2021 Feb 23.

49. Dear Healthcare Provider letter. Clarification on appropriate use and variations in carton and vial labeling of the antiviral Veklury® (remdesivir). From Gilead website (https://www.gilead.com/-/media/files/pdfs/remdesivir/dear-hcp-letter_veklury_remdesivir.pdf?la=en&hash=3FE840B3C4814EE770884861BBC8984C). Accessed 2020 Oct 24.
50. Inpatient treatment with anti-coronavirus immunoglobulin (ITAC). NCT04546581. Update posted 2020 Nov 13. (https://www.clinicaltrials.gov/ct2/show/NCT04546581).
51. US Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of baricitinib. Dated 2020 Nov. From FDA website. (https://www.fda.gov/media/143823/download).
52. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Apr 14. From IDSA website (https://www.idsociety.org/COVID19guidelines/). Accessed 2021 Apr 23. Updates may be available at IDSA website.
53. World Health Organization. Public health emergency SOLIDARITY trial: World Health Organization COVID-19 core protocol, version 10.0. 2020 Mar 22. From WHO website. Accessed 2020 Dec 7. (https://www.who.int/publications/m/item/an-international-randomised-trial-of-additional-treatments-for-covid-19-in-hospitalised-patients-who-are-all-receiving-the-local-standard-of-care).

Ruxolitinib

1. Incyte announces plans to initiate a phase 3 clinical trial of ruxolitinib (Jakafi®) as a treatment for patients with COVID-19 associated cytokine storm. Press release. Incyte: 2020 Apr 2. (https://investor.incyte.com/news-releases/news-release-details/incyte-announces-plans-initiate-phase-3-clinical-trial).
2. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 12. Available from https://clinicaltrials.gov/ct2/show/NCT04337359.
3. U.S. National Library of Medicine. ClinicalTrials.gov. 2021 Apr 15. Available from https://clinicaltrials.gov.
4. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033-4. PMID: 32192578. DOI: 10.1016/S0140-6736(20)30628-0.
5. Zhang W, Zhao Y, Zhang F et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020; 214: 108393. PMID: 32222466. DOI: 10.1016/j.clim.2020.108393.
7. Elli EM, Barate C, Mendicino F et al. Mechanisms underlying the anti-inflammatory and Immunosuppressive activity of ruxolitinib. Front Oncol. 2019; 9:1186. PMID: 31788449. DOI: 10.3389/fonc.2019.01186.
8. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 8. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 16. Updates may be available at NIH website.
9. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Feb 12. Available from https://clinicaltrials.gov/ct2/show/NCT04355793.
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Sep 30. Available from https://clinicaltrials.gov/ct2/show/NCT04362137.
11. Gaspari V, Zengarini C , Greco S et al. Side effects of ruxolitinib in patients with SARS-CoV-2 infection: two case reports. Int J Antimicrob Agents. 2020 Aug; 56(2):106023 [Epub ahead of print]. PMID: 32450201. DOI: 10.1016/j.ijantimicag.2020.106023.
12. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jun 23. Available from https://clinicaltrials.gov/ct2/show/NCT04377620.
13. Cao Y, Wei J, Zou L et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol. 2020; 146:137-46.e3. PMID: 32470486. DOI: 10.1016/j.jaci.2020.05.019.
14. La Rosée F, Bremer HC, Gehrke I et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia. 2020; 2020; 34:1805-15. PMID: 32518419. DOI: 10.1038/s41375-020-0891-0.
15. Giudice V, Pagliano P, Vatrella A et al. Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-related acute respiratory distress syndrome: a controlled study. Front Pharmacol. 2020 Jun 5; 11:857. [eCollection 2020.] PMID: 32581810. DOI: 10.3389/fphar.2020.00857.
16. Stebbing J, Phelan A, Griffin I et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020; 20:400-2. PMID: 32113509. DOI: 10.1016/S1473-3099(20)30132-8.
17. Vannucchi AM, Sordi B, Morettini A et al. Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study. Leukemia. 2020; 35:1121-33. PMID: 32814839. DOI: 10.1038/s41375-020-01018-y.
18. Capochiani E, Frediani B, Iervasi G et al. Ruxolitinib rapidly reduces acute respiratory distress syndrome in COVID-19 disease. Analysis of data collection from RESPIRE protocol. Front Med (Lausanne). 2020 Aug 4; 7:466. [eCollection 2020.] PMID: 32850921. DOI: 10.3389/fmed.2020.00466.
19. Incyte. Incyte announces results of phase 3 RUXCOVID study of ruxolitinib (Jakafi®) as a treatment for patients with COVID-19 associated cytokine storm. Press release. 2020 Dec 14. From Incyte website (https://investor.incyte.com/press-releases/press-releases/2020/Incyte-Announces-Results-of-Phase-3-RUXCOVID-Study-of-Ruxolitinib-Jakafi-as-a-Treatment-for-Patients-with-COVID-19-Associated-Cytokine-Storm/default.aspx).
20. Incyte. Incyte COVID-19 response. Updated 2020 Dec 14. From Incyte website (https://www.incyte.com/covid-19). Accessed 2021 Feb 12.
21. Incyte announces results from the phase 3 DEVENT study evaluating ruxolitinib (Jakafi®) as a treatment for patients with COVID-19 associated acute respiratory distress syndrome (ARDS) on mechanical ventilation. Press release. Incyte: 2021 Mar 18. (https://investor.incyte.com/press-releases/press-releases/2021/).
22. Incyte. Expanded access program of ruxolitinib for the emergency treatment of cytokine storm from COVID-19 infection. From Incyte website (https://www.incyteclinicaltrials.com). Accessed 2021 Apr 15.

Sarilumab:

1. Genentech, Inc, South San Francisco, CA. Actemra use in Coronavirus Disease 2019 (COVID-19) standard reply letter. 2020 Mar 16.
2. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). (Mandarin; English translation.) 2020 Mar 3.
3. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. Available on chinaXiv website. Accessed online 2020 Mar 19.

4. Sanofi and Regeneron begin global Kevzara® (sarilumab) clinical trial program in patients with severe COVID-19 [press release]. Cambridge, Mass and Tarrytown, NY; Sanofi: March 16, 2020. http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19. Accessed 2020 Mar 19.
5. Sanofi and Regeneron Pharmaceuticals, Inc, Cambridge, MA and Tarrytown, NY. Sarilumab and COVID-19 standard reply letter. 2020 Mar 24.
6. Sanofi Genzyme, Cambridge, MA: Personal communication.
7. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 25. Updates may be available at NIH website.
8. Benucci M, Giannasi G, Cecchini P et al. COVID-19 pneumonia treated with sarilumab: a clinical series of eight patients. J Med Virol. 2020 May 30 [Epub ahead of print]. PMID 32472703 DOI: 10.1002/jmv.26062
9. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial Kevzara® (sarilumab) in hospitalized COVID-19 patients [press release].Tarrytown, NY and Paris; Regeneron Pharmaceuticals, Inc. and Sanofi: April 27, 2020. Accessed 2020 Jun 11.
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 25. Available at https://clinicaltrials.gov.
11. Sanofi provides update on Kevzara® (sarilumab) phase 3 trial in severe and critically ill COVID-19 patients outside the U.S. [press release]. 2020 Sep 1. Available at: https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00. Accessed 2020 Sep 7.
12. Sanofi and Regeneron provide update on Kevzara® (sarilumab) phase 3 U.S. trial in COVID-19 patients [press release]. 2020 Jul 2. Available at: https://www.globenewswire.com/news-release/2020/07/02/2057183/0/en/Sanofi-and-Regeneron-provide-update-on-Kevzara-sarilumab-Phase-3-U-S-trial-in-COVID-19-patients.html. Accessed 2020 Sep 7.
13. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. New Engl J Med. 2021 Feb 25. [Epub ahead of print.] PMID: 33631065 DOI: 10.1056/NEJMoa2100433.

SARS-CoV-2-Specific Monoclonal Antibodies

1. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA. 2020 Jul 14; 324:131-132. PMID: 32539093 DOI: 10.1001/jama.2020.10245.
2. Zost SJ, Gilchuk P, Case JB et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature. 2020 Aug; 584:443-449. PMID: 32668443 DOI: 10.1038/s41586-020-2548-6.
3. Sharun K, Tiwari R, Yatoo MI et al. Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects. Expert Opin Biol Ther. 2020 Sep; 20:1033-1046. PMID: 32744917 DOI: 10.1080/14712598.2020.1796963.
4. Alsoussi WB, Turner JS, Case JB et al. A potently neutralizing antibody protects mice against SARS-CoV-2 infection. J Immunol. 2020 Aug 15; 205:915-922. PMID: 32591393 DOI: 10.4049/jimmunol.20000582.
5. Ejemel M, Li Q, Hou S et al. A cross-reactive human IgA monoclonal antibody blocks SARS-CoV-2 spike-ACE2 interactions. Nat Commun. 2020 Aug 21; 11:4198. PMID: 32826914 DOI: 10.1038/s41467-020-18058-8.
6. Jahanshahlu L, Rezaei N. Monoclonal antibody as a potential anti-COVID-19. Biomed Pharmacother. 2020 Sep; 129:110337. PMID: 32534226 DOI: 10.1016/j.biopha.2020.110337.
7. Ojha PK, Kar S, Krishna JG et al. Therapeutics for COVID-19: from computation to practices – where we are, where we are heading to. Mol Divers. 2020 Sep 2:1-35. PMID: 32880078 DOI: 10.1007/s11030-020-10134-x.
8. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Jan 8. Available at https://clinicaltrials.gov.
9. A Study of LY3819253 (LY-CoV555) in Participants Hospitalized for COVID-19. NCT04411628. Update posted 2020 Oct 30. (https://www.clinicaltrials.gov/ct2/show/study/NCT04411628).
10. A Study of LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Participants with Mild to Moderate COVID-19 Illness (BLAZE-1). NCT04427501. Update posted 2021 Apr 20. (https://www.clinicaltrials.gov/ct2/show/study/NCT04427501).
11. A Study of LY3819253 (LY-CoV555) and LY3832479 (LY-CoV016) in Preventing SARS-CoV-2 Infection and COVID-19 in Nursing Home Residents and Staff (BLAZE-2). Update posted 2021 Apr 20. NCT04497987. (https://www.clinicaltrials.gov/ct2/show/study/NCT04497987).
12. Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting. Press release. 2020 Sep 16. Available at https://investor.lilly.com/news-releases/news-release-details/lilly-announces-proof-concept-data-neutralizing-antibody-ly.
13. Jones BE, Brown-Augsburger PL, Corbett KS et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primary model of SARS-CoV-2 infection. bioRxiv. Posted Oct 1, 2020. Preprint (not peer reviewed). (https://www.biorxiv.org/content/10.1101/2020.09.30.318972v1).
14. VIR-7831 for the Early Treatment of COVID-19 in Outpatients (COMET-ICE). NCT04545060. Update posted 2021 Mar 29. (https://www.clinicaltrials.gov/ct2/show/study/NCT0455060).
15. Vir Biotechnology and GSK start phase 2/3 study of COVID-19 antibody treatment. Press release. 2020 Aug 31. Available at https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-start-phase-23-study-of-covid-19-antibody-treatment/.
16. Study to Evaluate STI-1499 (COVI-GUARD) in Patients with Moderate COVID-19. NCT04454398. Update posted 2021 Jan 8. (https://www.clinicaltrials.gov/ct2/show/study/NCT04454398).
17. Sorrento releases preclinical data for STI-1499 (COVI-Guard) and STI-2020 (COVI-AMG), potent neutralizing antibodies against SARS-CoV-2. Press release. 2020 Sep 29. Available at https://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-releases-preclinical-data-sti-1499-covi-guardtm-and-sti.
18. Cao X, Maruyama J, Zhou H et al. Discovery and development of human SARS-CoV-2 neutralizing antibodies using an unbiased phage display library approach. medRxiv. Posted 2020 Sep 29. Preprint (not peer reviewed). (https://www.biorxiv.org/content/10.1101/2020.09.27.316174v2).
19. AZD7442 – a Potential Combination Therapy for the Prevention and Treatment of COVID-19. NCT04507256. Updated 2021 Apr 8. (https://www.clinicaltrials.gov/ct2/show/study/NCT04507256).
20. AstraZeneca. Phase 1 clinical trial initiated for monoclonal antibody combination for the prevention and treatment of COVID-19. Press release. 2020 Aug 25. Available at https://www.astrazeneca.com/media-centre/press-releases/2020/phase-1-clinical-trial-initiated-for-monoclonal-antibody-combination-for-the-prevention-and-treatment-of-covid-19.html.
21. NIAID. Clinical trials of monoclonal antibodies to prevention COVID-19 now enrolling. Press release. 2020 Aug 10. Available at https://www.nih.gov/news-events/news-releases/clinical-trials-monoclonal-antibodies-prevent-covid-19-now-enrolling.

22. Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients with COVID-19. NCT04426695. Update posted 2020 Dec 30. (https://www.clinicaltrials.gov/ct2/show/study/NCT04426695).
23. Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients with COVID-19. NCT04425629. Update posted 2021 Apr 5. (https://www.clinicaltrials.gov/ct2/show/study/NCT04425629).
24. COVID-19 Study Assessing the Efficacy and Safety of Anti-Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2 Infection Asymptomatic in Healthy Adults and Adolescents Who are Household Contacts to an Individual with a Positive SARS-CoV-2 RT-PCR Assay. NCT04452318. Update posted 2021 Apr 8. (https://www.clinicaltrials.gov/ct2/show/study/NCT04452318).
25. Regeneron. REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients. Press release. 2020 Sep 14. Available at https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and.
26. Regeneron. RECOVERY COVID-19 phase 3 trial to evaluate Regeneron's REGN-COV2 investigational antibody cocktail in the UK. Press release. 2020 Sep 29. Available at https://newsroom.regeneron.com/news-releases/news-release-details/recovery-covid-19-phase-3-trial-evaluate-regenerons-regn-cov2.
27. Baum A, Fulton BO, Wloga E et al. Antibody cocktail to SARS-CoV-2 spike protein preventions rapid mutational escape seen with individual antibodies. Science. 2020 Aug 2; 369:1014-1018. PMID: 3254904 DOI: 10.1126/science.abd0831.
28. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV02 infection in rhesus macaques and hamsters. Science. 2020; 370:1110-1115. PMID: 33037066 DOI: 10.1126/science.abe2402.
29. Hansen J, Baum AL, Pascal KE et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science. 2020 Aug 21; 369:1010-1014. PMID: 32540901 DOI: 10.1126/science.abd0827.
30. Renn A, Fu Y, Hu X et al. Fruitful neutralizing antibody pipeline brings hope to defeat SARS-Cov-2. Trends in Pharmacol Sci. 2020 Jul 31; S0165-6147(20)30166-8. PMID: 32829936 DOI: 10.1016/j.tips.2020.07.004.
31. Padmanabhan P, Desikan R, Dixit NM. The quantitative landscape of the neutralizing antibody response to SARS-CoV-2. medRxiv. Posted 2020 Sep 28. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.09.25.20201996v1).
32. Lilly provides comprehensive update on progress of SARS-CoV-2 neutralizing antibody programs. Press release. 2020 Oct 7. Available at https://investor.lilly.com/news-releases/news-release-details/lilly-provides-comprehensive-update-progress-sars-cov-2.
33. A study of LY3832479 (LY-CoV016) in healthy participants. NCT04441931. Updated 2020 Oct 8. (https://www.clinicaltrials.gov/ct2/show/study/NCT04441931).
34. Vir Biotechnology and GSK announce global expansion to phase 3 of COMET-ICE study evaluating VIR-7831 for the treatment of COVID-19. Press release. 2020 Oct 6. Available at https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-global-expansion-to-phase-3-of-comet-ice-study-evaluating-vir-7831-for-the-treatment-of-covid-19/.
35. AstraZeneca. COVID-19 long-acting antibody (LAABB) combination AZD7442 rapidly advances into phase III clinical trials. Press release. 2020 Oct 9. Available at https://www.astrazeneca.com/media-centre/press-releases/2020/covid-19-long-acting-antibody-laab-combination-azd7442-rapidly-advances-into-phase-iii-clinical-trials.html.
36. Regeneron. Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. Press release. 2020 Oct 28. Available at https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates.
37. Regeneron. REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirement. Press release. 2020 Oct 30. Available at https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends.
38. Randomized evaluation of COVID-19 therapy (RECOVERY). NCT04381936. Update posted 2020 Dec 1. (https://www.clinicaltrials.gov/ct2/show/study/NCT04381936).
39. Chen P, Nirula A, Heller B et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med. 2020 Oct 28 [epub ahead of print]. PMID: 33113295 DOI: 10.1056/NEJMoa2029849.
40. ACTIV-3: therapeutics for inpatients with COVID-19 (TICO). NCT04501978. Update posted 2021 Jan 5. (https://www.clinicaltrials.gov/ct2/show/study/NCT04501978).
41. NIAID. Statement – NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. Press release. 2020 Oct 26. Available at https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study.
42. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of bamlanivimab for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). Reissued 2021 Mar 2. From FDA website. (https://www.fda.gov/media/143602/download).
43. US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of bamlanivimab. 2021 Mar 18. From FDA website. (https://www.fda.gov/media/143603/download).
44. US Food and Drug Administration. Fact sheet for patients, parents and caregivers: Emergency use authorization (EUA) of bamlanivimab for coronavirus disease 2019 (COVID-19). 2021 Jan 28. From FDA website. (https://www.fda.gov/media/143604/download).
45. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) receives FDA emergency use authorization for the treatment of recently diagnosed COVID-19. Press release. 2020 Nov 9. Available at https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-receives-fda.
46. US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR). ASPR's portfolio of COVID-19 MCMs: bamlanivimab. From HHS website (https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx).
47. ACTIV-2: A study for outpatients with COVID-19. NCT04518410. Update posted 2021 Apr 23. (https://www.clinicaltrials.gov/ct2/show/NCT04518410).
48. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of REGEN-COV® (casirivimab and imdevimab) for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). Reissued 2021 Feb 25. From FDA website. (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fda-letter.pdf).
49. Regeneron. Fact sheet for health care providers: Emergency use authorization (EUA) of REGEN-COV® (casirivimab and imdevimab). 2021 Mar. From FDA website. (https://www.fda.gov/media/145611/download).

50. Regeneron. Fact sheet for patients, parents, and caregivers: Emergency use authorization (EUA) of REGEN-COV® (casirivimab and imdevimab) for coronavirus disease 2019 (COVID-19). 2021 Mar. From FDA website. (https://www.fda.gov/media/145612/download).
51. US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR). ASPR's portfolio of COVID-19 MCMs: casirivimab/imdevimab. From HHS website (https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/default.aspx).
52. Regeneron. Dear healthcare provider letter: New name and packaging for Regeneron COVID-19 monoclonal antibodies (casirivimab and imdevimab) to be administered together (REGEN-COV®). 2021 Feb 3. From Regeneron website. (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-preventing-medication-errors.pdf).
53. Study to Evaluate the Safety, Pharmacokinetics and Efficacy of STI-2020 (COVI-AMG) in outpatients with COVID-19. NCT04584697. Update posted 2021 Feb 12. (https://www.clinicaltrials.gov/ct2/show/NCT04584697).
54. Phase III double-blind, placebo-controlled study of AZD7442 for pre-exposure prophylaxis of COVID-19 in adult (PROVENT). NCT04625725. Update posted 2021 Mar 8. (https://www.clinicaltrials.gov/ct2/show/NCT04625725).
55. Phase III double-blind, placebo-controlled study of AZD7442 for post-exposure prophylaxis of COVID-19 in adults (STORM CHASER). NCT04625972. Update posted 2021 Jan 11. (https://www.clinicaltrials.gov/ct2/show/NCT04625972).
56. US Food and Drug Administration. Frequently asked questions on the emergency use authorization of casirivimab and imdevimab. 2021 Feb 22. From FDA website. (https://www.fda.gov/media/143894/download).
57. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 8. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 8. Updates may be available at NIH website.
58. Weinreich DM, Sivapalasingam S, Norton T et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med. 2021; 384:238-251. PMID: 33332778 DOI: 10.1056/NEJMoa2035002.
59. ACTIV-2/TICO LY-CoV555 Study Group. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. N Engl J Med. 2020 Dec 22;NEJMoa2033130 [online ahead of print]. PMID: 33356051 DOI: 10.1056/NEJMoa2033130.
60. Regeneron. Regeneron announces encouraging initial data from COVID-19 antibody cocktail trial in hospitalized patients on low-flow oxygen. Press release. 2020 Dec 29. Available at https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-initial-data-covid-19-antibody.
61. Gottlieb RL, Nirula A, Chen et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021; 325:632-644. PMID: 33475701 DOI: 10.1001/jama.2021.0202.
62. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. Press release. 2021 Jan 21. Available at https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented.
63. Regeneron. Regeneron reports positive interim data with REGEN-COV antibody cocktail used as passive vaccine to prevent COVID-19. Press release. 2021 Jan 26. Available at https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody.
64. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of bamlanivimab and etesevimab for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). Reissued 2021 Feb 25. From FDA website. (https://www.fda.gov/media/145801/download).
65. US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021 Mar 18. From FDA website. (https://www.fda.gov/media/145802/download).
66. US Food and Drug Administration. Fact sheet for patients, parents, and caregivers: Emergency use authorization (EUA) of bamlanivimab and etesevimab for coronavirus disease 2019 (COVID-19). 2021 Feb 9. From FDA website. (https://www.fda.gov/media/145803/download).
67. US Food and Drug Administration. Frequently asked questions on the emergency use authorization for bamlanivimab and etesevimab. 2021 Feb 22. From FDA website. (https://www.fda.gov/media/145808/download).
68. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 2021 Apr 14. Accessed 2021 Apr 23. (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/). Updates may be available at IDSA website.
69. US Food and Drug Administration. Frequently asked questions on the emergency use authorization for bamlanivimab. 2021 Feb 10. From FDA website. (https://www.fda.gov/media/143605/download).
70. US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (ASPR). Overview of direct order process for COVID-19 therapeutics. (https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Documents/Overview%20of%20direct%20order%20process%20Fact%20Sheet-508.pdf). Accessed 2021 Feb 24.
71. Phase III of AZD7442 for treatment of COVID-19 in outpatient adults (TACKLE). NCT04723394. Update posted 2021 Feb 15. (https://www.clinicaltrials.gov/ct2/show/NCT04723394).
72. A study of immune system proteins in patients with mild to moderate COVID-19 illness (BLAZE-4). NCT04634409. Update posted 2021 Feb 24. (https://www.clinicaltrials.gov/ct2/show NCT04634409).
73. US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (ASPR). Letter to stakeholders. Update 2: COVID-19 variants/impact on mAb distribution. Accessed 2021 Mar 24.
74. US Centers for Disease Control and Prevention. COVID-19 variant proportions in the US. From CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Accessed 2021 Mar 24.
75. Lilly. Lilly, Vir Biotechnology and GSK announce positive topline data from the phase 2 BLAZE-4 trial evaluating bamlanivimab with VIR-7831 in low-risk adults with COVID-19. Press release. 2021 Mar 29. Available at https://investor.lilly.com/news-releases/news-release-details/lilly-vir-biotechnology-and-gsk-announce-positive-topline-data.
76. Regeneron. Phase 3 trial shows REGEN-COV (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized COVID-19 patients. Press release. 2021 Mar 23. Available at https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody.
77. Regeneron. Phase 3 prevention trial showed 81% reduced risk of symptomatic SARS-CoV-2 infections with subcutaneous administration of REGEN-COV (casirivimab with imdevimab). Press release. 2021 Apr 12. Available at https://investor.regeneron.com/news-releases/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars.

78. GlaxoSmithKline. Vir Biotechnology and GSK announce VIR-7831 reduces hospitalisation and risk of death in early treatment of adults with COVID-19. Press release. 2021 Mar 10. Available at https://www.gsk.com/en-gb/media/press-releases/vir-biotechnology-and-gsk-announce-vir-7831-reduces-hospitalisation-and-risk-of-death-in-early-treatment-of-adults-with-covid-19/.
79. Study to evaluate the safety and efficacy of a single dose of STI-2020 (COVI-AMG) to treat COVID-19. NCT04738175. Update posted 2021 Feb 4.(https://clinicaltrials.gov/ct2/show/NCT04738175).
80. Study to evaluate a single dose of STI-2020 (COVI-AMG) in hospitalized adults with COVID-19. NCT04771351. Update posted 2021 Apr 12. (https://clinicaltrials.gov/ct2/show/NCT04771351).
81. US Food and Drug Administration. Letter revoking emergency use authorization for use of bamlanivimab alone for the treatment of mild to moderate COVID-19. 2021 Apr 16. From FDA website. (https://www.fda.gov/media/147629/download).
82. US Food and Drug Administration. Frequently asked questions on the revocation of the emergency use authorization for bamlanivimab administered alone. 2021 Apr 16. From FDA website. (https://www.fda.gov/media/147639/download).

Siltuximab:

1. Janssen Biotech, Inc. Sylvant® (siltuximab) injection, for intravenous use prescribing information. Horsham, PA; 2018 May.
2. Ceribelli A, Motta F, De Santis M. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. J Autoimmun. 2020; 109:102442. PMID: 32253068. DOI: 10.1016/j.jaut.2020.102442.
3. Zhang W, Zhao Y, Zhang F et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020; 214:108393. PMID: 32222466. DOI: 10.1016/j.clim.2020.108393.
4. Gritti G, Raimondi F, Ripamonti D et al. IL-6 signaling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. medRxiv. Posted Jun 20, 2020. Preprint (not peer reviewed). Available at https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v4.full.pdf. DOI: https://doi.org/10.1101/2020.04.01.20048561.
5. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033-4. PMID: 32192578. DOI: 10.1016/S0140-6736(20)30628-0.
6. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 May 7. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04322188.
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 May 8. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04330638.
8. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 May 8. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04329650.
9. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 25. Updates may be available at NIH website.
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 25. Available at https://clinicaltrials.gov.

Sirolimus:

1. Stohr S, Costa R, Sandmann L et al. Host cell mTORC1 is required for HCV RNA replication. Gut. 2016; 65(12):2017-28. PMID 26276683 DOI: 10.1136/gutjnl-2014-308971
2. Kindrachuk J, Ork B, Hart BJ et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for middle east respiratory syndrome coronavirus infection as identified by temporal kinome analysis. Antimicrob Agents Chemother. 2015; 59(2):1088-99. PMID 25487801 DOI: 10.1128/AAC.03659-14
3. Wang CH, Chung FT, Lin SM et al. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. Crit Care Med. 2014; 42:313-321. PMID: 24105455 DOI: 10.1097/CCM.0b013e3182a2727d.
4. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Mar 22. Available at https://clinicaltrials.gov.
5. Zhou Y, Hou Y, Shen J et al. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discovery. 2020; 6 (14): 1-18.
6. Arabi YM, Fowler R, and Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med. 2020; 46(2): 315-28. PMID: 32040667 DOI: 10.1007/s00134-020-05943-5.
7. Omarjee L, Janin A, Perrot F et al. Targeting T-cell senescence and cytokine storm with rapamycin to prevent severe progression in COVID-19. Clin Immunol. 2020; 216:108464. PMID: 32405269 DOI:10.1016/j.clim.2020.108464

Thrombolytic Agents (t-PA [alteplase], tenecteplase):

1. Moore HB, Barrett CD, Moore EE et al. Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)?. J Trauma Acute Care Surg. 2020. 88(6): 713-714. DOI: 10.1097/TA.0000000000002694
2. Massachusetts Institute of Technology. MIT news: a stopgap measure to treat respiratory distress. From the MIT website. Accessed 2020 Apr 8. Available from http://news.mit.edu/2020/covid-19-treat-respiratory-patients-plasminogen-0324
3. Hardaway RM, Harke H, Tyroch AH et al. Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. Am Surg. 2001; 67: 377-82. PMID: 1130800
5. Deng Y, Liu W, Liu K et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020. PMID: 32209890 DOI: 10.1097/CM9.0000000000000824
6. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020; 9: 687-690. PMID: 32208840 DOI: 10.1080/22221751.2020.1741327
7. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994
8. American Society of Hematology. COVID-19 and coagulopathy: frequently asked questions (version 7.0; last updated Jan 29, 2021). From the ASH website. Accessed 2021 Mar 22.
9. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. J Thromb Haemost. 2020;18(7):1752-1755. PMID: 32267998 DOI :10.1111/jth.14828
10. Tang N, Li D, Wang X et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18: 844-847. PMID: 32073213 DOI: 10.1111/jth.14768

11. MacLaren R, Stringer KA. Emerging role of anticoagulants and fibrinolytics in the treatment of acute respiratory distress syndrome. Pharmacotherapy. 2007; 27: 860-73. PMID: 17542769 DOI: 10.1592/phco.27.6.860
12. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Mar 23. Available at https://clinicaltrials.gov
13. Choudhury R, Barrett CD, Moore HB et al. Salvage use of tissue plasminogen activator (tPA) in the setting of acute respiratory distress syndrome (ARDS) due to COVID-19 in the USA: a Markov decision analysis. World J Emerg Surg. 2020; 15: 29. PMID: 32312290 DOI: 10.1186/s13017-020-00305-4
14. Barrett CD, Moore HB, Yaffe MB et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. J Thromb Haemost. 2020. PMID: 32302462 DOI: 10.1111/jth.14860
15. Dunn JS, Nayar R, Campos J et al. Feasibility of tissue plasminogen activator formulated for pulmonary delivery. Pharm Res. 2005; 22: 1700-7. PMID: 16180128 DOI: 10.1007/s11095-005-6335-8
16. Ranucci M, Ballotta A, Di Dedda U et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020. PMID: 32302448 DOI: 10.1111/jth.14854
17. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 26. Updates may be available at NIH website.
18. US Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Updated 2020 Nov 18. From CDC website. Accessed 2020 Nov 29. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).
19. Whyte CS, Morrow GB, Mitchell JL et al. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost. 2020; 18(7):1548-1555. PMID: 32329246 DOI:10.1111/jth.14872
20. Christie DB 3rd, Nemec HM, Scott AM et al. Early outcomes with utilization of tissue plasminogen activator in COVID-19 associated respiratory distress: a series of five cases. J Trauma Acute Care Surg. 2020. PMID: 32427774 DOI:10.1097/TA.0000000000002787
21. Goyal A, Saigal S, Niwariya Y et al. Successful use of tPA for thrombolysis in COVID related ARDS: a case series. J Thromb Thrombolysis. 2021;51(2):293-296. PMID: 32617806 DOI: 10.1007/s11239-020-02208-2
22. Arachchillage DJ, Stacey A, Akor F et al. Thrombolysis restores perfusion in COVID-19 hypoxia. Br J Haematol. 2020;190(5):e270-e274. PMID: 32735730 DOI: 10.1111/bjh.17050. Epub 2020 Aug 17.
23. Wright FL, Vogler TO, Moore EE et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg. 2020;231(2):193-203.e1. PMID: 32422349 DOI:10.1016/j.jamcollsurg.2020.05.007
24. Poor HD, Ventetuolo CE, Tolbert T et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis [published online ahead of print, 2020 May 13]. Clin Transl Med. 2020;10.1002/ctm2.44. PMID: 32508062 DOI:10.1002/ctm2.44
25. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. Chest. 2020 Sep;158(3):1143-1163. PMID: 32502594 DOI: 10.1016/j.chest.2020.05.559. Epub 2020 Jun 2.
26. Barnes GD, Burnett A, Allen A et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2020;50(1):72-81. PMID: 32440883 DOI: 10.1007/s11239-020-02138-z
27. Orfanos S, El Husseini I, Nahass T et al. Observational study of the use of recombinant tissue-type plasminogen activator in COVID-19 shows a decrease in physiological dead space. ERJ Open Res. 2020 Oct 5;6(4):00455-2020. PMID: 33043052 DOI: 10.1183/23120541.00455-2020
28. Ghia S, Bhatt H, Lazar M. Role of tissue plasminogen activator for diffuse pulmonary microemboli in coronavirus disease 2019 patient. J Cardiothorac Vasc Anesth. 2020 Aug 31 [Epub ahead of print]:S1053-0770(20)30858-2. PMID: 32962933 DOI: 10.1053/j.jvca.2020.08.063
29. Barrett CD, Oren-Grinberg A, Chao E et al. Rescue therapy for severe COVID-19-associated acute respiratory distress syndrome with tissue plasminogen activator: A case series. J Trauma Acute Care Surg. 2020 Sep;89(3):453-457. PMID: 32427773 DOI: 10.1097/TA.0000000000002786
30. Price LC, Garfield B, Bleakley C et al. Rescue therapy with thrombolysis in patients with severe COVID-19-associated acute respiratory distress syndrome. Pulm Circ. 2020 Dec 15;10(4):2045894020973906. PMID: 33403100 DOI: 10.1177/2045894020973906.
31. Kosanovic D, Yaroshetskiy AI, Tsareva NA et al. Recombinant tissue plasminogen activator treatment for COVID-19 associated ARDS and acute cor pulmonale. Int J Infect Dis. 2021 Jan 13 [Online ahead of print];104:108-110. PMID: 33352323 DOI: 10.1016/j.ijid.2020.12.04333352323.
32. Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol. 2021;77(15):1903-1921. PMID: 33741176 DOI: 10.1016/j.jacc.2021.02.035.

Tocilizumab:

1. Genentech, Inc, South San Francisco, CA. Actemra use in Coronavirus Disease 2019 (COVID-19) standard reply letter. 2020 Apr 20.
2. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). (Mandarin; English translation.) 2020 Mar 3.
3. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. Available on chinaXiv website. Accessed online 2020 Mar 19.
4. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 1. Available from https://clinicaltrials.gov/ct2/show/study/NCT04317092. NLM identifier: NCT04317092.
5. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 26. Available at https://clinicaltrials.gov.
6. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 16: pii: S0140- 6736(20)30628-0 [Epub ahead of print]. PMID 32192578 DOI: 10.1016/S0140-6736(20)30628-0.
7. F. Hoffmann-La Roche Ltd. Roche initiates Phase III clinical trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 pneumonia [press release]. Basel, Switzerland; Roche; March 19, 2020. https://www.roche.com/dam/jcr:f26cbbb1-999d-42d8-bbea-34f2cf25f4b9/en/19032020-mr-actemra-covid-19-trial-en.pdf. Accessed 2020 Apr 2.
8. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 2. Available from https://clinicaltrials.gov/ct2/show/study/NCT04320615. NLM identifier: NCT04320615.

9. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 25. Updates may be available at NIH website.
10. Luo P, Liu Y, Qiu L et al. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020 Apr 6. [Epub ahead of print.] PubMed: 32253759 DOI: 10.1002/jmv.25801. Available from https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25801.
11. World Health Organization. WHO R&D Blueprint. COVID-19. Informal consultation on the potential role of IL-6/IL-1 antagonists in the clinical management of COVID 19 infection. 2020 Mar 25. Available at https://www.who.int/blueprint/priority-diseases/key-action/Expert_group_IL6_IL1_call_25_mar2020.pdf. Accessed 2020 Apr 27.
12. Alberici F, Delbarba E, Manenti C et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020 Apr 21. [Epub ahead of print.] Available at https://doi.org/10.1016/j.kint.2020.04.002.
13. Zhang X, Song K, Tong F et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020; 4:1307-10. PubMed 32243501 DOI: 10.1182/bloodadvances.2020001907.
14. Liu B, Li M, Zhou et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;102452. [Epub ahead of print.] DOI: 10.1016/j.jaut.2020.102452. Available at https://doi.org/10.1016/j.kint.2020.04.002
15. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jun 22. Available from https://clinicaltrials.gov/ct2/show/study/NCT04331808. NLM identifier: NCT04331808.
16. Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia [press release]. Paris; Assistance Publique - Hôpitaux de Paris. April 27, 2020. Accessed 2020 Jun 22.
17. Sciascia S, Apra F, Baffa A et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020; 38:529-532. PubMed: 32359035.
18. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 associated pneumonia [press release]. 2020 Jul 29. Available at: https://www.roche.com/media/releases/med-cor-2020-07-29.htm. Accessed 2020 Sep 8.
19. Stone JH, Frigault MJ, Serling-Boyd NJ et al for the BACC Bay Tocilizumab Trial Investigators. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020 Oct 21 [online ahead of print]. PubMed: 33085857 DOI: 10.1056/NEJMoa2028836.
20. Hermine O, Mariette X, Tharaux PL et al for the CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs. usual care in adults hospitalized with COVID-19 and moderate to severe pneumonia: a randomized clinical trial. JAMA Intern Med. 2020 Oct 20 [online ahead of print]. PubMed: 33080017 DOI: 10.1001/jamainternmed.2020.6820.
21. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. New Engl J Med. 2021 Feb 25. [Epub ahead of print.] PMID: 33631065 DOI: 10.1056/NEJMoa2100433.
22. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397:1637-1645..PMID: 33933206 DOI: 10.1016/S0140-6736(21)00676-0. PMID: 33933206 DOI:10.1016/S0140-6736(21)00676-0.

Umifenovir:

1. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020; 81(1):e1-e5. PMID: 32171872 DOI: 10.1016/j.jinf.2020.03.002
2. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Mar 31. Available from https://clinicaltrials.gov/ct2/show/study/NCT04252885. NLM identifier: NCT04252885.
4. Blaising J, Polyak SJ, Pecheur EI. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res. 2014; 107:88-94. PMID: 24769245 DOI: 10.1016/j.antiviral.2014.04.006
5. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020; 14:58-60. PMID: 32147628 DOI: 10.5582/ddt.2020.01012
6. Chen C, Zhang Y, Huang J, et al. Favipiravir versus arbidol for COVID-19: A randomized clinical trial. MedRxiv. Posted April 15, 2020. Preprint (not peer reviewed). DOI: https://doi.org/10.1101/2020.03.17.20037432
7. National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19 patients (tentative 8th edition). Updated 2020 Sep 8. English translation available at http://regional.chinadaily.com.cn/pdf/DiagnosisandTreatmentProtocolforCOVID-19Patients(Tentative8thEdition).pdf. Accessed 2021 Jan 6.
8. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020; 81(1):e21-e23. PMID: 32283143 DOI: 10.1016/j.jinf.2020.03.060
9. Lian N, Xie H, Lin S, et al. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study. Clin Microbiol Infect. 2020; 26(7):917-921. PMID: 32344167 DOI: 10.1016/j.cmi.2020.04.026
10. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: An exploratory randomized controlled trial. Med (N Y). 2020; 1(1):105-113.e4. PMCID: PMC7235585 DOI:10.1016/j.medj.2020.04.001
11. Kivrak A, Ulaş B, Kivrak H. A comparative analysis for anti-viral drugs: Their efficiency against SARS-CoV-2 [published online ahead of print, 2020 Nov 30]. Int Immunopharmacol. 2020;90:107232. PMID: 33290969 DOI:10.1016/j.intimp.2020.107232
12. Qiu T, Liang S, Dabbous M, et al. Chinese guidelines related to novel coronavirus pneumonia. J Mark Access Health Policy. 2020 Oct 8;8(1):1818446. PMID: 33133431 DOI:10.1080/20016689.2020.1818446
13. Huang D, Yu H, Wang T, et al. Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis [published online ahead of print, 2020 Jul 3]. J Med Virol. 2020 Jul 3;10.1002/jmv.26256. PMID: 32617989 DOI:10.1002/jmv.26256

Vitamin D:

1. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 8. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 16. Updates may be available at NIH website.
2. Joint guidance on Vitamin D in the era of COVID-19 from the ASBMR, AACE, Endocrine Society, ECTS, NOF, and IOF. Available at https://www.asbmr.org/ASBMRStatementsDetail/joint-guidance-on-vitamin-d-in-era-of-covid-19-fro. Accessed 2020 Jul 23.

3. National Institute for Health and Care Excellence (NICE), Public Health England. COVID-19 rapid guideline: vitamin D. 2020 Dec 17. Available at https://www.nice.org.uk/guidance/ng187/.
4. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 16. Available at https://clinicaltrials.gov.
5. Martineau AR, Jolliffe DA, Hooper RL et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017; 356:i6583. PMID: 28202713. DOI: 10.1136/bmj.i6583.
6. Amrein K, Schnedl C, Holl A et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014; 312:1520-30. PMID: 25268295. DOI: 10.1001/jama.2014.13204.
7. The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early high-dose vitamin D3 for critically ill, vitamin D–deficient patients. N Engl J Med. 2019; 381:2529-40. PMID: 31826336. DOI: 10.1056/NEJMoa1911124.
8. Science M, Maguire JL, Russell ML et al. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. Clin Infect Dis. 2013; 57:392-7. PMID: 23677871. DOI: 10.1093/cid/cit289.
9. Lu D, Zhang J, Ma C et al. Link between community-acquired pneumonia and vitamin D levels in older patients. Z Gerontol Geriatr. 2018; 51:435-9. PMID: 28477055. DOI: 10.1007/s00391-017-1237-z.
10. Gruber-Bzura BM. Vitamin D and influenza—prevention or therapy? Int J Mol Sci. 2018; 19:2419. PMID: 30115864. DOI: 10.3390/ijms19082419.
11. Gysin DV, Dao D, Gysin CM et al. Effect of vitamin D3 supplementation on respiratory tract infections in healthy individuals: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2016; 11:e0162996. PMID: 27631625. DOI: 10.1371/journal.pone.0162996.
12. Grant WB, Lahore H, McDonnell SL et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020; 12:988. PMID: 32252338. DOI: 10.3390/nu12040988.
13. Aranow C. Vitamin D and the immune system. J Investig Med. 2011; 59:881-6. PMID: 21527855. DOI: 10.2310/JIM.0b013e31821b8755.
14. Lanham-New SA, Webb AR, Cashman KD et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutr Prev Health. 2020; 3:106-10. PMID: 33230499. DOI:10.1136/bmjnph-2020-000089.
15. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020; 32:1195-8. PMID: 32377965. DOI: 10.1007/s40520-020-01570-8.
16. De Smet D, De Smet K, Herroelen P et al. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. Am J Clin Pathol. 2021; 155:381-8. PMID: 33236114 . DOI: 10.1093/ajcp/aqaa252.
17. Meltzer DO, Best TJ, Zhang H et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open. 2020: Sep 1;3:e2019722. PMID: 32880651. DOI: 10.1001/jamanetworkopen.2020.19722.
18. D'Avolio A, Avataneo V, Manca A et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients. 2020 12:1359. PMID: 32397511. DOI: 10.3390/nu12051359.
19. Hastie CE, Mackay DF, Ho F et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr. 2020; 14:561-5. PMID: 32413819. DOI: 10.1016/j.dsx.2020.04.050.
20. Parva NR, Tadepalli S, Singh P et al. Prevalence of vitamin D deficiency and associated risk factors in the US population (2011-2012). Cureus. 2018; 10:e2741. PMID: 30087817. DOI: 10.7759/cureus.2741.
21. Pereira-Santos M, Costa PRF, Assis AMO et al. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015; 16:341-9. PMID: 25688659. DOI: 10.1111/obr.12239.
22. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, metaanalysis, and meta-regression. Diabetes Metab Syndr. 2020; 14:395-403. PMID: 32334395. DOI: 10.1016/j.dsx.2020.04.018.
23. Chen S, Sun Y, Agrawal DK. Vitamin D deficiency and essential hypertension. J Am Soc Hypertens. 2015; 9:885-901. PMID: 26419755. DOI: 10.1016/j.jash.2015.08.009.
24. Lippi G, Wong J, Henry BM. Hypertension in patients with coronavirus disease 2019 (COVID‐19): a pooled analysis. Pol Arch Intern Med. 2020; 130:304-9. PMID: 32231171. DOI: 10.20452/pamw.15272.
25. Kanwal A, Agarwala A, Martin LW et al. COVID-19 and hypertension: what we know and don't know. 2020 Jul 6. Available at https://www.acc.org/latest-in-cardiology/articles/2020/07/06/08/15/covid-19-and-hypertension.
26. Institute of Medicine. Dietary reference intakes for adequacy: calcium and vitamin D. In: Ross CA, Taylor CL, Yaktine AL et al, eds. Dietary reference intakes for calcium and vitamin D. Washington DC: The National Academies Press; 2011:345-402. PMID: 21796828. DOI: 10.17226/1350.
27. Barrera FJ, Shekhar S, Wurth R et al. Prevalence of diabetes and hypertension and their associated risks for poor outcomes in Covid-19 patients. J Endocr Soc. 2020 Jul 21;4(9):bvaa102 (eCollection 2020 Sep 1). PMID: 32885126. DOI: 10.1210/jendso/bvaa102.
28. Maghbooli Z, Sahraian MA, Ebrahimi M et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PLoS One. 2020; 15:e0239799. [eCollection 2020.] PMID: 32976513. DOI: 10.1371/journal.pone.0239799.
29. Kaufman HW, Niles JK, Kroll MH et al. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS One. 2020; 15:e0239252. [eCollection 2020.] PMID: 32941512. DOI: 10.1371/journal.pone.0239252.
30. Xu J, Yang J, Chen J et al. Vitamin D alleviates lipopolysaccharide‐induced acute lung injury via regulation of the renin‐angiotensin system. Mol Med Rep. 2017; 16:7432-8. PMID: 28944831. DOI: 10.3892/mmr.2017.7546.
31. Jovic TH, Ali SR, Ibrahim N et al. Could vitamins help in the fight against COVID-19? Nutrients. 2020; 12:2550. PMID: 32842513. DOI: 10.3390/nu12092550.
32. Carpagnano GE, Di Lecce V, Quaranta VN et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID‐19. J Endocrinol Invest. 2021; 44:765-71. PMID: 32772324. DOI: 10.1007/s40618-020-01370-x.
33. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol. 2020 Oct;203:105751. [Epub ahead of print.] PMID: 32871238. DOI: 10.1016/j.jsbmb.2020.105751.

34. Butler-Laporte G, Nakanishi T, Mooser V et al. Vitamin D and Covid-19 susceptibility and severity: a Mendelian randomization study. medRxiv. Posted 2020 Sep 10. Preprint (not peer reviewed). DOI: https://doi.org/10.1101/2020.09.08.20190975.
35. Annweiler G, Corvaisier M, Gautier J et al. Vitamin D supplementation associated to better survival in hospitalized frail patients: the GERIA-COVID quasi-experimental study. Nutrients. 2020; 12:3377. PMID: 33147894. DOI: 10.3390/nu12113377.
36. Pereira M, Damascena AD, Azevedo LMG et al. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2020 Nov 4;1-9. [Epub ahead of print.] PMID: 33146028. DOI: 10.1080/10408398.2020.1841090.
37. Jain A, Chaurasia R, Sengar NS et al. Analysis of vitamin D level among asymptomatic and critically ill COVID‐19 patients and its correlation with inflammatory markers. Sci Rep. 2020 Nov 19;10(1):20191. PMID: 33214648. DOI: 10.1038/s41598-020-77093-z.
38. Murai IH, Fernandes AL, Sales LP et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA. 2021; 325:1053-60. PMID: 33595634. DOI: 10.1001/jama.2020.26848.
39. Louca P, Murray B, Klaser K et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. BMJ Nutr Prev Health. 2021;0. DOI:10.1136/bmjnph-2021-000250.

Zinc:

1. Bauer SR, Kapoor A, Rath M et al. What is the role of supplementation with ascorbic acid, zinc, vitamin D, or N-acetylcysteine for prevention or treatment of COVID-19? Cleve Clin J Med. 2020 Jun 8 [Online ahead of print]. PubMed: 32513807 DOI: 10.3949/ccjm.87a.ccc046.
2. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jul 19. Available from https://clinicaltrials.gov/ct2/show/study/NCT04370782. NLM identifier: NCT04370782.
3. Zabetakis I, Lordan R, Norton C. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients. 2020; 12:1466. PubMed: 32438620 DOI: 10.3390/nu12051466.
4. McCarty MF, DiNicolantonio JJ. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. Prog Cardiovasc Dis. 2020 Feb 12 [online ahead of print]. PubMed: 32061635 DOI: 10.1016/j.pcad.2020.02.007.
5. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2021 Apr 26. Available at https://clinicaltrials.gov.
6. Adams, KK, Baker WL, Sobieraj DM. Myth busters: dietary supplements and COVID-19. Ann Pharmacother. 2020; 54:820-826. PubMed: 32396382 DOI: 10.1177/1060028020928052.
7. Singh M, Das RR. Zinc for the common cold. Cochrane Database of Systematic Reviews. 2013 Jun 18 (6); CD001364. PubMed: 23775705 DOI: 10.1002/14651858.
8. National Institutes of Health. Office of Dietary Supplements. Zinc: fact sheet for professionals. Accessed 2020 Jul 20. Available from https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/.
9. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated 2021 Apr 21. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2021 Apr 26. Updates may be available at NIH website.
10. Carlucci P, Ahuja T, Petrilli C et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. MedRxiv. Posted 2020 May 8. Preprint (not peer reviewed). Available at: https://www.medrxiv.org/content/10.1101/2020.05.02.20080036v1. DOI: https://doi.org/10.1101/2020.05.02.20080036.
11. Thomas S, Patel D, Bittel B et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open. 2021; Feb 1;4(2):e210369. DOI: 10.1001/jamanetworkopen.2021.0369. PMID: 33576820.
12. Abd-Elsalam S, Soliman S, Esmail ES et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine?: a Randomized, Multicenter Trial. Biol Trace Elem Res. 2020 Nov 27 [online ahead of print]. PubMed: 3324380 DOI: 10.1007/s12011-020-02512-1.
13. Yao JS, Paguio JA, Dee EC et al. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. Chest. 2021; 159:108-111. Letter. PubMed 32710890 DOI: 10.1016/j.chest.2020.06.082.
14. Frontera JA, Rahimian JO, Yaghi S et al. Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study. Res Sq. Posted 2020 Oct 26. Preprint (not peer reviewed). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7605567/pdf/nihpp-rs94509v1.pdf. PubMed: 33140042 DOI: 10.21203/rs.3.rs-94509/v1.