Assessment of Evidence for COVID-19-Related Treatments

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

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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 Hydroxychloroquine	8:30.08 Antimalarial	In vitro activity against some viruses, including coronaviruses [1-3] Chloroquine: 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] Chloroquine: Active in vitro against SARS-CoV and MERS-CoV [2, 3, 5, 9]	**Only limited clinical trial data available** to date to support use of chloroquine or hydroxychloroquine for treatment or prevention of COVID-19 **Multiple clinical trials initiated** using various dosages in pts with COVID-19 in China and other countries [3, 4, 10] **Clinical experience** in 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 [4-7]	**Various dosages recommended or being investigated** **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 of chloroquine or hydroxychloroquine for treatment or prevention of COVID-19 not established 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 and identify optimal dose and duration

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		Chloroquine: Active in vitro against SARS-CoV and MERS-CoV [2, 3, 5, 9] Hydroxychloroquine: In vitro activity against SARS-CoV-2 reported; additional study needed, but may be more potent than chloroquine in vitro [8] Both drugs have immunomodulatory activity that theoretically could contribute to an anti-inflammatory response in patients with viral infections [1-3] Known pharmacokinetics and toxicity profile		**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] **Consider:** 500 mg of chloroquine phosphate is equivalent to 300 mg of chloroquine base **Oral hydroxychloroquine:** 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 [8] **Oral hydroxychloroquine:** 400 mg daily for 5 days [4, 10] **Oral hydroxychloroquine:** 100-200 mg twice daily for 5-14 days [4] **Oral hydroxychloroquine:** 200 mg 3 times daily for 10 days [7]	Chloroquine and hydroxychloroquine are suggested as possible options and are included in some guidelines for treatment of COVID-19
Lopinavir and Ritonavir (LPV/RTV; Kaletra®)	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]	**COVID-19 Randomized, open-label trial** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard of care (99 pts) vs standard of 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 of care** (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard of 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	**COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily for 14 days [3] **COVID-19:** LPV 400 mg/RTV 100 mg orally twice daily with or without arbidol (200 mg every 8 hours) for up to 21 days [6] **COVID-19:** LPV 400 mg/RTV 100 mg orally with or without interferon (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ribavirin for up to 10 days [5, 13] **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]	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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			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] **COVID-19 Retrospective cohort study** in adults evaluated use of LPV/RTV with or without Arbidol (influenza antiviral not licensed in US). Primary end point was negative conversion rate of coronavirus and progression or improvement of pneumonia. At 7 days, SARS-CoV-2 undetectable in nasopharyngeal specimens in 6/17 pts treated with LPV/RTV alone vs 12/16 pts treated with both drugs; at 14 days, undetectable in 9/17 pts (53%) vs 15/16 pts (94%). [6] **COVID-19 Clinical Experience:** Data accumulating on LPV/RTV used with or without interferon in pts with COVID-19 outside of clinical trials. [5, 12, 14] **SARS and MERS Clinical Experience:** Evidence of some clinical benefit when used in conjunction with ribavirin and/or interferon. [1, 8, 9, 10, 11]	**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]	
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]	Dosage of oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours. [1] Dosages of oseltamivir from registered trials (either recruiting, or not yet recruiting) vary, but include 300 mg orally daily, 75 mg orally once or twice daily, and 4–6 mg/kg orally (frequency not specified). [5]	No data to date support use in the treatment of COVID-19

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			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)		
Remdesivir	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] Pharmacokinetic data available from evaluations for Ebola	**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** sponsored by NIAID initiated to evaluate safety and efficacy of remdesivir in hospitalized pts with laboratory-confirmed COVID-19 [13] **Various clinical trials** initiated in China and other countries **Compassionate use access:** May be available from manufacturer (Gilead) for pts with confirmed COVID-19 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]	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

SUPPORTING AGENTS

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Corticosteroids (general)	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 corticosteroids in patients with SARS and MERS showed no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes). [1] Systemic corticosteroid therapy (e.g., dexamethasone) has been studied for the treatment of acute respiratory distress syndrome (ARDS). [8, 9] Conflicting results reported for use of corticosteroids (e.g., hydrocortisone) for treatment of sepsis. [4]		WHO and CDC recommend that corticosteroids **not** be routinely used in patients with COVID-19 for treatment of viral pneumonia or ARDS unless indicated for another reason (e.g., asthma or COPD exacerbation, septic shock). [1, 2, 3, 8, 9] Existing evidence is inconclusive for treatment of COVID-19 patients. [3, 5, 7] Prudent use with low-to-moderate doses and short courses of treatment advised. [7, 8] **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] 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

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					difference in efficacy of corticosteroids in different patient populations, including those with septic shock, pneumonia, or ARDS. [4] For treatment of sepsis, clinicians considering corticosteroids for patients with COVID-19 should balance the potential small reduction in mortality with potential effects of prolonged coronavirus shedding. [1] If corticosteroids prescribed, monitor and treat adverse effects including hyperglycemia, hypernatremia, and hypokalemia. [1, 4]
Methylprednisolone (DEPO-Medrol®, SOLU-Medrol®)	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 this retrospective study not provided. [6] Based on expert consensus statement from Chinese Thoracic Society, dosage of methylpredniso-lone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent). [7] Regimens used in China were typically methylpredniso-lone 40-80 mg IV daily for a course of 3-6 days. [8]	Findings suggest that for patients with COVID-19 pneumonia who progressed to ARDS, methylprednisolone treatment may be beneficial. Results should be interpreted with caution because of potential bias (drug used in sickest patients) and small sample size. Randomized controlled studies are needed. [6]
Nitric oxide (inhaled)	48:48 Vasodilating agent	To treat acute respiratory distress syndrome (ARDS), a potential complication of respiratory viruses such as coronaviruses [2, 3]	In vitro evidence indicates that inhaled nitric oxide can inhibit replication of severe acute respiratory syndrome coronavirus (SARS-CoV)[1] Results of a small pilot study conducted in China during the SARS-CoV outbreak in 2004 showed that treatment with inhaled nitric oxide reversed pulmonary hypertension, improved severe hypoxia, and shortened the duration of ventilatory support [2, 3]	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]	Therapeutic guidelines state that inhaled nitric oxide may be considered in ARDS patients with severe hypoxemia; however, routine use not recommended because of a lack of mortality benefit and possible harm (e.g., nephrotoxicity) [4, 5, 6] Although no current data specifically on treatment of COVID-19, there are 2 registered clinical trials that will evaluate inhaled nitric oxide (NCT04290871, NCT04290858) in COVID-19 patients [3]

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Sarilumab (Kefzara®)	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 (e.g., fever, organ failure, death) in severely ill patients [1, 2]	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] Clinicaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=2&rank=4	Not available (see Trials or Clinical Experience)	
Sirolimus	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 MER-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®)	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 (e.g., fever, organ failure, death) in severely ill patients [1, 2, 3]	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]	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]	**In China**, tocilizumab can be used to treat coronavirus patients with serious lung damage and high IL-6 levels [2] Published data to support use currently are limited [1]

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			Currently no other known clinical trial evidence supporting efficacy and safety of tocilizumab against Coronavirus [1] **China**: Nonrandomized clinical trial evaluating efficacy & safety in 188 coronavirus patients under way through 5/10/20. **Results not yet available.** Chinese Clinical Trial Registry link: http://www.chictr.org.cn/showproj.aspx?		

OTHER

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)	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 is increased in patients treated with ACE inhibitors or ARBs.[1, 4] 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]
Ibuprofen	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.**

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
					A statement attributed to WHO spokesperson Christian Lindmeier recommending paracetamol and avoiding ibuprofen as a self-medication was widely circulated in the media; however, such a position could not be found on the WHO website or other official sources. WHO has stated "after a rapid review of the literature, is not aware of published clinical or population-based data on this topic." As of 3/18/20 (via Twitter) "WHO does not recommend against the use of ibuprofen." https://twitter.com/WHO/status/1240409217997189128 In addition, there have been unsubstantiated reports of younger, healthy patients who took ibuprofen and suffered severe outcomes with COVID-19. Official case reports are lacking. On 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.**

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

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

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