Assessment of Evidence for COVID-19-Related Treatments: Updated 5/4/2020

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Select entries were updated on 5/4/2020; these can be identified by the date that appears in the Drug(s) column.

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ANTIVIRAL AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Baloxavir *3/20/20*	8:18.92 Antiviral	Antiviral active against influenza viruses	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 China: Two randomized clinical trials registered, but not yet recruiting. Chinese Clinical Trial Registry links [1]: ChiCTR2000029544 CHiCTR2000029548	Protocol in one registered Chinese trial (2000029548) specifies a baloxavir marboxil dosage of 80 mg orally on day 1, 80 mg orally on day 4, and 80 mg orally on day 7 as needed, not to exceed 3 total doses. [1]	No data to date support use in the treatment of COVID-19
Chloroquine Phosphate ***Updated 4/29/20***	8:30.08 Antimalarial	In vitro activity against various viruses, including coronaviruses [1-3, 13, 14] In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; some evidence it may block infection in Vero E6 cells exposed to SARS-CoV-2 [1, 4, 12] Active in vitro against SARS-CoV-1 and MERS-CoV [2, 3, 5, 9] Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections [1-3, 13, 15-16] Known pharmacokinetics and toxicity profile	**Only limited clinical trial data available** to date to evaluate use of chloroquine for treatment or prevention of COVID-19 **Clinical experience** in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 [4-6] **Double-blind randomized phase 2b study in Brazil (Borba et al)** to evaluate two different chloroquine dosages as adjunctive therapy in hospitalized adults with severe COVID-19 (NCT04323527): The first 81 enrolled pts were randomized 1:1 to receive high-dose chloroquine (600 mg twice daily for 10 days) or lower-dose chloroquine (450 mg twice daily on day 1, then 450 mg once daily on days 2-5); all pts also received azithromycin and ceftriaxone and some also received oseltamivir. An unplanned interim analysis was performed and the high-dose arm of the study was halted because of toxicity concerns, particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm. By day 13, 16/41 pts (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QT_c >500 msec occurred more frequently in the	**Optimal dosage and duration of treatment not known** [20, 25] **Consider:** 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base [17] **Various dosages recommended or being investigated for treatment of COVID-19** **Oral chloroquine phosphate dosage suggested in the EUA:** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation [25] **Oral chloroquine phosphate:** 500 mg twice daily for 7 days (adults 18-65 years weighing >50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing <50 kg) [11] **Oral chloroquine phosphate**: Initial dose of 600 mg (of chloroquine) followed by 300 mg (of chloroquine) 12 hours later on day 1, then 300 mg (of chloroquine) twice daily on days 2 -5 [4]	Efficacy and safety of chloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. [11] NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of chloroquine for the *treatment* of COVID-19.[35] IDSA recommends that chloroquine be used for the *treatment* of COVID-19 in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel does not recommend the use of

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			high-dose group (18.9%) than in the lower-dose group (11.1%). The high-dose arm included more pts prone to cardiac complications than the lower-dose arm. Data were insufficient to evaluate efficacy. Study continuing using only the lower dosage. [37] Multiple clinical trials to evaluate chloroquine for the *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10] NCT04323527 NCT04328493 NCT04331600 NCT04333628 NCT04353336 NCT04360759 NCT04362332 Several clinical trials to evaluate chloroquine for *prevention* of COVID-19 in the healthcare setting are registered at clinicaltrials.gov: [10] NCT04303507 NCT04333732 NCT04349371		any agents, including chloroquine, for preexposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for *prevention* of SARS-CoV-2 infection outside of clinical trials. [35] Because chloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; [36, 39] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects. [35, 36, 39] FDA issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of chloroquine or hydroxychloroquine (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of chloroquine or hydroxychloroquine outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch. [39] **Emergency use authorization (EUA) for chloroquine:** FDA issued an EUA that permits distribution of the drug from the strategic national stockpile (SNS) for use **only** in adults and adolescents weighing 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available or participation not feasible. [24, 25] To request the drug, healthcare providers should contact local or state health departments; [25] distribution to states will be managed by the Office of the Assistant Secretary for Preparedness and Response (ASPR) and FEMA. [29] To mitigate risks of this

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					unapproved use, the EUA includes certain mandatory requirements (including adverse event reporting to FDA MedWatch). [24, 25] FDA states that, based on the totality of scientific evidence available, it is reasonable to believe that the drug may be effective in treating COVID-19 and that, when used under the EUA conditions, known and potential benefits outweigh known and potential risks. [24] Consult the EUA, [24] EUA fact sheet for healthcare providers, [25] and EUA fact sheet for patients and parent/caregivers [27] for additional information.
Favipiravir (Avigan®, Favilavir) ***Updated 4/29/20***	8:18.92 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [1–5] In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug [1, 5, 16] Licensed in Japan and China for treatment of influenza [2, 4, 6]	**Only very limited clinical trial data available** to date to evaluate use of favipiravir in the treatment of COVID-19 **Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir (Arbidol®; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe disease compared with the group receiving umifenovir. [6] **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	A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days was used in one open-label COVID-19 study [6] A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 14 days was used in one open-label COVID-19 study [15] Protocol in one ongoing trial (NCT04336904) for treatment of moderate COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 600 mg three times daily thereafter for up to 14 days [7] Protocol in one ongoing trial (NCT04346628) for treatment of mild COVID-19 specifies a favipiravir dosage of 1800 mg on day 1, then 800 mg twice daily on days 2–10 [7] Protocol in one ongoing trial (NCT04349241) for treatment of non-severe COVID-19 specifies a favipiravir dosage of 1600 mg every 12 hours on day 1, then 600 mg every 12 hours on days 2–10 [7] Protocol in one ongoing trial (NCT04358549) for treatment of	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 dose and duration Early embryonic deaths and teratogenicity observed in animal studies. Favipiravir is contraindicated in women with known or suspected pregnancy and precautions should be taken to avoid pregnancy during treatment with the drug. [14] If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g [17, 18]

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			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] **Italy:** Randomized, placebo-controlled multicenter trial (NCT04336904) to evaluate efficacy and safety of favipiravir in pts with moderate COVID-19 (started 3/25/20; estimated completion date 7/20) [7] **US**: Randomized, controlled open-label proof-of-concept trial (NCT04358549) of favipiravir for the treatment of COVID-19 [7, 10] **US**: Randomized, open-label trial (NCT04346628) to evaluate efficacy of favipiravir in pts with mild, uncomplicated COVID-19 [7] **Multiple clinical trials initiated** in pts with COVID-19 in China, Japan, and other countries to evaluate favipiravir alone or in conjunction with other antivirals or other agents: [7-9] NCT04310228 NCT04319900 NCT04303299 NCT04333589 NCT04336904 NCT04345419 NCT04351295 NCT04349241 NCT04356495 NCT04358549 NCT04359615 ChiCTR2000029544 ChiCTR2000030113 ChiCTR2000029548 ChiCTR2000030894 ChiCTR2000030987 ChiCTR2000029996 JapicCTI-205238 JPRN-jRCTs031190226 JPRN-jRCTs041190120	COVID-19 specifies a favipiravir dosage of 1800 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 [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] 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]	

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HIV Protease Inhibitors *Updated 4/24/20*	8:18.08.08 HIV Protease Inhibitors	**Lopinavir (LPV):** In vitro activity against SARS-CoV-2 in Vero E6 cells; [19] also has in vitro activity against SARS-CoV-1 and MERS-CoV; [1, 2, 9] some evidence of benefit in animal studies for treatment of MERS-CoV [2, 7, 9, 11] **Atazanavir (ATV):** ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells, [17, 19] human epithelial pulmonary cells (A549), [17] and human monocytes [17] **Darunavir (DRV):** In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations in Caco-2 cells; [18] in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells [19] **Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):** In vitro activity against SARS-CoV-2 in Vero E6 cells [19]	**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, **time to clinical improvement was not shorter with LPV/RTV compared with standard care** (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group. The 28-day mortality rate was numerically lower in LPV/RTV group (19.2% vs 25% in ITT population; 16.7% vs 25% in modified ITT population). Some evidence that LPV/RTV initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. **No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death.** LPV/RTV stopped early in 13 pts because of adverse effects. [3] **LPV/RTV retrospective cohort study in China** evaluated use of LPV/RTV with or without umifenovir (Arbidol®) in adults. Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 6/17 pts (35%) treated with LPV/RTV alone vs 12/16 (75%) treated with both drugs; chest CT scans were improving in 29% of pts treated with LPV/RTV alone vs 69% of pts treated with both drugs. [6] (See Umifenovir in this Evidence Table.) **LPV/RTV Clinical Experience (COVID-19):** Only limited data on LPV/RTV used with or	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days [3, 16] **LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours) [6] **LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days [13] with or without interferon (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ribavirin for up to 10 days [5, 13] **LPV/RTV (SARS):** LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours) [1] **LPV/RTV (MERS):** LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α ; LPV 400 mg/RTV 100 mg orally twice daily with interferon β1b (0.25 mg/mL sub-Q on alternate days) for 14 days [1, 4, 8]	**LPV/RTV:** Efficacy for the treatment of COVID-19, with or without other antivirals, not definitely established **Darunavir:** No data to date to support use in the treatment of COVID-19. Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/cobicistat for treatment of COVID-19 and initial unpublished results from a study in China indicated that a 5-day regimen of DRV/cobicistat was not effective for treatment of COVID-19 [21] **Atazanavir, Nelfinavir, Saquinavir, Tipranavir:** No data to date to support use in the treatment of COVID-19 NIH COVID-19 Treatment Guidelines Panel recommends against the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial [22] IDSA recommends that LPV/RTV be used for the treatment of COVID-19 only in the context of a clinical trial [23]

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			without interferon in pts with COVID-19 outside of clinical trials. [5, 12, 14. 16] **LPV/RTV Clinical Experience (SARS and MERS):** Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon. [1, 8, 9, 10, 11] **LPV/RTV COVID-19 Clinical Trials at clinicaltrials.gov:** NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease) [15] NCT04276688 (LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone) [15] NCT04328012 (LPV/RTV vs hydroxychloroquine vs losartan vs placebo) [15] **Darunavir COVID-19 Clinical Trials:** NCT04252274: Open-label randomized trial in China to evaluate DRV/cobicistat [15] NTC04303299: Open-label randomized trial in Thailand to evaluate DRV/RTV in conjunction with other antivirals [15] ChiCTR2000029541: Open-label randomized trial in China to evaluate DRV/cobicistat vs LPV/RTV [20]		
Hydroxychloroquine (Plaquenil®) ***Updated 4/29/20***	8:30.08 Antimalarial	In vitro activity against various viruses, including coronaviruses [5, 8. 12-14] In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed [8, 12] Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections [3, 8, 13, 15, 16]	**Only limited clinical trial data available** to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19 **Clinical experience** in treating pts with COVID-19 accumulating; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 [7, 18] **Hydroxychloroquine small pilot study conducted in China:** 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; [18] **both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV**. [30] Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts	**Optimal dosage and duration of treatment not known** [20, 26] **Various dosages recommended or being investigated** for treatment of COVID-19 **Oral hydroxychloroquine sulfate dosage suggested in the EUA:** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation [26] **Oral hydroxychloroquine sulfate:** 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 [8, 20]	Efficacy and safety of hydroxychloroquine for *treatment* or *prevention* of COVID-19 not established [10, 24, 39] Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19 Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. (See Azithromycin in this Evidence Table.)

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		Known pharmacokinetics and toxicity profile Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects; [13, 14] may have more favorable dose-related toxicity profile than chloroquine, [13-16] but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs [13, 20]	(86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up). [18] **Hydroxychloroquine randomized, parallel-group study in adults in China (ChiCTR2000029559):** 31 pts with COVID-19 and pneumonia received **hydroxychloroquine sulfate** (200 mg twice daily for 5 days) **and standard treatment (O_2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids)** and 31 other pts received **standard treatment alone** (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group). [31] **Note:** This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in	**Oral hydroxychloroquine sulfate:** 400 mg once or twice daily for 5-10 days [10, 18] **Oral hydroxychloroquine sulfate:** 600 mg twice daily on day 1, then 400 mg daily on days 2-5 [20] **Oral hydroxychloroquine sulfate:** 100-200 mg twice daily for 5-14 days [4] **Oral hydroxychloroquine sulfate:** 200 mg 3 times daily for 10 days [7, 34]	Additional data needed regarding toxicity profile when used in patients with COVID-19 Hydroxychloroquine suggested as possible option and included in Chinese guidelines for treatment of COVID-19. [11] NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against use of hydroxychloroquine for the *treatment* of COVID-19. [35] IDSA recommends that hydroxychloroquine be used for the *treatment* of COVID-19 in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the *treatment* of COVID-19, except in the context of a clinical trial. [35] IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the *treatment* of COVID-19 only in the context of a clinical trial. [38] NIH COVID-19 Treatment Guidelines Panel does not recommend the use of any agents, including hydroxychloroquine, for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) for *prevention* of SARS-CoV-2 infection outside of clinical trials. [35] Because hydroxychloroquine is associated with QT prolongation, caution is advised in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; [36, 39] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects [35, 36, 39]

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

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			COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O_2. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. [33] **Note:** In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit. **Hydroxychloroquine with azithromycin uncontrolled, retrospective, observational study in France (Gautret et al):** 80 adults with confirmed COVID-19 (including 6 pts included in a previous study by the same group) were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O_2 saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O_2; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. [34] **Note:** Almost all pts were considered low risk for clinical		

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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			nasopharyngeal samples at day 6 or 7. [7, 18] RT-PCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; [19, 21] however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined. [22, 23] Multiple clinical trials to evaluate hydroxychloroquine for *treatment* of COVID-19 are registered at clinicaltrials.gov (some listed below): [10] NCT04329923 NCT04332991 NCT04334967 NCT04335552 NCT04341727 NCT04345692 NCT04350450 NCT04351620 NCT04353037 NCT04362332 Multiple clinical trials to evaluate hydroxychloroquine for *prevention* of COVID-19 in the healthcare setting or in household contacts of pts with the disease are registered at clinicaltrials.gov (some listed below): [10] NCT04303507 NCT04318015 NCT04318444 NCT04328961 NCT04330144 NCT04331834 NCT04333225 NCT04341441 NCT04352946 NCT04359537 NCT04363450		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Neuraminidase inhibitors (e.g., oseltamivir) *3/20/20*	8:18.28	Antivirals active against influenza viruses	In a **retrospective case series** of 99 patients with COVID-19 at single center in Wuhan from 1/1/20 to 1/20/20, 76% of patients received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died. [1] While oseltamivir is noted to have been widely used for confirmed or suspected COVID-19 cases in hospitals in China, there has been no exact evidence to date that oseltamivir is effective in the treatment of COVID-19. [2] Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture. [4] Clinicaltrials.gov trials for COVID-19 that include oseltamivir[5]: NCT04303299 (not yet recruiting) NCT04261270 (recruiting) NCT04255017 (recruiting)	Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours. [1] Dosages of oseltamivir from registered trials (either recruiting, or not yet recruiting) vary, but include 300 mg orally daily, 75 mg orally once or twice daily, and 4–6 mg/kg orally (frequency not specified). [5]	No data to date support use in the treatment of COVID-19
Remdesivir ***Updated 5/4/20***	8:18.32 Antiviral	Broad-spectrum antiviral (nucleotide analog prodrug) with activity against various viruses, including coronaviruses [24] In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells [1, 18] In Rhesus macaques infected with SARS-CoV-2, treatment with a 6-day regimen of IV remdesivir initiated 12 hours after virus inoculation was associated with some benefits (lower disease severity scores, fewer pulmonary infiltrates,	**Various clinical trials** initiated in US, China, and other countries **Randomized, double-blind, placebo-controlled trial in hospitalized adults with severe COVID-19 in China (NCT04257656; Wang et al):** Pts were randomized 2:1 to receive remdesivir (200 mg IV on day 1, then 100 mg IV once daily on days 2-10) or placebo initiated within 12 days of symptom onset. Primary outcome was time to clinical improvement within 28 days after randomization or hospital discharge, whichever came first. ITT population included 158 pts treated with remdesivir and 78 pts treated with placebo; 32% of pts also received interferon α-2b, 28% also received LPV/RTV, and 66% also received corticosteroids during hospitalization.	**Optimal dosage and duration of treatment not known** [25, 26] Phase 3 trial protocol (severe COVID-19): 200 mg IV on day 1, then 100 mg IV daily on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2); [10] 200 mg IV on day 1, then 100 mg IV daily on days 2 -10 (extension arms that include pts who are or are not receiving mechanical ventilation) [10] Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) [11]	Not commercially available; most promising direct-acting antiviral (DAA) currently being investigated for COVID-19 Efficacy and safety of remdesivir for treatment of COVID-19 not established NIH COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against the use of remdesivir for the treatment of COVID-19 [20] **Emergency use authorization (EUA) for remdesivir:** FDA issued an EUA on May 1, 2020 that permits use of the drug for the treatment of COVID-19 *only* in hospitalized adults and children with

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		lower virus titers in bronchoalveolar lavage samples) compared with vehicle control; remdesivir treatment did not reduce viral loads or infectious virus titers in nose, throat, or rectal swabs compared with vehicle control [19] In vitro activity against SARS-CoV and MERS-CoV; active in animal models of SARS and MERS; prevented MERS in Rhesus macaques when given before infection and provided benefits when given after animal already infected [1-8] Pharmacokinetic data available from evaluations for Ebola	**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 adults with severe COVID-19 (NCT04292899)** sponsored by the manufacturer (Gilead): Initial study protocol designed to evaluate safety and antiviral activity of 5- and 10-day regimens of remdesivir (200 mg IV on day 1, followed by 100 mg once daily for total of 5 or 10 days) in conjunction with standard of care in pts not receiving mechanical ventilation; [10] protocol subsequently modified to add extension arms to evaluate safety and efficacy of 10-day regimen of remdesivir in conjunction with standard of care in pts who are or are not receiving mechanical ventilation. [10] **Manufacturer announced** that data available for the initial 397 pts **not** requiring mechanical ventilation at study entry (200 received a 5-day regimen and 197 received a 10-day regimen)	NIAID adaptive study protocol: 200 mg IV on day 1, then 100 mg IV for-duration of hospitalization up to 10 days total [13] Compassionate use access protocol: 200 mg IV on day 1, then 100 mg IV on days 2-10 [16] **Emergency use authorization (EUA) dosage recommended for adults and children weighing 40 kg or more:** Loading dose of 200 mg by IV infusion on day 1, followed by 100 mg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 100 mg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts **not** requiring mechanical ventilation and/or ECMO). [26] **Emergency use authorization (EUA) dosage recommended for children weighing 3.5 to less than 40 kg:** 5 mg/kg by IV infusion on day 1, followed by 2.5 mg/kg by IV infusion once daily on days 2-10 (for pts requiring invasive mechanical ventilation and/or ECMO) or followed by 2.5 mg/kg by IV infusion once daily on days 2-5 with option to extend treatment up to day 10 if needed (for pts **not** requiring mechanical ventilation and/or ECMO). [26]	suspected or laboratory-confirmed COVID-19 who have severe disease (defined as oxygen saturation [SpO_2] 94% or lower on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO) and requires that the drug be administered by a healthcare provider in an inpatient hospital setting via IV infusion at dosages recommended in the EUA. [25, 26] Distribution of remdesivir under this EUA is controlled by the US government for use consistent with the terms and conditions of the EUA. The manufacturer (Gilead) will supply remdesivir to authorized distributors, or directly to a US government agency, who will distribute the drug to hospitals and other healthcare facilities as directed by the US government, in collaboration with state and local government authorities, as needed. [25] The EUA requires that healthcare facilities and healthcare providers administering remdesivir comply with certain mandatory record keeping and reporting requirements (including adverse event reporting to FDA MedWatch). [25, 26] Consult the EUA, [25] EUA fact sheet for healthcare providers, [26] and EUA fact sheet for patients and parent/caregivers [27] for additional information.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			indicate similar clinical improvement with both treatment durations. **Time to clinical improvement for 50% of pts was 10 days in the 5-day treatment group vs 11 days in the 10-day treatment group. At day 14, 129/200 pts (64.5%) in the 5-day group and 106/197 pts (53.8%) in the 10-day group achieved clinical recovery.** Pts who received remdesivir within 10 days of symptom onset had improved outcomes compared with those treated after more than 10 days of symptoms. [23] **Note:** Data regarding this initial pt population (e.g., disease severity and comorbidities at study enrollment, additional supportive treatment received) not provided to date. **Phase 3 randomized, open-label trial in pts with moderate COVID-19 (NCT04292730)** sponsored by the manufacturer (Gilead) is evaluating safety and antiviral activity of 5- and 10-day regimens of remdesivir in conjunction with standard of care compared with standard of care alone [11] **Phase 3 adaptive, randomized, placebo-controlled trial (NCT04280705) in hospitalized adults sponsored by NIAID:** Pts received remdesivir (200 mg IV on day 1, then 100 mg once daily for duration of hospitalization up to 10 days total) or placebo. [13] **Sponsor announced** that preliminary data analysis (total of 1063 pts) indicated **shorter median time to recovery in remdesivir group (11 days) vs placebo group (15 days)** and suggested that remdesivir treatment may have provided a survival benefit (mortality rate 8% in remdesivir group vs 11.6% in placebo group). [22] **Note:** Data regarding the pt population (e.g., disease severity and comorbidities at study enrollment, time to initiation of treatment after symptom onset, additional supportive treatment received) not provided to date.		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Expanded access IND protocol (NCT04323761): The manufacturer (Gilead) has established a protocol for emergency access to remdesivir for the treatment of severe acute COVID-19 [17] **Compassionate use access:** The manufacturer (Gilead) is transitioning from individual compassionate use requests to an expanded access program for emergency access to the drug for severely ill pts with confirmed COVID-19. New individual compassionate use requests cannot be accepted, with the possible exception of requests for pregnant women and children <18 years of age with confirmed infections and severe manifestations of the disease. [15] https://rdvcu.gilead.com/ **Compassionate use access (NCT04302766):** May be available for DoD personnel through treatment IND protocol sponsored by US Army Medical Research and Development Command [12] **Data from the manufacturer's compassionate use program:** Preliminary data are available for a cohort of 53 adults from 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		

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			reported in 32 pts (60%); 12 pts (23%) had serious adverse effects (e.g., multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 pts (8%) discontinued the drug because of adverse effects. [16] **Note:** Data presented for this small cohort of pts offers only limited information regarding efficacy and safety of remdesivir for treatment of COVID-19. There was no control group and, although supportive therapy could be provided at the discretion of the clinician, it is unclear whether pts at any of the various study sites also received other therapeutic agents being used for treatment of COVID-19. In addition, data were not presented regarding the effects of remdesivir on viral load		
Umifenovir (Arbidol®) *Updated 4/24/20*	8:18.92 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [4] Although data limited, in vitro activity against SARS-CoV-1 [4] and SARS-CoV-2 [5] reported Licensed in China, Russia, Ukraine, and possibly other countries for prophylaxis and treatment of influenza [4]	**Retrospective cohort study** in 50 adults with COVID-19 in China suggests better viral suppression with umifenovir vs LPV/RTV. All pts received conventional therapy, including interferon α-2b. At 7 days after hospital admission, SARS-CoV-2 was undetectable in 50% of pts treated with umifenovir vs 23.5% treated with LPV-RTV; at 14 days, viral load undetectable in all pts treated with umifenovir vs 44.1% treated with LPV/RTV. Duration of positive SARS-CoV-2 RNA positive test was shorter with umifenovir vs LPV-RTV [8] **Retrospective cohort study** in 33 adults with COVID-19 in China suggests more favorable outcome with LPV/RTV plus umifenovir vs LPV/RTV alone: Primary end point was negative conversion in nasopharyngeal samples and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 12/16 pts (75%) treated with LPV/RTV plus umifenovir vs 6/17 pts (35%) treated with LPV/RTV alone; at 14 days, undetectable in 15/16 pts (94%) treated with both drugs vs 9/17 pts (53%) treated with LPV/RTV alone. At 7 days, chest CT scans were improving in 11/16 pts (69%) treated with both drugs vs 5/17 pts (29%) treated with LPV/RTV alone [1]	**Dosage recommended for treatment of COVID-19 in China:** Adults, 200 mg orally 3 times daily for no more than 10 days [5, 7] **Dosage used or being investigated in COVID-19 clinical trials:** 200 mg orally 3 times daily for duration of 7-10 days or longer [2, 3, 6, 8]	Not commercially available in the US Included in some guidelines for treatment of COVID-19 [7] Published data to support use in treatment of COVID-19 currently are limited

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			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.) **Clinical trials initiated in China:** NCT04252885: Randomized, single-center, open-label trial evaluating efficacy of umifenovir in conjunction with standard of care vs LPV/RTV in conjunction with standard of care in adults with COVID-19 [2] NCT04260594: Randomized, open-label trial evaluating efficacy and safety of umifenovir in conjunction with standard of		

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Anakinra *Updated 4/24/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant human interleukin-1 (IL-1) receptor antagonist; [1] may potentially combat cytokine release syndrome (CRS) symptoms in severely ill patients [2, 3, 4]	Currently no known published clinical trial evidence supporting efficacy or safety of anakinra in treating COVID-19 Encouraging preliminary results reported in China with another disease-modifying antirheumatic drug, tocilizumab [5, 6] **Italy:** Phase 3 randomized, open-label, multicenter trial (NCT04324021) initiated by the manufacturer (Swedish Orphan Biovitrum) to evaluate efficacy and safety of anakinra or emapalumab with standard of care in reducing hyperinflammation and respiratory distress in patients with COVID-19 is recruiting [3]	Various dosage regimens are being studied [3] Trial protocol in Italy (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days [3] Some studies under way in Greece and Belgium are evaluating 100 mg given subcutaneously once daily for 10 or 28 days, respectively, or until hospital discharge (Note: Anakinra is approved only for subcutaneous administration in the U.S.) [1, 7]	Insufficient clinical data to recommend either for or against use in the treatment of COVID-19 [7] Safety profile well established in patients with sepsis and has been studied extensively in pediatric patients with rheumatologic conditions [7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Other noncomparative, open-label trials are recruiting in Greece (NCT04356366, NCT04339712) and Belgium (NCT04330638) [3]		
Ascorbic acid *Updated 4/8/20*	88:12 (Vitamin C)	Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection-induced oxidative stress [3-5, 7] Presence of infection may decrease vitamin C concentrations [2-5]	**Phase 2 randomized, placebo-controlled trial** (NCT04264533) initiated in China to evaluate high-dose IV ascorbic acid in ICU patients with severe COVID-19-associated pneumonia [1] **Other infections:** Sepsis: Meta-analysis of several small studies suggested beneficial effects from IV ascorbic acid; however, primary end points not improved in CITRIS-ALI study (NCT02106975) in patients with sepsis and ARDS or in VITAMINS study (NCT03333278) in patients with septic shock; additional studies under way [4, 6, 8, 9, 10] Pneumonia: Limited study data available regarding ascorbic acid (oral) in hospitalized patients with pneumonia [2, 3] Common cold: Effect of oral supplementation studied extensively; decreases duration of symptoms, may decrease incidence of common cold in individuals under heavy physical stress but not in overall population [2, 3]	Phase 2 trial protocol (NCT04264533): Ascorbic acid 12 g IV every 12 hours for 7 days (12 g of drug diluted in sterile water for injection to total volume of 50 mL and infused IV at rate of 12 mL/hour) [1] Various dosages of IV ascorbic acid used in sepsis studies; 50 mg/kg every 6 hours for 4 days used in CITRIS-ALI study; 1.5 g every 6 hours until shock resolution or for up to 10 days used in VITAMINS study [4, 8, 9, 10] Note: May interfere with laboratory tests based on oxidation-reduction reactions (e.g., blood and urine glucose testing, nitrite and bilirubin concentrations, leukocyte counts). Manufacturer states to delay oxidation-reduction reaction-based tests until 24 hours after infusion, if possible [11]	Current data not specific to COVID-19; additional study needed [6]
Azithromycin *Updated 4/24/20*	8:12.12 Macrolides	Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) [1, 3-5] No data to date on in vitro activity against coronaviruses, including SARS-CoV-2 Has immunomodulatory and anti-inflammatory	**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 treatment in certain viral infections:** 500 mg once daily has been used [13] **COVID-19:** 500 mg on day 1, then 250 mg daily on days 2-5 in conjunction with 10-day regimen of hydroxychloroquine has been used [7, 18, 19]	Current data insufficient to establish pros and cons of adjunctive use of azithromycin in management of COVID-19 Additional data needed before any conclusions can be made regarding possible benefits of using a combined regimen of hydroxychloroquine and azithromycin in pts with COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated [2, 6, 8, 9, 11-14, 17] Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza) [10, 13] Has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the management of certain respiratory conditions (e.g., bronchiectasis, bronchiolitis, cystic fibrosis, COPD exacerbations, ARDS) [6, 8, 17]	**Adjunctive therapy in certain respiratory conditions:** Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS). [8] In a retrospective cohort study in pts with moderate or severe ARDS, a statistically significant improvement in 90-day survival was reported in those who received adjunctive azithromycin. [8] **Clinical experience in pts with COVID-19:** Has been used for antibacterial coverage in hospitalized pts with COVID-19 [15] **Use in conjunction with hydroxychloroquine in pts with COVID-19:** Azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) has been used in addition to a 10-day regimen of hydroxychloroquine (600 mg daily) in an open-label nonrandomized study in France (6 pts), [7] open-label uncontrolled study in France (11 pts), [18] and uncontrolled observational study in France (80 pts).[19] Data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in pts with COVID-19. (See Hydroxychloroquine in this Evidence Table.)		NIH COVID-19 Treatment Guidelines Panel recommends against the use of a combined regimen of hydroxychloroquine and azithromycin for the treatment of COVID-19, except in the context of a clinical trial. [21] (See Hydroxychloroquine in this Evidence Table.) IDSA recommends that a combined regimen of hydroxychloroquine and azithromycin be used for the treatment of COVID-19 only in the context of a clinical trial. [22] Because both azithromycin and hydroxychloroquine are associated with QT prolongation, caution is advised if considering use of both drugs in pts at risk for QT prolongation or receiving other drugs associated with arrhythmias; [20] diagnostic testing and monitoring recommended to minimize risk of adverse effects, including drug-induced cardiac effects [20]
Baricitinib (Olumiant®) *Updated 4/24/20*	92:36 Disease - modifying Anti-rheumatic Drug	Janus kinase (JAK) 1 and 2 inhibitor; disrupts regulators of endocytosis (AP2-associated protein kinase 1 [AAK1] and cyclin G-associated kinase [GAK]), 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	Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19 Baricitinib to be included as an arm in NIAID's Adaptive COVID-19 Treatment Trial [3] **Adaptive phase 2/3 clinical trial:** Open-label study planned to evaluate safety and efficacy of baricitinib in hospitalized patients with COVID-19 (NCT04340232) [6] Other planned clinical trials will evaluate baricitinib in combination with or without an antiviral agent for the treatment of COVID-19 (NCT04346147, NCT04320277, NCT04345289, NCT04321993) [7, 8, 9, 10]	Therapeutic dosages of baricitinib (2 or 4 mg orally once daily) are sufficient to inhibit AAK1 [1, 2, 5] Dosage information not yet available (see Trials or Clinical Experience)	Minimal interaction with CYP enzymes and drug transporters and low protein binding of baricitinib allow for combined use with antiviral agents and other drugs [4] NIH COVID-19 Treatment Guidelines Panel recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]			
Colchicine *Added 4/24/20*	92:16 Antigout Agents	Exerts broad anti-inflammatory and immunomodulatory effects through multiple mechanisms, including inhibition of NOD-like receptor protein 3 (NLRP3) inflammasome assembly and disruption of cytoskeletal functions through inhibition of microtubule polymerization [2,3,5,6] May combat the hyperinflammatory state of COVID-19 (e.g., cytokine storm) by suppressing proinflammatory cytokines and chemokines [2] NLRP3 inflammasone activation results in release of interleukins, including IL-1β [3,5,6,8,11] 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]	Minimal anecdotal experience and no clinical trial data reported to date in COVID-19 [4] **Phase 3, randomized, double-blind, placebo-controlled study** (NCT04322682; COLCORONA) initiated in adults with COVID-19 and at least one high-risk criterion to evaluate effect of colchicine on mortality, hospitalization rate, and need for mechanical ventilation; study excludes enrollment of currently hospitalized patients; enrollment target is approximately 6000 pts [1] Other registered randomized, open-label, parallel-group studies (not yet recruiting) will evaluate effects of colchicine plus standard treatment vs standard treatment alone on various outcome measures (e.g., mortality, markers of myocardial damage, clinical status, need for mechanical ventilation, duration of hospitalization) in adults with COVID-19: NCT04326790, NCT04322565, NCT04328480, NCT04350320, NCT04355143 [2,3]	Dosage in NCT04322682: Colchicine 0.5 mg orally twice daily for 3 days, then 0.5 mg once daily for 27 days [1] Consider possible need for colchicine dosage adjustment; [2] manufacturer-recommended dosages for labeled indications depend on patient's age, renal and hepatic function, and concomitant use of interacting drugs, including protease inhibitors (e.g., lopinavir/ritonavir), other moderate or potent CYP3A4 inhibitors, and P-glycoprotein (P-gp) inhibitors [5] Use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated [5]	Safety and efficacy for treatment of COVID-19 not established

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		Potential to limit COVID-19 -related myocardial damage also has been hypothesized [2,3] based on the drug's mechanisms of action and promising results of ongoing research on colchicine in various cardiac conditions [3,6-10] SARS-CoV-1 envelope (E) protein, a viroporin involved in replication and virulence, activates the NLRP3 inflammasome in vitro in Vero E6 cells by forming calcium-permeable ion channels, leading to increased IL-1β production [2,12,13]			
Corticosteroids (general) ***Updated 5/1/20***	68:04 Adrenals	Potent anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9] Evidence suggests that cytokine storm, a hyperinflammatory state resembling secondary hemophagocytic lymphohistiocytosis (HLH), is a contributing factor in COVID-19-associated mortality. [8, 18] Immunosuppression from corticosteroids has been proposed as a treatment option for such hyperinflammation. [18] May improve dysregulated immune response caused	**Observational studies:** Evidence suggests that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). [1, 25] Uncontrolled observational data from the recent COVID-19 outbreak in China suggest a possible treatment benefit of methylprednisolone in COVID-19 patients with acute respiratory distress syndrome (ARDS). [6, 13] (See Methylprednisolone in this Evidence Table.) Pending results of randomized controlled clinical studies specifically evaluating corticosteroids for COVID-19, indirect evidence from studies in patients with community-acquired pneumonia, ARDS, and other viral infections has been used to inform treatment decisions for COVID-19 patients. [3, 5, 8, 9, 12, 15-17, 25] Systemic corticosteroid therapy has been studied in several randomized controlled studies for the treatment of ARDS; overall	In general, low to moderate dosages of corticosteroids are recommended in intubated patients with ARDS. [8] Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days. [8] Some experts suggest that equivalent dosages of dexamethasone (i.e., 7-15 mg daily, typically 10 mg daily) may have an advantage of producing less fluid retention, since dexamethasone has less mineralocorticoid activity. [8] This dosage of dexamethasone is consistent with those used in the DEXA-ARDS trial. [8, 17] Higher dosages have been suggested for cytokine storm. [8] (See Comments column.)	Data on the use of corticosteroids in COVID-19 are limited. [3, 5, 7, 24, 25] The benefits and risks of corticosteroid therapy should be carefully weighed before use in patients with COVID-19. [1, 7] NIH, CDC, WHO, IDSA, and other experts have issued guidelines for the use of corticosteroids in patients with COVID-19 based on the currently available information. Recommendations are made according to the severity of illness, indications, and underlying medical conditions and should be considered on a case-by-case basis. [1, 2, 8, 12, 24, 25] **General recommendations:** WHO, CDC, NIH, and IDSA generally recommend against the routine use of corticosteroids for the treatment of COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock). [1, 2, 3, 8, 9, 24, 25] **Non-critical patients:** Corticosteroids generally should not be used in the treatment of early or mild disease since

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		by sepsis (possible complication of infection with COVID-19) and increase BP when low [4, 11]	evidence is low to moderate in quality and most studies were performed prior to the prelung protection strategy era. [5, 8, 9, 14, 17] In a recent multicenter, unblinded, randomized controlled study (DEXA-ARDS trial), the effects of dexamethasone in conjunction with conventional care were evaluated in hospitalized patients with moderate-to-severe ARDS receiving lung-protective mechanical ventilation. [17] Treatment with IV dexamethasone at a dosage of 20 mg once daily on days 1-5, followed by 10 mg once daily on days 6-10 resulted in reduced duration of mechanical ventilation and reduced overall mortality (i.e., 15% increase in 60-day survival) compared with conventional treatment alone. [17] Based on results of this study, a clinical trial (NCT04325061) has been initiated to specifically evaluate the use of dexamethasone in patients with ARDS due to COVID-19. [21] Other clinical trials have been initiated in various countries to evaluate use of IV corticosteroids (e.g., dexamethasone, hydrocortisone), oral corticosteroids (e.g., prednisone), or inhaled corticosteroids (e.g., budesonide) for treatment of COVID-19 pneumonia or ARDS, including the following trials registered at clinicaltrials.gov: [22] NCT04327401 NCT04344288 NCT04344730 NCT04348305 NCT04355637 NCT04359511 NCT04360876 (For registered clinical trials evaluating use of methylprednisolone, see Methylprednisolone in this Evidence Table.) Randomized controlled studies evaluating use of corticosteroids (e.g., hydrocortisone, dexamethasone, methylprednisolone, prednisolone) in septic shock suggest a small, but uncertain mortality reduction. [3,4]		the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding. [3, 8, 24] NIH recommends against the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients unless they are in the intensive care unit. [24] **Critically ill patients:** The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). [12] However, these experts generally support a **weak** recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. [12] NIH also recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated COVID-19 patients without ARDS. However, the NIH panel states that there is insufficient evidence for or against the use of systemic corticosteroids in mechanically ventilated patients with COVID-19 and ARDS. [24] IDSA suggests against using corticosteroids in hospitalized patients with COVID-19 pneumonia; however, in those with ARDS due to COVID-19, systemic corticosteroids may be used in the context of a clinical trial. [25] **Cytokine storm:** There is no well-established or evidence-based treatment for cytokine storm in patients with COVID-19. [8] However, some experts

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					suggest that use of more potent immunosuppression with corticosteroids may be beneficial in such patients. [8] These experts suggest higher dosages of corticosteroids (e.g., IV methylprednisolone 60-125 mg every 6 hours for up to 3 days) followed by tapering of the dose when inflammatory markers (e.g., C-reactive protein levels) begin to decrease. [8] The decision to use corticosteroids in patients with early signs of cytokine storm should be balanced with the known adverse effects. [24] **Septic shock:** The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different than the effects seen in those with ARDS. [12] The Surviving Sepsis Campaign and NIH suggest the use of low-dose corticosteroid therapy (e.g., hydrocortisone 200 mg daily as an IV infusion or intermittent doses) over no corticosteroid therapy in adults with COVID-19 and refractory shock. [12, 24] Clinicians considering corticosteroids for such patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding. [1] If corticosteroids are prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia. [1, 4] **Patients receiving corticosteroid therapy for chronic conditions**: NIH states that oral corticosteroids used for the treatment of an underlying condition prior to COVID-19 infection (e.g., primary or secondary adrenal insufficiency, rheumatologic diseases) should not be discontinued. Supplemental or stress dosages of corticosteroids may be indicated on an individual basis in patients with such conditions. The guidelines

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					also recommend that inhaled corticosteroids used daily for the management of asthma and COPD to control airway inflammation should not be discontinued in patients with COVID-19. [24] Endocrinology experts state that patients with primary or secondary adrenal insufficiency who are receiving prolonged corticosteroid therapy should follow usual steroid "sick day rules" since these individuals may not be able to mount a normal stress response in the event of COVID-19 infection. [19, 26] If such individuals develop symptoms such as fever and a dry continuous cough, they should immediately double their daily oral corticosteroid dosage and continue with this regimen until the fever subsides. [19] These guidelines also apply to patients who are receiving prolonged therapy (> 3 months) with corticosteroids for underlying inflammatory conditions, including asthma, allergy, and rheumatoid arthritis. [19] In such patients whose condition worsens or in those experiencing vomiting or diarrhea, treatment with parenteral corticosteroids may be necessary. [19, 26] Administration of physiologic stress doses of corticosteroids (e.g., IV hydrocortisone 50-100 mg 3 times daily) and not pharmacologic doses should be considered in all cases to avoid potentially fatal adrenal failure.[19, 20] Additional study is needed to determine the optimum corticosteroid stress dosage regimens in patients with COVID-19. [26, 27] There is some evidence suggesting that continuous IV infusion of hydrocortisone (following an initial IV bolus dose) may provide more stable circulating cortisol concentrations in patients with adrenal insufficiency and reduce the potentially harmful effects of peak and trough concentrations of cortisol on the immune system. [26, 27]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					Pregnancy considerations: For pregnant women with COVID-19, NIH guidelines state that the antenatal use of corticosteroids that cross the placenta (i.e., betamethasone, dexamethasone) is generally reserved for when administration is required for fetal benefit. Other systemic corticosteroids do not cross the placenta, and pregnancy is not a reason to restrict their use if otherwise indicated. ACOG recommends against administration of antenatal corticosteroids for fetal benefit in the late preterm period (i.e., 34 weeks and 0 days through 36 weeks and 6 days) in patients with suspected or confirmed COVID-19 because the benefits of such therapy in late preterm are less well established. Treatment should be individualized, weighing the neonatal benefits of antenatal corticosteroid therapy with the risks of potential harm to the pregnant patient. [24]
COVID-19 Convalescent Plasma *Added 4/17/20*		Theoretically, plasma obtained from pts who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2, including neutralizing antibody, may provide short-term *passive* immunity that could prevent infection or could be beneficial in the treatment of pts with COVID-19 in terms of decreasing viral load and improving outcomes. [1-5] In SARS pts in 2003-2005, use of convalescent plasma obtained from pts who had recovered from the disease was reported to provide some benefits (e.g., shorter duration of hospitalization, decreased mortality); [6-8, 14] SARS pts who	**Uncontrolled pilot study of COVID-19 convalescent plasma in China:** Ten adults with severe COVID-19 received a single transfusion of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody titers of 1:640 or greater) **with standard care**; 9 pts also received umifenovir [Arbidol®], some pts also received ribavirin, oseltamivir, peramivir, and/or interferon α, and 6 pts also received methylprednisolone. Time from onset of symptoms to transfusion of convalescent plasma was 10-20 days (mean 16.5 days). COVID-19 symptoms (fever, cough, shortness of breath, chest pain) improved in all pts within 1-3 days after the transfusion and all pts showed improvement on chest CTs. Titers of neutralizing antibody increased in 5 pts after the transfusion, but did not increase in 4 pts. Prior to the transfusion, RT-PCR tests for SARS-CoV-2 RNA were positive in 7 pts and negative in 3 pts; after transfusion, SARS-CoV-2 RNA was undetectable in 3 pts		Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established. [11] Most appropriate criteria for selection of pts 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] Optimal timing of donor plasma collection in relation to recovery from COVID-19, most appropriate methods of antibody testing, and minimum titers of SARS-CoV-2 antibody in convalescent plasma that may be associated with clinical benefits in pts with COVID-19 not determined. [1-5] Logistics of obtaining, processing, storing, and distributing COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]	on day 2, 3 pts on day 3, and 1 pt on day 6.[9] **Uncontrolled case series in China:** Five critically ill adults with rapidly progressing severe COVID-19 and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation who had high viral loads despite antiviral treatment received 2 transfusions of COVID-19 convalescent plasma (containing SARS-CoV-2 neutralizing antibody end point dilution titers of 80-480 depending on the donor) **in conjunction with** continued methylprednisolone therapy and various antiviral treatments that included LPV/RTV, favipiravir, umifenovir (Arbidol®), darunavir, and/or interferon α-1b. Pts received the convalescent plasma transfusions 10-22 days after hospital admission. Following the transfusions, body temperature normalized within 3 days in 4/5 pts, sequential organ failure assessment (SOFA) scores improved in all pts (decreased from initial scores of 2-10 to 1-4 on day 12), titers of SARS-CoV-2 IgG, IgM, and neutralizing antibody increased in all pts, and viral loads decreased and became negative within 12 days. [10] **Efficacy data not available from controlled clinical studies to date.** [1] **Multiple clinical trials initiated in the US and other countries** to evaluate use of COVID-19 convalescent plasma, including the following trials registered at clinicaltrials.gov: NCT04323800 (US) NCT04338360 (US) NCT04340050 (US) NCT04343261 (US) NCT04343755 (US) NCT04344015 (US) NCT04344535 (US) NCT04344977 (US) NCT04264858 NCT04292340 NCT04327349		convalescent plasma evolving. [1-5, 11, 14, 15] FDA does not collect COVID-19 convalescent plasma and does not provide such plasma; healthcare providers and acute care facilities obtain COVID-19 convalescent plasma from FDA-registered establishments. [11] Potential risks associated with COVID-19 convalescent plasma therapy (e.g., inadvertent transmission of other infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury [TRALI], antibody-dependent enhancement that may exacerbate clinical severity) and steps to mitigate such risks not determined. [1-5] **FDA issued a guidance for industry to provide recommendations to healthcare providers and investigators regarding administration and study of investigational COVID-19 convalescent plasma**. This guidance document includes recommendations regarding pathways for access to COVID-19 convalescent plasma, pt eligibility criteria to receive such plasma, collection of such plasma (including donor eligibility and qualifications), product labeling, and recordkeeping. [11] **FDA states that COVID-19 convalescent plasma is regulated as an investigational product and there currently are 3 available pathways for administering or studying use of such plasma**: 1). **Clinical Trials:** Requests to study use of COVID-19 convalescent plasma should be submitted to FDA under the traditional investigational new drug (IND) regulatory pathway. [11] 2). **Expanded Access IND:** For pts with serious or immediately life-threatening COVID-19 who are not eligible or are

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			NCT04332380 NCT04332835 NCT04333251 NCT04333355 NCT04342182 NCT04345523 NCT04345679		unable to participate in randomized critical trials, an expanded access IND can be used. A National Expanded Access Treatment Protocol has been established to facilitate access through participation of acute care facilities under an IND that is already in place. [11] Information on a protocol that is in place is available at https://www.uscovidplasma.org. [12] 3). **Single Patient Emergency IND (eIND)**: Licensed physicians seeking to administer COVID-19 convalescent plasma to an individual pt may request an eIND from the FDA. Consult the FDA guidance document for specific information on applying for an eIND. [11] FDA guidance suggests that collection of donor plasma at least 28 days after complete resolution of symptoms or collection at least 14 days after resolution of symptoms *and* negative results for COVID-19 (based on one or more nasopharyngeal swabs or by a molecular diagnostic blood test) be considered. [11] FDA guidance suggests that a minimum neutralizing antibody titer of at least 1:160 in donor plasma should be considered. [11] FDA guidance suggests that the following pt eligibility criteria to receive COVID-19 convalescent plasma be considered: Laboratory-confirmed COVID-19 with **severe** disease (defined as one or more of the following: shortness of breath, respiratory frequency 30/minute or greater, blood oxygen saturation 93% or lower, PaO_2/FiO_2 ratio less than 300, lung infiltrates greater than 50% within 24-48 hours) or with **life-threatening disease** (defined as one or more of the following: respiratory failure, septic shock, multiple organ dysfunction or failure) and informed consent provided by the pt or healthcare proxy. [11]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Epoprostenol (inhaled) *Added 4/3/20*	48:48 Vasodilating Agent	Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19 [1-9] **Inhaled** epoprostenol has been suggested as an alternative to inhaled nitric oxide due to its similar efficacy, lower potential for systemic adverse effects, lower cost, and ease of delivery [1, 2, 9]	No studies evaluating use specifically in COVID-19 patients [10] Experience in patients with ARDS indicates that inhaled epoprostenol can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients; however, data demonstrating clinical benefit are lacking [3, 6-9]	Various dosages of inhaled epoprostenol have been used in ARDS studies [2, 9] Dosages up to 50 ng/kg per minute have been used (titrated to response). [1-4, 6, 9] To provide a clinically important increase in PaO_2 and reduction in pulmonary artery pressure, data from these studies suggest that the most effective and safe dosage appears to be 20-30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients [9]	Additional studies are needed to evaluate the potential role of inhaled epoprostenol in the treatment of ARDS [6-9] The Surviving Sepsis Campaign states that due to the lack of adequately powered randomized controlled studies, a recommendation cannot be made for or against use of inhaled prostacyclins in COVID-19 patients with severe ARDS [10]
Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®) ***Updated 5/1/20***	68:04 Adrenal	Potent anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9] (See Corticosteroids in this Evidence Table.)	**Retrospective, observational, single-center study:** In 201 patients with confirmed COVID-19 pneumonia who developed ARDS, methylprednisolone appeared to reduce the risk of death. [6] Among patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46%) patients died, while of those who did not receive methylprednisolone, 21 of 34 (61.8%) died. [6] **Retrospective, observational, single-center study:** In 46 patients with confirmed severe COVID-19 pneumonia that progressed to acute respiratory failure, use of methylprednisolone was associated with improvement in clinical symptoms (i.e., fever, hypoxia) and a shortened disease course in patients who received the drug compared with those who did not. [13] Death occurred in 3 patients during hospitalization; 2 of these patients received methylprednisolone. [13] **Open-label, multicenter, randomized controlled study** (NCT04244591) was recently completed in China that compared use of methylprednisolone in conjunction with standard care in patients with confirmed COVID-19 infection that progressed to	Dosage used in the retrospective study (Wu et al) not provided. [6] Dosage used in the retrospective study (Wang et al) was 1-2 mg/kg daily IV for 5-7 days. [13] Dosage used in the randomized, controlled study (NCT04244591) was 40 mg IV every 12 hours for 5 days. [23]	Findings from observational studies suggest that for patients with COVID-19 pneumonia who progress to ARDS, methylprednisolone treatment may be beneficial. However, results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Confirmation from randomized controlled studies is needed. [6, 13] (See Corticosteroids in this Evidence Table.)

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			acute respiratory failure; results have not yet been posted. [23] Multiple clinical trials have been initiated in various countries to evaluate use of methylprednisolone for *treatment* of COVID-19 pneumonia or severe acute respiratory syndrome, including the following trials registered at clinicaltrials.gov: [22] NCT03852537 NCT04263402 NCT04323592 NCT04329650 NCT04343729 A non-randomized pilot study registered at clinicaltrials.gov (NCT04355247) has been initiated to evaluate use of methylprednisolone for the *prevention* of COVID-19 cytokine storm and progression to respiratory failure. [22]		
Nitric oxide (inhaled) *Updated 4/22/20*	48:48 Vasodilating Agent	Selective pulmonary vasodilator; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a potential complication of COVID-19 [2, 3, 9] In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and SARS-CoV-2 suggests potential effectiveness for COVID-19 [1]	No studies evaluating use specifically in COVID-19 patients [10] In a small pilot study (Chen et al.) conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide in ICU patients with SARS reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support [2, 3] Randomized controlled studies of inhaled nitric oxide in ARDS patients generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment) [4, 5, 6, 9]	In the Chen et al. study in severe SARS patients, inhaled nitric oxide therapy was given for ≥3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, then weaned on day 4; therapy was resumed at 10 ppm if deteriorating oxygenation occurred) [2] Phase 2 clinical trial protocol (NCT04306393) for treatment of mechanically ventilated COVID-19 patients: 80 ppm for the first 48 hours, followed by 40 ppm and then subsequently wean [3]	Therapeutic guidelines for the treatment of ARDS state that inhaled nitric oxide may be considered in patients with severe hypoxemia not responsive to conventional ventilation strategies; however, routine use not recommended [4, 5, 6, 9, 10] The Surviving Sepsis Campaign suggests a trial of inhaled pulmonary vasodilator therapy as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies; if rapid improvement in oxygenation is not observed, treatment should be tapered off [10] Clinical trials evaluating inhaled nitric oxide for the treatment or prevention of COVID-19 are planned or underway (NCT04338828, NCT04305457, NCT04306393, NCT04312243) [3, 7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					On March 20th, 2020, Bellerophon Therapeutics announced that the FDA granted emergency expanded access allowing its inhaled nitric oxide delivery system (INOpulse®) to be immediately used for the treatment of COVID-19 [8]
Ruxolitinib (Jakafi®) *Updated 4/24/20*	10:00 Antineoplastic Agents	Janus kinase (JAK) 1 and 2 inhibitor; [7] may potentially combat cytokine release syndrome (CRS) in severely ill patients [4, 5] Ability to inhibit a variety of proinflammatory cytokines, including interferon, has been raised as a possible concern with the use of JAK inhibitors in the management of hyperinflammation resulting from viral infections such as COVID-19 [5, 7]	Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19 **Phase 3 clinical trial** evaluating ruxolitinib plus standard of care vs standard of care alone is being initiated pending FDA approval of the protocol in patients with COVID-19-associated cytokine storm (sponsored by Incyte in U.S. and Novartis outside of U.S.) [1] **Expanded-access (managed-access, compassionate use) program** (NCT04337359) being initiated for eligible adults and children ≥6 years of age with severe or very severe COVID-19 illness; address inquiries to Incyte (855-463-3463 or medinfo@incyte.com) [1, 2] Other noncomparative, open-label clinical trials registered but not yet recruiting (NCT04331665, NCT04334044, NCT04338958); small parallel-group or uncontrolled studies also registered in Chinese Clinical Trial Registry (ChiCTR2000029580, ChiCTR2000030170) [3, 6]	Various dosages are being evaluated [2, 3, 6]	NIH COVID-19 Treatment Guidelines Panel recommends against use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial; the panel states that at present the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit [8]
Sarilumab (Kefzara®) ***Updated 5/1/20***	92:36 Disease-modifying Antirheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients [1, 2, 5]	Currently no known published clinical trial evidence supporting efficacy or safety in treatment of patients with COVID-19 However, based on encouraging results in China with a similar drug, tocilizumab, a U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently under way [3, 4]	Not available (see Trials or Clinical Experience)	NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of sarilumab in the treatment of COVID-19 [7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Clinicaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4 **For compassionate use access or investigator-sponsored clinical studies, contact the manufacturer (Sanofi Genzyme) for further information (1-800-633-1610)** [6]		
Sirolimus (Rapamune®) *Updated 4/22/20*	92:44 Immunosuppressive agent (mTOR inhibitor)	mTOR complex 1 (mTORC1) is involved in the replication of various viruses, including coronavirus [1, 2, 5] In vitro studies demonstrated inhibitory activity against MERS-CoV infection [2]	In an open-label, prospective randomized study in 38 patients with confirmed H1N1 pneumonia, treatment with sirolimus 2 mg daily in conjunction with corticosteroids for 14 days was associated with improved patient outcomes (e.g., shortened duration of mechanical ventilation, improved hypoxia and multiorgan function) [3] A randomized, double-blind, placebo-controlled trial (NCT04341675) has been initiated to evaluate the use of sirolimus in hospitalized patients with COVID-19 [4]	Dosage being investigated in NCT04341675 trial: 6 mg orally on day 1 followed by 2 mg daily for a maximum treatment duration of 14 days or until hospital discharge [4]	Although possible clinical application, current data not specific to COVID-19; additional study needed [5]
Tocilizumab (Actemra®) ***Updated 5/1/20***	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms in severely ill COVID-19 patients [1-3, 6, 10, 14]	Case reports and observational studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world [1, 3, 10, 12] In preliminary data from a non-peer-reviewed, single-arm, observational Chinese trial (Xu et al.) involving 21 patients with severe or critical COVID-19 infection, patients demonstrated rapid fever reduction and a reduced need for supplemental oxygen within several days after receiving tocilizumab (initially given as a single 400-mg dose by IV infusion; this dose was repeated within 12 hours in 3 patients because of continued fever) [3] In a retrospective, observational study in China (Luo et al.) involving 15 patients moderately to critically ill with COVID-19, tocilizumab (80-600 mg per dose) was given, and was used in conjunction with methylprednisolone in 8 of the patients.	IV infusion: **China** recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. No more than 2 doses should be given; maximum single dose is 800 mg [2] **US/Global randomized, placebo-controlled trial (manufacturer sponsored; COVACTA):** Will evaluate an initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); one additional dose may be given if symptoms worsen or show no improvement [8]	**In China**, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels [2] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of tocilizumab in the treatment of COVID-19 [9] The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study [14]

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

OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) *Updated 4/29/20*	24:32 Renin-Angiotensin-Aldosterone System Inhibitor	**Hypothetical harm:** Human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2).[1, 4, 5] Expression of ACE2 may be increased in patients treated with ACE inhibitors or ARBs.[1, 4, 8] Increased expression of ACE2 may potentially facilitate COVID-19 infections.[1] **Hypothetical benefit:** ACE inhibitors or ARBs may have a protective effect against lung damage or may have paradoxical effect in terms of virus binding.[1, 2, 6]	Data are lacking; no evidence of harm or benefit with regards to COVID-19 infection.[1,2,3] Clinical trial underway: Initiation of losartan in adult patients with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score. (NCT04312009)[7]		American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) recommend to continue treatment with renin-angiotensin-aldosterone system (RAAS) antagonists in those patients who are currently prescribed such agents.[2, 3] NIH COVID-19 Treatment Guidelines Panel states patients who are receiving an ACE inhibitor or ARB for cardiovascular disease (or other indications) should continue receiving these drugs; recommends against use of ACE inhibitors or ARBs for the treatment of COVID-19 except in the context of a clinical trial. [9] Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections.[1, 4] Abrupt withdrawal of RAAS inhibitors in high-risk patients (e.g., heart failure patients, patients with prior myocardial infarction) may lead to clinical instability and adverse health outcomes. [8]
Anticoagulants (low molecular weight heparin [LMWH], unfractionated heparin [UFH]) *Updated 4/29/20*	20:12.04.16 (Heparins)	A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which may contribute to their risk of poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-6, 14, 16] Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), a high	Limited data from China suggest that patients with severe COVID-19 infection or markedly elevated levels of D-dimer (>6 x ULN) have decreased mortality when given prophylactic doses of LMWH or UFH.[4] A randomized open-label clinical trial (NCT04345848) is currently being conducted to evaluate prophylactic- and therapeutic-dose anticoagulation in hospitalized adults with severe COVID-19 infection. [12]		Additional study is needed to understand the anticoagulant needs of COVID-19 patients. [9, 11] Several organizations have published interim guidance for the management of COVID-19-associated coagulopathy. [4, 5, 9] The International Society for Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH) recommend that all hospitalized COVID-19 patients, including non-ICU patients, receive prophylactic-dose LMWH unless contraindicated (e.g., active bleeding, platelet count <25×10^9/L, fibrinogen

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		incidence of venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. [1-6, 8, 11, 16, 18] Early anticoagulation in patients with severe COVID-19 infection may prevent clot formation and reduce thrombotic complications. [2, 4, 5, 14] An additional benefit may be the anti-inflammatory effect of heparins. [5, 7, 8, 17]			less than 0.5 g/L). [4, 5] Abnormal PT or aPTT is not a contraindication for prophylaxis. [4, 5] UFH also may be considered for thromboprophylaxis; practical concerns (e.g., convenience of administration and risk of medical staff exposure) may influence institutional choice of anticoagulant. [8, 9] Because thrombotic complications have continued to occur in some COVID-19 patients despite thromboprophylaxis, some clinicians have suggested the use of high prophylactic doses. [11, 17] The American Society of Hematology (ASH) states that therapeutic anticoagulation is not required in COVID-19 patients unless there is documented VTE or atrial fibrillation. [4] The efficacy of intermediate or full therapeutic anticoagulation for critically ill COVID-19 patients without documented VTE is being evaluated. [4] In patients already on anticoagulation for VTE or atrial fibrillation, therapeutic doses of anticoagulant therapy should continue but may need to be held if the platelet count is less than 30-50 x 10^9/L or if fibrinogen is less than 1 g/L. [4] However, some clinicians recommend that therapeutic anticoagulation (with a preference for UFH rather than LMWH) be considered in critically ill patients with COVID-19; since these patients have a severe hypercoagulable state associated with progressive end-organ dysfunction, more aggressive anticoagulation is recommended to prevent significant clinical deterioration. [14] The risk of venous thromboembolism and anticoagulation requirements should be assessed in all patients on an individual basis. [4, 5, 10, 17, 18]

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					Bleeding appears to be infrequent in COVID-19 patients. [5] However, standard risk factors for bleeding should be considered and patients should be individually assessed to balance risk of thrombosis with risk of bleeding. [4]
HMG-CoA Reductase Inhibitors (statins) ***Added 4/29/20***	24:06 Antilipemic Agents	In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects which may prevent acute lung injury. [1] Statins affect ACE2 as part of their function in reducing endothelial dysfunction. [2, 8]	Data are lacking on the use of statins in patients with COVID-19. Preliminary findings have shown mixed results with other respiratory illnesses; some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients hospitalized with influenza and/or pneumonia. [3-6] Clinical trials are evaluating the effectiveness of statins (with and without other potential treatment agents) for the treatment of COVID-19. [9, 10] (NCT04348695, NCT04333407)		NIH COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy; [2] recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. [2] Patients with cardiovascular disease are at an increased risk of serious COVID-19 infections. [3] In patients with active COVID-19 who may develop severe rhabdomyolysis, it may be advisable to withhold statin therapy for a short period of time. [3] Most statins are substrates for the CYP450 system; potential for drug interactions. [7] Clinicians should ensure that their high-risk primary prevention (for ASCVD) patients are on guideline-directed statin therapy. [3]
Immune Globulin (IGIV, IVIG, γ-globulin) *Added 4/17/20*	80:04 Immune Globulin	Commercially available immune globulin (IGIV, IVIG, γ-globulin) is derived from pooled plasma; contains many antibodies normally present in adult human blood; used for replacement therapy in pts with primary humoral immunodeficiency unable to produce sufficient IgG antibodies and also used to provide *passive* immunity	**SARS Experience:** IGIV has been used in some pts for the treatment of SARS. [4-7, 15] Benefits in such pts were unclear because of comorbidities, differences in stage of illness, and effect of other treatments; [5] IGIV may have contributed to hypercoagulable state and thrombotic complications in some pts. [6, 7] **COVID-19 case reports in China (Cao et al):** Treatment with IGIV at the early stage of clinical deterioration was reported to provide some clinical benefit in 3 adults with	IGIV dosage of 0.3-0.5 g/kg daily for 5 days has been used in some pts with COVID-19; [8] IGIV dosage of 0.5 g/kg daily for 5 days being investigated in a clinical trial in China. [12]	Role of commercially available immune globulin (IGIV, IVIG, γ-globulin) in the treatment of COVID-19 unclear. The Surviving Sepsis Campaign COVID-19 subcommittee suggests that IGIV not be used routinely in critically ill adults with COVID-19 because efficacy data not available, currently available IGIV preparations may not contain antibodies against SARS-CoV-2, and IGIV can be associated with increased risk of severe adverse effects (e.g., anaphylaxis,

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		to certain viral infections in other individuals. [1] May modulate immune responses to infections. [2] Commercially available preparations of immune globulin (IGIV, IVIG, γ-globulin) may contain antibodies against some previously circulating coronaviruses; [2] however, depending on time of donor plasma collection, such preparations may not contain antibodies against SARS-CoV-2. [3, 13]	severe COVID-19; 2 pts also received antivirals and 1 pt also received short-term steroid treatment. Patients were afebrile within 1-2 days and breathing difficulties gradually improved within 3-5 days of IGIV administration. [8] **COVID-19 clinical experience in China:** IGIV has been used as an adjunct in the treatment of COVID-19. [9-11] **Efficacy data not available from controlled clinical studies to date.** **COVID-19 clinical trial in China (NCT04261426):** Open-label randomized trial initiated to evaluate efficacy and safety of IGIV with standard care for treatment of severe COVID-19 [12]		aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury). [13] IGIV mentioned in Chinese guidelines as other therapeutic measure for treatment of severe and critical cases of COVID-19 in children. [14]
Ivermectin *Updated 4/24/20*	8:08 Anthelmintic	In vitro activity against some human and animal viruses [1-6] In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug [1]	Currently no known published data regarding efficacy or safety in the treatment of COVID-19		No data to date to support use in the treatment of COVID-19 Ivermectin plasma concentrations attained with dosages recommended for treatment of parasitic infections are substantially lower than concentrations associated with in vitro inhibition of SARS-CoV-2 [7] FDA issued a warning concerning possible inappropriate use of ivermectin products intended for animals as an attempt to self-medicate for the treatment of COVID-19 [8]
Nebulized drugs *Added 3/27/20*		**Potential harm:** Concern that use of nebulized drugs (e.g., albuterol) for the management of respiratory conditions in patients with COVID-19 infection may distribute the virus into the air and expose close contacts.[1, 2]	Nebulizer treatment used in clinical practice to treat influenza and other respiratory infections is thought to generate droplets or aerosols. In one study, nebulized saline delivered droplets in the small- and medium-size aerosol/droplet range. These results may have infection control implications for airborne infections, including severe acute respiratory syndrome and pandemic influenza infection. [3]		American College of Allergy, Asthma & Immunology (ACAAI) recommends that nebulized albuterol should be administered in a location that minimizes exposure to close contacts who do not have COVID-19 infection. In the home, choose a location where air is not recirculated (e.g., porch, patio, or garage) or areas where surfaces can be cleaned easily or may not need cleaning. [1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose inhalers because of the risk of the virus becoming airborne when treating patients infected with COVID-19. [2]
Niclosamide *3/20/20*	8:08 Anthelmintic	Broad antiviral activity In vitro evidence of activity against SARS-CoV and MERS-CoV [1,2]	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 In drug repurposing screens, was found to inhibit replication and antigen synthesis of SARS-CoV; did not interfere with virion's attachment into cells [1, 2]		Not commercially available in the US No data to date support use in treatment of COVID-19
Nitazoxanide *Updated 5/1/20*	8:30.92 Antiprotozoal	In vitro activity against various viruses, including coronaviruses [4, 5] Structurally similar to niclosamide [3, 5] In vitro evidence of activity against SARS-CoV-2 [1] In vitro activity against MERS-CoV [4] Suppresses production of proinflammatory cytokines in peripheral blood mononuclear cells; suppresses IL-6 in mice [4]	Currently no known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 **Experience in treating influenza:** In a randomized, placebo-controlled study in 624 otherwise healthy adult and adolescent patients with acute uncomplicated influenza, treatment with nitazoxanide reduced duration of symptoms by approximately 1 day [6] **Experience in treating influenza-like illness:** In two studies for the treatment of influenza-like illness symptoms associated with viral respiratory infection in 186 adults and pediatric pts, treatment with nitazoxanide reduced duration of symptoms (4 days versus ≥7 days with placebo). [7] In another study in 260 adults and pediatric pts hospitalized with influenza-like illness (≥50% with pneumonia at presentation), treatment with nitazoxanide did not reduce the duration of hospital stay (primary end point) or duration of symptoms [7] **COVID-19**: Randomized, double-blind, placebo-controlled proof-of-concept trial (NCT04348409) initiated to evaluate nitazoxanide for treatment of moderate COVID-19 [8]	**Dosages investigated for treatment of influenza and influenza-like illness or being investigated for other viral infections:** Adults and adolescents (≥12 years of age): 500 or 600 mg orally twice daily for 5 days [6, 7, 8] Protocol in one ongoing trial (NCT04348409) for treatment of moderate COVID-19 specifies a nitazoxanide dosage of 600 mg twice daily for 7 days [8] Protocol in two ongoing trials (NCT04343248, NCT04359680) evaluating pre- and/or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses specifies a nitazoxanide dosage of 600 mg orally twice daily for 6 weeks [8]	Current data not specific to COVID-19; additional study needed [1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			Two randomized, double-blind, placebo-controlled clinical trials have been initiated by the manufacturer (Romark) to evaluate efficacy and safety for pre- or post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in healthcare workers (NCT04359680) and post-exposure prophylaxis of COVID-19 and other viral respiratory illnesses in elderly residents of long-term care facilities (NCT04343248) [8] **Multiple other clinical trials planned or initiated** to evaluate nitazoxanide in combination with other drugs (chloroquine, hydroxychloroquine, or ivermectin) or alone for treatment of COVID-19 [8]		
Nonsteroidal Anti-inflammatory Agents (NSAIAs) *Updated 4/29/20*	28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)	**Ibuprofen:** Speculative link between ibuprofen and increased ACE2 expression **leading to worse outcomes** in COVID-19 patients, and should NOT be used in patients with COVID-19 [1] **Indomethacin:** Possible antiviral activity against **other** coronaviruses SARS-CoV & CanineCoV (interferes with viral RNA synthesis) [6]	**Ibuprofen:** None; anecdotal [1] **Indomethacin:** Speculative; one **in vitro & animal model** study with other coronaviruses SARS-CoV & CanineCoV [6]		**Ibuprofen:** A letter published in The Lancet Respir Med stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2; however, this appears to be based on animal studies. [1, 4] A statement attributed to WHO spokesperson Christian Lindmeier recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position could not be found on the WHO website or other official sources. WHO has stated "after a rapid review of the literature, is not aware of published clinical or population-based data on this topic." As of 3/18/20 (via Twitter) "WHO does not recommend against the use of ibuprofen." https://twitter.com/WHO/status/1240409217997189128 In addition, there have been unsubstantiated reports of younger, healthy patients who took ibuprofen and suffered severe outcomes with COVID-19. Official case reports are lacking.

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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Tissue Plasminogen Activator (t-PA; alteplase) *Updated 4/29/20*	20:12.20 Thrombolytic agents	A consistent finding in patients with severe COVID-19 is a hypercoagulable state, which may contribute to their risk of poor outcomes (e.g., progressive respiratory failure, acute respiratory distress syndrome [ARDS], death). [1-3, 5-9, 14, 16] Coagulation abnormalities observed in these patients include prothrombotic disseminated intravascular coagulation (DIC), a high incidence of venous thromboembolism, elevated D-dimer levels, high fibrinogen levels, and microvascular and macrovascular thrombosis. [1, 2, 5-10, 13, 14, 16] In patients with ARDS (regardless of the cause), pathologic findings include fibrin deposition in the alveoli and formation of microthrombi in the pulmonary vasculature. [1, 11, 14] Treatment with t-PA may restore microvascular patency and limit progression of ARDS in patients with COVID-19 [1, 14]	Results of a small phase 1 study conducted in 2001 suggest possible benefit of plasminogen activators for the treatment of ARDS.[1-3] In this study, 20 patients with ARDS secondary to trauma and/or sepsis who failed to respond to standard ventilator therapy and were not expected to survive were treated with urokinase or streptokinase; such therapy improved PaO_2 and also appeared to improve survival. [1-3] A registered open-label randomized trial (NCT04357730) will evaluate systemic fibrinolytic therapy with t-PA versus standard of care in mechanically ventilated COVID-19 patients with severe respiratory failure [12] A registered open-label nonrandomized pilot study (NCT04356833) will evaluate an inhaled formulation of t-PA (via nebulization) in patients with ARDS due to COVID-19; [12] the inhaled formulation of t-PA is investigational at this time [15]	The open-label systemic fibrinolytic therapy trial (NCT04357730) will evaluate t-PA (alteplase) dosages of 50 mg (administered as a 10-mg IV bolus followed by IV administration of the remaining 40 mg over a total time of 2 hours) and 100 mg (administered as a 10-mg IV bolus dose followed by IV administration of the remaining 90 mg over a total time of 2 hours); a heparin infusion will be initiated immediately following completion of the alteplase infusion [12] Other dosage regimens have been evaluated in patients with ARDS associated with COVID-19, including an initial t-PA (alteplase) dose of 25 mg administered IV over 2 hours, followed by an IV infusion of 25 mg of t-PA over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg (Beth Israel Deaconess et al study); however, the optimum dose, route of administration, and duration of treatment remain to be determined. [1, 9, 14]	t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who do not have access to mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). [1, 13, 14] However, there are currently no clinical trial data to inform this practice and a lack of clinical experience with the use of fibrinolytic agents in ARDS patients in general. [11] Several institutions (Beth Israel Deaconess, University of Colorado Anschultz Medical Campus, Denver Health) are currently testing the use of t-PA as salvage therapy in patients with severe COVID-19 under the FDA compassionate use program. [2, 4] Preliminary findings from the first few cases reported an initial, but transient improvement in PaO_2/FiO_2 (P/F) ratio. [9] The American Society of Hematology states that treatment of the underlying pathology is paramount in COVID-19 patients with coagulopathies; supportive care should be individualized and standard risk factors for bleeding should be considered. [8]

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. PMID 32171062 DOI: 10.1016/S2213-2600(20)30116-8
2. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in covid-19. From American College of Cardiology website. Accessed Mar 18 2020. Available from https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.
3. Position statement of the ESC council on hypertension on ACE-inhibitors and angiotensin receptor blockers. From European Society of Cardiology website. Accessed 2020 Mar 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. 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.2020.395:565-574. 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. PMID 32129518 DOI: 10.1002/ddr.21656.
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Mar 19. Available from https://clinicaltrials.gov/ct2/show/study/NCT04312009. NLM identifier: NCT04312009.
8. Vaduganathan M, Vardeny O, Michel T. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020. PMID 32227760 DOI: 10.1056/NEJMsr2005760
9. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 27.

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 2020 Apr 22. 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 Mar 16: pii: S0140- 6736(20)30628-0 [Epub ahead of print]. 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. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 22.

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. From the ASH website. Accessed 2020 Apr 15. Available from https://www.hematology.org/covid-19/covid-19-and-coagulopathy
5. International Society of Thrombosis and Haemostasis Interim Guidance on Recognition and Management of Coagulopathy in COVID-19. From the ISTH website. Accessed 2020 Apr 15. Available from https://onlinelibrary.wiley.com/doi/epdf/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. 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
8. MedPage Today. Anticoagulation Guidance Emerging for Severe COVID-19. From the MedPage Today website. Accessed 2020 Apr 15. Available from https://www.medpagetoday.com/infectiousdisease/covid19/85865
9. Dixon DL, Van Tassell BW, Vecchi A. Cardiovascular Considerations in Treating Patients with Coronavirus (COVID-19). J Cardiovasc Pharmacol. 2020. 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 2020 Mar 15. Available at https://www.clinicaltrials.gov/ct2/show/NCT04345848?term=NCT04345848&draw=2&rank=1
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
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. Beun R, Kusadasi N, Sikma M. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. Int J Lab Hematol. 2020. PMID: 32311843 DOI: 10.1111/ijlh.13230

Ascorbic acid:

1. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Mar 31. (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 pii: E292. 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.

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 Developing Countries. 2009; 3:159-161.
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: (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; In Press. (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; :1-9. (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; (PubMed 32031570) (DOI 10.1001/jama.2020.1585)
16. US Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Information for Clinicians on Therapeutic Options for COVID-19 Patients. From CDC website. Accessed 2020 Mar 24. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html).
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. Médecine et Maladies Infectieuses. 2020. Preprint. https://doi.org/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: an observational study. Preprint. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf?fbclid=IwAR0-uBG8W7rsx0YxGUfILvwl-Hr5uKs0VGyQEFqkhSL0pk3IvyQ7BF_KAwE
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 COVID-19. Mayo Clin Proc. Preprint. DOI: 10.1016/j.mayocp.2020.03.024.
21. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website. Accessed 2020 Apr 21. Available at https://www.covid19treatmentguidelines.nih.gov/.
22. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Accessed 2020 Apr 22. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.

Baloxavir:

1. Chinese Clinical Trial Registry. Accessed 2020 March 19. Available at http://www.chictr.org.cn/enindex.aspx.
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

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. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 21.

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; In Press. (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; In Press. (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 Apr 26. Available at https://www.clinicaltrials.gov/.
11. National Health Commission (NHC) & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (http://busan. china-consulate.org/chn/zt/4/P020200310548447287942.pdf)
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; :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; In Press. (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, Li L et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ. 2020; Mar. (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. US Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Information for Clinicians on Therapeutic Options for COVID-19 Patients. From CDC website. Accessed 2020 Mar 26. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html).
21. CDC. 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 March 26, 2020).
22. Pan Y, Zhang D, Yang P et al. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020. pii: S1473-3099(20)30113-4. (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. 2020 Mar 28. From FDA website. (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 28. 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 28. 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. From FDA website. (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. 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.fda.gov/media/136537/download)
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. Preprint. 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; Mar 30. Epub. 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; Apr 11. Epub. PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663.
35. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website. Accessed 2020 Apr 21. Available at https://www.covid19treatmentguidelines.nih.gov/.
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. Preprint (not peer reviewed). 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. From IDSA website. Accessed 2020 Apr 22. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
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. Preprint (not peer reviewed). (https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf).

Colchicine:

1. U.S. National Library of Medicine. ClinicalTrials.gov. Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19). Accessed 2020 Apr 20. Available from https://clinicaltrials.gov/ct2/show/NCT04322682.
2. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 20. 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: . 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. 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; . 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.

Corticosteroids, including methylprednisolone:

1. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed 2020 Mar 19. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
2. Centers for Disease Control. Healthcare professionals: Frequently asked questions and answers. From CDC website. Accessed 2020 Apr 14. 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 Mar 13. 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.
10. National Health Commission & State Administration of traditional Chinese medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. From China consulate website. Accessed 2020 Mar 20. http://busan.china-consulate.org/chn/zt/4/P020200310548447287942.pdf.
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; Mar 27. doi: 10.1097/CCM.0000000000004363. PMID: 32224769.
13. Wang Y, Jiang W, He Q et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv. 2020.03.06.20032342; doi: https://doi.org/10.1101/2020.03.06.20032342.
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.
21. U.S. National Library of Medicine. Efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19 (DEXA-COVID19). ClinicalTrials.gov. Accessed 2020 Apr 16. Available from https://clinicaltrials.gov/ct2/show/NCT04325061.
22. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 21. 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 Apr 21. Available from https://clinicaltrials.gov/ct2/show/NCT04244591.
24. National Institutes of Health. COVID-19 treatment guidelines. From NIH website. Accessed 2020 Apr 21. Available from https://www.covid19treatmentguidelines.nih.gov/concomitant-medications/.
25. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Accessed 2020 Apr 28. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
26. Isidori AM, Pofi R, Hasenmajer V et al. Use of glucocorticoids in patients with adrenal insufficiency and COVID-19 infection. Lancet Diabetes Endocrinol. 2020 Apr 23. 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 Mar 14. PMID: 32170323. DOI: 10.1210/clinem/dgaa133.

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. Epub. (https://doi.org/10.1172/JCI138745). 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. Epub. DOI: 10.1111/vox.12926.

3. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. Editorial. JAMA. 2020; Mar 27. Epub. 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 Apr 6. Epub. (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; Mar 27. Epub. PMID: 32219420 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. April 2020 (updated April 13, 2020). From FDA website. Accessed 2020 Apr 15. (https://www.fda.gov/media/136798/download)
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 collection: Donor eligibility, processing, labeling, and distribution. Dated 2020 Apr 4. From aabb website. (http://aabb.org).
15. American Red Cross. Coronavirus (COVID-19) convalescent plasma clinician information. From American Red Cross website. Accessed 2020 Apr 16. (https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients/clinician-registration.html).

Epoprostenol:

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. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363

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, ofaa105. DOI: 10.1093/ofid/ofaa105

6. Chen C, Huang J, Cheng Z et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020. DOI: 10.1101/2020.03.17.20037432
7. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr27. Available at http://www.clinicaltrials.gov.
8. Chinese Clinical Trial Registry. Accessed 2020 Apr 23. Available at http://www.chictr.org/cn.
9. NIPH Clinical Trials Search: NIPH Clinical Trials Search of Japan. Accessed 2020 Apr 8. 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. 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. 2020. 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. 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

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; (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; (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; (IDIS) (PubMed 32171872) (DOI 10.1016/j.jinf.2020.03.002) (URL)
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. (IDIS) (PubMed 26198719) (DOI 10.1093/infdis/jiv392) (URL)
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; (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; (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. (PubMed 32125362) (DOI 10.1001/jama.2020.3204)
13. National Health Commission (NHC) & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (URL http://busan. china-consulate.org/chn/zt/4/P020200310548447287942.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; (PubMed 32171076) (DOI 10.1016/S0140-6736 (20)30566-3)
15. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 3. 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 inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. 2020. Preprint. DOI: 10.1101/2020.04.04.020925.
18. De Meyer S, Bojkova D, Cinati J, et al. Lack of antiviral activity of Darunavir against SARS-CoV-2. 2020. Preprint. DOI: 10.1101/2020.04.03.20052548.
19. Yamamoto N, Matsuyam S, Hoshino T, et al. Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro. 2020. Preprint. DOI: 10.1101/2020.04.06.026476.
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 Apr 9. 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. From NIH website. Accessed 2020 Apr 21. Available at https://www.covid19treatmentguidelines.nih.gov/
23. Infectious Diseases Society of America. IDSA guidelines on the treatment and management of patients with COVID-19. From IDSA website. Accessed 2020 Apr 22. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

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. PMID: 32227357 DOI: 10.1002/ddr.21666
2. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 21.
3. Is there a role for statin therapy in acute viral infections? From JACC 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 multi-state 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. 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. PMID: 32198163 DOI: 10.1128/mBio.00398-20
9. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 23. Available from https://www.clinicaltrials.gov/ct2/show/NCT04348695?term=statins&cond=covid&draw=2&rank=1. NLM identifier: NCT04348695
10. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 23. Available from https://www.clinicaltrials.gov/ct2/show/NCT04333407?term=statins&cond=covid&draw=2&rank=2. NLM identifier: NCT04333407

Immune Globulin (IGIV, IVIG, γ-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 Apr 13. Available from https://www.clinicaltrials.gov/ct2/show/NCT04261426.
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. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363.
14. National Health Commission (NHC) & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia.
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

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. Preprint. (https://www.sciencedirect.com/science/article/pii/S0166354220302011?via%3Dihub).
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. 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. 2020. Preprint. (https://doi.org/10.1101/2020.04.11.20061804). DOI: 10.1101/2020.04.11.20061804.
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).

Nebulized drugs:

1. American College of Allergy, Asthma & Immunology. COVID-19 and asthma: What you need to know moving forward. From ACAAI website. Accessed 2020 Mar 24. Available from https://acaai.org/news/covid-19-and-asthma-what-you-need-know-moving-forward.
2. American College of Allergy, Asthma & Immunology. ACAII announces U.S. albuterol inhaler shortage: a message to asthma sufferers about a shortage of albuterol metered-dose inhalers. From Allergic Living website. Accessed 2020 Mar 25. 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.

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. 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 2020 Mar 19. Available at https://clinicaltrials.gov.

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: 32125140 DOI: 10.1021/acsinfectdis.0c00052
2. Xu J, Shi PY, Li H et al. Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential. ACS Infect Dis. 2020. PMID: 15215127. DOI: 10.1128/AAC.48.7.2693-2696.2004

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. PMID: 15215127. DOI: 10.1128/AAC.48.7.2693-2696.2004
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 2020 Apr 29. Available at https://clinicaltrials.gov.

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 Apr 20. 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: PMID: 31197492 DOI: 10.1186/s13613-019-0540-9.
7. Biospace. Mallinckrodt Evaluates the Potential Role for Inhaled Nitric Oxide to Treat COVID-19 Associated Lung Complications, Engages with Scientific, Governmental and Regulatory Agencies. From the Biospace website. Accessed 2020 Mar 24. https://www.biospace.com/article/releases/mallinckrodt-evaluates-the-potential-role-for-inhaled-nitric-oxide-to-treat-covid-19-associated-lung-complications-engages-with-scientific-governmental-and-regulatory-agencies/.
8. FDA Grants Bellerophon Emergency Expanded Access for INOpulse® for the Treatment of COVID-19 Virus [press release]. Warren, NJ; Bellerophon Therapeutics, Inc: 2020 Mar 20. http://investors.bellerophon.com/news-releases/news-release-details/fda-grants-bellerophon-emergency-expanded-access-inopulser. Accessed 2020 Mar 24.
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. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363
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. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363

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. PMID: 32171062 DOI: 10.1016/S2213-2600(20)30116-8
2. 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). Intensive Care Med. 2020. PubMed: 32222812 DOI: 10.1007/s00134-020-06022-5
3. Sodhi M, Etminan M, Safety of Ibuprofen in Patients with COVID-19; Causal or Confounded? CHEST. 2020. PubMed: 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. PubMed: 32247213 DOI: 10.1016/j.dsx.2020.03.012
5. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 27.
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

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; (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; (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; :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; (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; (PubMed 32173241) (DOI 10.1016/j.jmii.2020.02.012)
15. Gilead Sciences. Company statement on access to remdesivir outside of clinical trials. Accessed 2020 Mar 23. (https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-access-to-remdesivir-outside-of-clinical-trials)
16. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020. Epub. DOI: 10.1056/NEJMoa2007016.
17. Expanded access treatment protocol: remdesivir (RDV; GS-5734) for the treatment of SARS-CoV2 (CoV) infection (COVID-19). NCT04323761. (https://www.clinicaltrials.gov/ct2/show/NCT04323761?cond=NCT04323761).
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. Preprint. (not peer reviewed). (https://doi.org/10.1101/2020.04.15.043166).
20. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website. Accessed 2020 Apr 21. Available at https://www.covid19treatmentguidelines.nih.gov/.
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; Apr 9. Epub. DOI: 10.1016/S0140-6736(20)31022-9. (https://doi.org/10.1016/S0140-6736(20)31022-9)
22. National Institutes of Health. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. Press release. 2020 Apr 29. Available at https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19.
23. Gilead Sciences. Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. Press release. 2020 Apr 29. Available at https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19.
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 Apr 13 [Epub ahead of print]. PMID: 32284326 DOI: 10.1074/jbc.RA120.013679
25. 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. (https://www.fda.gov/media/137564/download)
26. 26. US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of remdesivir (GS-5734). From FDA website. (https://www.fda.gov/media/137566/download)

27. 27. US Food and Drug Administration. Fact sheet for patients and parent/caregivers: Emergency use authorization (EUA) of remdesivir for coronavirus disease 2019 (COVID-19). From FDA website. (https://www.fda.gov/media/137565/download)

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 2020 Apr 7. Available from https://clinicaltrials.gov/ct2/show/NCT04337359.
3. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 7. Available from https://clinicaltrials.gov/ct2/results?cond=COVID&term=ruxolitinib&cntry=&state=&city=&dist=.
4. 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.
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. Chinese Clinical Trial Registry. Accessed 2020 Apr 7. Available at http://www.chictr.org.cn/enindex.aspx.
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. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 21.

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. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 22.

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 2020 Apr 17. 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.

Tissue Plasminogen Activator (t-PA; alteplase):

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. 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
4. Beth Israel Deaconess Medical Center. BIDMC launches clinical trial to assess common anti-clotting medication for treatment of COVID-19-related respiratory failure. From the BIDMC website. Accessed 2020 Apr 8. Available from https://www.bidmc.org/about-bidmc/news/2020/04/covid-19-anti-clotting-medication
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. From the ASH website. Accessed 2020 Apr 9. Available from https://www.hematology.org/covid-19/covid-19-and-coagulopathy
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. 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 2020 Apr 22. 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

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 2020 Apr 27. 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. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Apr 22.
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

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. PubMed: 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.
3. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Apr 1. Available from https://clinicaltrials.gov/ct2/show/study/NCT04260594. NLM identifier: NCT04260594
4. Blaising J, Polyak SJ, Pecheur EI. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res. 2014; 107:88-94. PubMed: 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. PubMed: 32147628 DOI: 10.5582/ddt.2020.01012
6. Chen C, Huang J, Cheng Z, et al. Favipiravir versus arbidol for COVID-19: A randomized clinical trial. MedRxiv. Posted March 27, 2020 DOI: https://doi.org/10.1101/2020.03.17.20037432
7. National Health Commission (NHC) & State Administration of Traditional Chinese Medicine (Trial Version 7). Diagnosis and treatment protocol for novel coronavirus pneumonia. (http://busan.china-consulate.org/chn/zt/4/P020200310548447287942.pdf)
8. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020. [Epub ahead of print]. PubMed: 32283143 DOI: 10.1016/j.jinf.2020.03.060