Assessment of Evidence for COVID-19-Related Treatments: Updated 4/8/2020

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Select entries were updated on 4/8/2020; 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	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 4/8/20***	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 **Multiple clinical trials initiated** in China and other countries to evaluate various chloroquine dosages for treatment of pts with COVID-19 [4, 10] **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] At least one clinical trial is being initiated to evaluate chloroquine for *prevention* of COVID-19 in the healthcare setting (NCT04303507) [10]	**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 10 days [4] **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]	Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established [10, 24] 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 Data needed regarding toxicity profile when used in patients with COVID-19 Chloroquine suggested as possible option and included in some guidelines for treatment of COVID-19 **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]

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				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]	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). [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) ***Added 4/3/20***	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] 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]	**Oral favipiravir:** 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days [6]	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

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			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 ChiCTR2000029544 ChiCTR2000030113 ChiCTR2000029548 ChiCTR2000030894 ChiCTR2000030987 JPRN-jRCTs031190226 JPRN-jRCTs041190120		
Hydroxychloroquine (Plaquenil®) ***Updated 4/8/20***	8:30.08 Antimalarial	In vitro activity against various viruses, including coronaviruses [5, 8. 12-14] In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; may be more potent than chloroquine in vitro, but some data are conflicting and additional study needed [8, 12] Has immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections [3, 8, 13, 15, 16] Known pharmacokinetics and toxicity profile Hydroxyl analog of chloroquine with similar mechanisms of action and adverse effects; [13, 14] may have more favorable dose-related toxicity profile than	**Only limited clinical trial data available** to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19 **Multiple clinical trials initiated** in US, China, and other countries to evaluate various hydroxychloroquine dosages for treatment of pts with COVID-19 [4, 10] **Clinical experience** in treating pts with COVID-19 accumulating; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19 [7, 18] **Hydroxychloroquine small pilot study conducted in China:** 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; [18] **both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV**. [30] Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median	**Optimal dosage and duration of treatment not known** [20, 26] **Various dosages recommended or being investigated** for treatment of COVID-19 **Oral hydroxychloroquine sulfate dosage suggested in the EUA:** For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 800 mg on day 1, then 400 mg daily for 4-7 days of total treatment based on clinical evaluation [26] **Oral hydroxychloroquine sulfate:** 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 [8, 20] **Oral hydroxychloroquine sulfate:** 400 mg once or twice daily for 5-10 days [10, 18] **Oral hydroxychloroquine sulfate:** 600 mg twice daily on day 1, then 400 mg daily on days 2-5 [20]	Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 not established [10, 24] 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.) Data needed regarding toxicity profile when used in patients with COVID-19 Hydroxychloroquine suggested as possible option and included in some guidelines for treatment of COVID-19

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		chloroquine, [13-16] but cardiotoxicity (e.g., prolonged QT interval) is a concern with both drugs [13, 20]	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 TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and	**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]	**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). [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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			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:** 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:** 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5).		

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			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, observational study in France:** 80 adults with confirmed COVID-19 were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O_2 saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O_2; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. [34] **Note:** Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were		

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			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. **Efficacy measures:** Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. [7, 18] RT-PCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; [19, 21] however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined. [22, 23] Various clinical trials are being initiated in the US and elsewhere to evaluate hydroxychloroquine for *prevention* of COVID-19 in the healthcare setting or in household contacts of pts with the disease: [10] NCT04328961 NCT04303507 NCT04318444 NCT04318015 NCT04330144		
Lopinavir and Ritonavir (LPV/RTV; Kaletra®) ***Updated 4/8/20***	8:18.08.08 HIV Protease Inhibitor	Antiretroviral with in vitro activity against SARS-CoV and MERS-CoV [1, 2, 9, 11]; some evidence of benefit in animal studies for treatment of MERS-CoV [2, 7, 9, 11] Published data currently lacking on in vitro activity against SARS-CoV-2 [9]	**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: 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	**COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days [3, 16] **COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours) [6] **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	Efficacy for treatment of COVID-19 not definitely established Additional study needed to evaluate possible clinical benefits of early use of LPV/RPV in COVID-19 Additional study needed to evaluate benefits of concomitant use of LPV/RTV with other antivirals for COVID-19; usually used in conjunction with other antivirals (e.g., ribavirin with or without an interferon) for SARS and MERS

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			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] **Retrospective cohort study** in 33 adults in China evaluated use of LPV/RTV with or without umifenovir (Arbidol®). 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 35% of pts treated with LPV/RTV alone vs 75% of pts treated with both drugs and 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.) **COVID-19 trials** at Clinicaltrials.gov that include LPV/RTV [15]: NCT04307693 (LPV/RTV vs hydroxychloroquine in pts with mild disease) NCT04276688 (LPV/RTV with ribavirin and interferon β-1b vs LPV/RTV alone) NCT04328012 (LPV/RTV vs hydroxychloroquine vs losartan vs placebo) **COVID-19 Clinical Experience:** Only limited data on LPV/RTV used with or without interferon in pts with COVID-19 outside of clinical trials. [5, 12, 14. 16] **SARS and MERS Clinical Experience:** Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon. [1, 8, 9, 10, 11]	equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ribavirin for up to 10 days [5, 13] **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] **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]	

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Neuraminidase inhibitors (e.g., oseltamivir)	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 3/24/20***	8:18.92 Antivirals, Miscellaneous	Broad-spectrum antiviral with activity against coronaviruses Previously tested for SARS, MERS, and Ebola In vitro evidence of activity against SARS-CoV-2 [1] 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]	**Phase 3 randomized, open-label trial (NCT04292899)** initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- and 10-day regimens of Remdesivir in conjunction with standard of care in pts with severe COVID-19 [10] **Phase 3 randomized, open-label trial (NCT04292730)** initiated by the manufacturer (Gilead) to evaluate safety and antiviral activity of 5- or 10-day regimens of remdesivir in conjunction with standard of care in pts with moderate COVID-19 compared with standard of care alone [11] **Phase 2 randomized, placebo-controlled trial (NCT04280705)** sponsored by NIAID initiated to evaluate safety and efficacy of remdesivir in hospitalized pts with laboratory-confirmed COVID-19 [13]	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] Phase 3 trial protocol (moderate COVID-19): 200 mg IV on day 1, then 100 mg IV on days 2-5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2-10 (arm 2) [11] NIAID study protocol: 200 mg IV on day 1, then 100 mg IV for duration of hospitalization up to 10 days total [13]	Not commercially available; most promising antiviral currently being investigated for COVID-19 Safety and efficacy not established; additional data needed

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		Pharmacokinetic data available from evaluations for Ebola	**Various clinical trials** initiated in China and other countries **Expanded access and 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. During this transition, 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]		
Umifenovir (Arbidol®) ***Added 4/3/20***	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 and Russia for prophylaxis and treatment of influenza [4]	**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] **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	**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]	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

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			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 care in adults with COVID-19 [3]		

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Anakinra ***Added 4/1/20***	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) to be 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 (estimated start date 3/20) [3]	Phase 3 trial protocol (COVID-19 with hyperinflammation and respiratory distress): 100 mg by IV infusion every 6 hours (total of 400 mg daily) for 15 days [3] (Note: Anakinra is approved only for subcutaneous administration in the U.S.) [1]	No data to date support use in the treatment of COVID-19

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
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 4/8/20***	8:12.12 Macrolides	Antibacterial with some in vitro activity against some viruses (e.g., influenza A H1N1, Zika) [1, 3-5] No data to date on in vitro activity against coronaviruses, including SARS-CoV-2 Has immunomodulatory and anti-inflammatory effects, including effects on proinflammatory cytokines; precise mechanisms of such effects not fully elucidated [2, 6, 8, 9, 11-14, 17]	**Adjunctive therapy in certain respiratory viral infections:** Although contradictory results reported, some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with some viral infections (e.g., influenza). [10, 12, 13] However, in a retrospective cohort study in critically ill pts with laboratory-confirmed MERS, there was no statistically significant difference in 90-day mortality rates or clearance of MERS-CoV RNA between those who received macrolide therapy and those who did not. [12] **Adjunctive therapy in certain respiratory conditions:** Some evidence of beneficial immunomodulatory or anti-inflammatory effects when used in pts with certain respiratory conditions (e.g., ARDS). [8]	**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 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 and in those with chronic medical conditions (e.g., renal failure, hepatic disease; [16, 20] diagnostic testing and monitoring recommended to minimize risk of drug-induced cardiac effects [20]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
		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]	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.)		
Corticosteroids (general) ***Updated 4/8/20***	68:04 Adrenals	Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9] May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low [4, 11]	**Observational studies:** Evidence suggests that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). [1] No randomized controlled clinical studies with corticosteroids for COVID-19 or other coronaviruses have been conducted; however, 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, 16] Systemic corticosteroid therapy has been studied in several randomized controlled studies for the treatment of acute respiratory distress syndrome (ARDS); overall evidence is low to moderate in quality and		Existing evidence is inconclusive for use of corticosteroids in the treatment of COVID-19 patients. [3, 5,7] WHO and CDC recommend that corticosteroids **not** be routinely used in patients with COVID-19 unless indicated for another reason (e.g., asthma or COPD exacerbation, refractory septic shock). [1, 2, 3, 8, 9] Corticosteroids generally should not be used in early or mild disease since the drugs can inhibit immune response, reduce pathogen clearance, and increase viral shedding. [3, 8] Based on limited information from observational studies with methylprednisolone, [6, 13] (see Methylprednisolone in this Evidence Table), some experts state

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			most studies were performed prior to the prelung protection strategy era. [5, 8, 9, 14] 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] International clinical practice guidelines make a **weak** recommendation for use of corticosteroids in patients with sepsis. [4] Recommendation applies to all patients with sepsis with no meaningful difference in efficacy of corticosteroids in different patient populations, including those with septic shock, pneumonia, or ARDS. [4]		that corticosteroid therapy may be considered in severe cases of COVID-19 with ARDS provided the drugs are given in low doses over a short duration. [7, 8, 10, 12] **WHO and expert consensus statement from Chinese Thoracic Society:** Basic principles should be followed when using corticosteroids: (1) benefits and risks should be carefully weighed before using corticosteroids (2) corticosteroids should be used prudently in critically ill patients with 2019-nCoV pneumonia; (3) for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases, further use of corticosteroids should be cautious and (4) dosage should be low to moderate (≤ 0.5–1 mg/kg daily of methylprednisolone or equivalent) and duration should be short (≤7 days). [1, 7] Chinese health authority states that corticosteroids can be used in patients with COVID-19 who experience progressive deterioration for a short period of time (3-5 days) and at dosages not exceeding methylprednisolone 1-2 mg/kg daily or equivalent. [10] The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). [12] However, these experts generally support a **weak** recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. [12]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					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 suggests a weak recommendation to use low-dose corticosteroid therapy over no corticosteroid therapy in adults with COVID-19 and refractory shock. [12] For treatment of sepsis, 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]
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] (Note: Epoprostenol is labeled only for IV administration in the US.)	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 4/8/20***	68:04 Adrenal	Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [3, 9]	**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]	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] Based on expert consensus statement from Chinese Thoracic Society, dosage of methylprednisolone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent). [7]	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
			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]	Regimens used in China were typically methylprednisolone 40-80 mg IV daily for a course of 3-6 days. [8]	
Nitric oxide (inhaled) ***Updated 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 [2, 3, 9] In vitro evidence of direct antiviral activity against severe acute respiratory syndrome coronavirus (SARS-CoV); genetic similarity between SARS-CoV and COVID-19 suggests potential effectiveness for COVID-19 [1]	No studies evaluating use specifically in COVID-19 patients [10] In a small pilot study conducted in China during the 2003 SARS-CoV outbreak, treatment with inhaled nitric oxide 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]	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) in a pilot study in SARS-CoV patients [2] Phase 2 clinical trial protocol (NCT04306393) for treatment of severe ARDS in ventilated 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 treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243) [3,7] On March 20th, 2020, Bellerophon Therapeutics announced that the FDA granted emergency expanded access allowing its inhaled nitric oxide delivery system (INOpulse®) to be immediately used for the treatment of COVID-19 [8]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Sarilumab (Kefzara®) ***Updated 3/27/20***	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients [1, 2, 5]	Currently no known published clinical trial evidence supporting efficacy or safety against Coronavirus. 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)	
Sirolimus *3/20/20*	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] Currently a registered clinical trial (NCT03901001 not yet recruiting) designed to evaluate adjunctive use of sirolimus and oseltamivir in patients hospitalized with influenza [4, 6]	Dosage of sirolimus in the open-label trial was 2 mg daily orally, administered in conjunction with oral prednisolone 20 mg daily for 14 days; patients also received oseltamivir 75 mg twice daily for 10 days [3]	Although possible clinical application, current data not specific to 2019-nCoV/ SARS-CoV2-2; additional study needed [5]
Tocilizumab (Actemra®) *Updated 4/3/20*	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, 2, 3, 6]	Case study/series describing use of tocilizumab in patients with COVID-19 reported from various areas of the world [1, 3] In preliminary data from a non-peer-reviewed, single-arm Chinese trial 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] Currently no other known clinical trial evidence supporting efficacy and safety of tocilizumab against Coronavirus [1]	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):** 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] Published data to support use currently are limited [1, 7]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			China: Randomized, multicenter, controlled clinical trial evaluating efficacy & safety in 188 patients with COVID-19 under way through 5/10/20. **Results not yet available.** Chinese Clinical Trial Registry link: http://www.chictr.org.cn/showprojen.aspx?proj=49409 **US/Global randomized, placebo-controlled trial:** Manufacturer (Roche) conducting a randomized, double-blind, placebo-controlled phase 3 trial (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] **Multiple other clinical trials planned or initiated** using tocilizumab in COVID-19 patients in China and Europe [5]		

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs) ***Updated 4/3/20***	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] 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]
Ibuprofen *3/20/20*	28:08.04 Nonsteroidal Anti-inflammatory Agent (NSAIA)	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]	None; anecdotal [1]		A letter published in The Lancet Respir Med [1] stated that increased expression of ACE2 could facilitate infection with COVID-19. The letter states that thiazolidinediones and ibuprofen can increase ACE2. **No sources have been cited for this.** 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					In addition, there have been unsubstantiated reports of younger, healthy patients who took ibuprofen and suffered severe outcomes with COVID-19. Official case reports are lacking. On March 19, 2020, 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.**
Indomethacin	28:08.04 Nonsteroidal Anti-inflammatory Agents (NSAIA)	Possible antiviral activity against **other** coronaviruses SARS-CoV & CanineCoV (interferes with viral RNA synthesis) [1]	Speculative; one **in vitro & animal model** study with other coronaviruses SARS-CoV & CanineCoV [1]		
Ivermectin ***Added 4/8/20***	8:08 Anthelmintic	In vitro activity against some human and animal viruses [1-6] In vitro evidence of activity against SARS-CoV-2 in Vero-hSLAM cells infected with the virus [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 Only data available to date are results of a single in vitro study

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Nebulized drugs **Added *3/27/20***		**Potential harm:** Concern that use of nebulized drugs (e.g., albuterol) for the management of respiratory conditions in patients with COVID-19 infection may distribute the virus into the air and expose close contacts.[1, 2]	Nebulizer treatment used in clinical practice to treat influenza and other respiratory infections is thought to generate droplets or aerosols. In one study, nebulized saline delivered droplets in the small- and medium-size aerosol/droplet range. These results may have infection control implications for airborne infections, including severe acute respiratory syndrome and pandemic influenza infection. [3]		American College of Allergy, Asthma & Immunology (ACAAI) recommends that nebulized albuterol should be administered in a location that minimizes exposure to close contacts who do not have COVID-19 infection. In the home, choose a location where air is not recirculated (e.g., porch, patio, or garage) or areas where surfaces can be cleaned easily or may not need cleaning. [1] In hospitals, clinicians typically use nebulizers to deliver medications such as albuterol, but are being encouraged to switch to use of metered-dose inhalers because of the risk of the virus becoming airborne when treating patients infected with COVID-19. [2]
Niclosamide	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 ***Added 4/1/20***	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 **Other infections (influenza):** In a randomized, placebo-controlled phase 2b/3 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] **Other infections (influenza-like illness):** In two phase 2 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]	**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]	Current data not specific to COVID-19; additional study needed [1]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
			In another phase 2 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]		

[a] See US prescribing information for additional information on dosage and administration of drugs commercially available in the US for other labeled indications.

REFERENCES

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020. 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

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 Mar 30. Available from https://clinicaltrials.gov/ct2/show/study/NCT04324021. NLM identifier: NCT04324021.
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.

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.

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

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 2. 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, 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.
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: an observational study. Preprint. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf?fbclid=IwAR0-uBG8W7rsx0YxGUfILvwl-Hr5uKs0VGyQEFqkhSL0pk3IvyQ7BF_KAwE

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 7. 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 7. 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.

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 Mar 31. Available at http://www.clinicaltrials.gov.
8. Chinese Clinical Trial Registry. Accessed 2020 Mar 31. Available at http://www.chictr.org/cn.
9. NIPH Clinical Trials Search: NIPH Clinical Trials Search of Japan. Accessed 2020 Mar 31. Available at https://rctportal.niph.go.jp/en.

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

Indomethacin:

1. 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

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.

Lopinavir and Ritonavir:

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.

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 Mar 31. 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 2. 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

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. 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)

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.

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 Mar 19. 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.

Tocilizumab:

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. 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 1. 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.

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)