The Medical Letter®
on Drugs and Therapeutics

Treatments Considered for COVID-19 (Updated July 6, 2020)

The table below lists pertinent evidence on the clinical effectiveness and safety of some drugs and other therapies being considered for COVID-19. Most authorities recommend use of these drugs only in the setting of a clinical trial or when access via clinical trial is not available. **Inclusion in this table is not a recommendation for use for treatment of COVID-19.** The information on these drugs is evolving rapidly and The Medical Letter does not warrant that all the material in this publication is current, accurate, or complete in every respect.

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INVESTIGATIONAL DRUGS

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antivirals			
FAVIPIRAVIR – *AVIGAN* (FUGIFILM) **Dosage:** ▪ 1600 mg PO bid on day 1, then 600 mg bid on days 2-7[1] ▪ Some suggest a dosage of 2400-3000 mg bid on day 1, then 1200-1800 mg bid[2]	**Q Cai et al. 2020**[1] **Population:** hospitalized, non-severe (n=80) **Design:** open-label, non-randomized **Results:** shorter viral clearance time (4 vs 11 days) and improvements in chest CT (91.4% vs 62.2%) with favipiravir vs lopinavir/ritonavir; results should be interpreted with caution[1] **Chen et al. 2020**[3] **Population:** hospitalized patients (n=236) **Design:** ▪ randomized, open-label ▪ favipiravir vs arbidol (an influenza drug not available in the US); both in addition to standard therapy **Results:** ▪ clinical recovery rate at day 7 was similar for favipiravir and arbidol (51.67% vs 61.21%; p=0.1396) ▪ in patients with moderate disease, clinical recovery rates were higher with favipiravir than arbidol (71.43% vs 55.86%; p=0.0199) **Limitations**: ▪ not peer-reviewed	**Adverse Effects:** ▪ Elevated LFTs, diarrhea, and elevated serum uric acid **Drug Interactions:** ▪ May increase serum concentrations of some drugs such as acetaminophen, penicillins, tazobactam, repaglinide, pioglitazone and rosiglitazone, oseltamivir, theophylline, and progestins	▪ Not FDA-approved and not available yet in the US; approved in other countries for treatment of influenza ▪ Viral RNA polymerase inhibitor ▪ Limited data available to date; may be less effective for patients with more severe disease ▪ Randomized controlled trial of favipiravir alone and in combination with tocilizumab ongoing in China **Pregnancy:** ▪ Contraindicated for use in pregnant women[4] ▪ Teratogenic effects in animal studies ▪ Men taking the drug should avoid intercourse with pregnant women during treatment and for at least 7 days after the last dose

1. Q Cai et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Available at : https://www.researchgate.net/publication/340000976_experimental_treatment_with_favipiravir_for_covid-19_an_open-label_control_study. Accessed April 2, 2020.
2. JM Sanders et al. Pharmacologic treatment for coronavirus disease 2019 (COVID-19). A review. JAMA 2020 April 13 (epub).
3. C Chen et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. Available at: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v2.article-info. Accessed April 1, 2020.
4. FG Hayden and N Shindo. Influenza virus polymerase inhibitors in clinical development. Curr Opin Infect Dis. 2019; 32:176.

REMDESIVIR (GILEAD)

Dosage[1]:

- Adults ≥40 kg: 200 mg IV on day 1, then 100 mg IV once/day for a total of 5 or 10 days[2]
- Infuse over 30-120 minutes
- In addition to standard care
- Not recommended if eGFR <30 ml/min or ALT >5x ULN
- NIH guidelines recommend a duration of 5 days for hospitalized patients with severe COVID-19 who are not intubated; duration may be extended up to 10 days for mechanically ventilated patients, those on extracorporeal membrane oxygenation, or in those who have not improved after 5 days of treatment

NIAID. ACTT-1. NEJM 2020[3] *(added 5/4/20; updated 5/25/20)*

Population: 1063 hospitalized patients with advanced disease and lung involvement (88.7% had severe disease)

Design:

- randomized, double-blind, placebo-controlled trial in US, Europe and Asia
- 200 mg on day 1, then 100 mg once/day days 2-10 or until discharge or death
  median time from symptom onset to randomization was 9 days

Results:

- recovery time 31% shorter with remdesivir (11 days vs 15 days with placebo ; p<0.001)
- lower mortality rate at 14 days (7.1% vs 11.9%; not statistically significant)
- effect appeared to be greatest in hospitalized patients requiring oxygen (baseline ordinal score of 5; this category had largest sample size); mortality difference between remdesivir and placebo groups appeared smaller in patients who did not require oxygen (ordinal score of 4) and in those who required mechanical ventilation (ordinal score of 6)

Limitations:

- preliminary report

Adverse Effects:

- Safety not established; additional data needed
- Elevated liver enzymes and infusion-related reactions, including hypotension, nausea, vomiting, sweating, and shivering

Drug Interactions: *(updated 6/18/2020)*

- No human drug trial conducted
  Substrate for CYP2C8, CYP2D6, and CYP3A4, and for Organic Anion Transporting Polypeptides 1B1 (OAPT1B1) and P-glycoprotein (Pgp) transporters *in vitro*.[2] Strong inducers of these enzymes/transporters may decrease serum concentrations of remdesivir[5,6]
- Inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP.
- Clinical relevance has not been established.
- FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[12] *(added 6/18/2020)*
- Broad-spectrum nucleotide analog prodrug that inhibits viral RNA replication by blocking RNA-dependent RNA polymerase
- Has *in vivo* and *in vitro* activity against Ebola virus and coronaviruses (MERS and SARS) and *in vitro* activity against SARS-CoV-2
- NIH guidelines recommend remdesivir in hospitalized patients with SpO_2≤94% on ambient air or those who require supplemental oxygen and in those on mechanical ventilation or extracorporeal membrane oxygenation[7] *(updated 6/16/2020)*
- NIH guidelines state there are insufficient data to recommend for or against use in patients with mild or moderate COVID-19[7] *(updated 6/16/2020)*
- Available FDA issued an Emergency Use Authorization on May 1, 2020 to allow use of remdesivir for treatment of COVID-19 in hospitalized patients with severe illness (SpO2 ≤ 94% on room air or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation [ECMO])[2] *(added 5/4/2020)*
- 31% shorter recovery time with remdesivir (11 days vs 15 days with placebo) reported in a randomized, double-blind trial *(updated 5/25/2020)*[3]

REMDESIVIR (CONTINUED)

J Grein et al. NEJM 2020[4]

Population: 53 hospitalized patients in US, Canada, Europe and Japan with SaO_2 ≤94% on O_2 or room air (n=61)
- 57% on mechanical compassionate ventilation

Design:
- report on use

Results:
- median follow-up 18 days
- 68% had improvement in O_2 support class; 57% were extubated; 47% discharged; 18% died

JD Goldman et al. NEJM 2020[9]

Population: hospitalized patients w/oxygen saturation ≤94% on ambient air, radiologic evidence of pneumonia

Design:
- randomized, open-label (n = 397)
- remdesivir x 5 days vs 10 days

Results:
- baseline clinical status significantly worse in patients in the 10-day group
- no significant differences between 5 and 10 days of treatment were reported
- 64% in the 5-day group and 54% in the 10-day group achieved clinical improvement of ≥2 points on a 7-point ordinal scale by day 14
- in a post-hoc analysis, among patients on mechanical ventilation or ECMO at day 5, 40% in the 5-day group died by day 14 vs 17% in the 10-day group

Limitations: open-label, no placebo group

- An editorial in NEJM suggests priority be given to a 5-day course of remdesivir for patients at early stages of severe disease[10]

Pregnancy:
- No data are available in pregnant women

REMDESIVIR (CONTINUED)	**SIMPLE Trial 2020**[11] *(added 6/1/2020)* **Population:** hospitalized patients with moderate COVID-19 (pneumonia, but not reduced oxygen levels) (n = 584) **Design:** randomized, open-label; remdesivir x 5 days or 10 days in addition to standard care or standard care alone **Results:** ▪ significantly more patients taking remdesivir x 5 days had clinical improvement of ≥1 point on an ordinal scale than those who received standard care alone (76% vs 66%; p=0.026) ▪ treatment with remdesivir x 10 days did not reach statistical significance (70% vs 66%) **Limitations:** not yet published

1. Dosage used for treatment of COVID-19.
2. https://www.fda.gov/media/137566/download
3. JH Beigel et al. Remdesivir for the treatment of Covid-19 – preliminary report. N Engl J Med 2020 May 22 (epub).
4. J Grein et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med 2020 April 10 (epub).
5. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.
6. Interactions with experimental COVID-19 therapies. Liverpool Drug Interaction Group, Pharmacology Research Labs, University of Liverpool. Available at: www.covid19-druginteractions.org. Accessed March 27, 2020.
7. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed June 16, 2020.
8. FDA. Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Accessed May 4, 2020.
9. JD Goldman et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020 May 27 (epub).
10. R Dolin and MS Hirsch. Remdesivir – an important first step. N Engl J Med 2020 May 27 (epub).
11. Gilead Press Release. June 1, 2020. Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19. Accessed June 1, 2020.
12. FDA. Remdesivir by Gildead Sciences: FDA warns of newly discovered potential drug interaction that may reduce effectiveness of treatment. June 15, 2020. Available at: https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce. Accessed June 18, 2020.

Convalescent Plasma

CONVALESCENT PLASMA

Dosage:

- Optimal dosage not established
- One or two 200-ml infusions[1]

- Case series of 5 critically ill patients with COVID-19 and ARDS in China; administration of convalescent plasma improved clinical status (e.g., body temperature normalized, viral load decreased, antibody titers increased, ARDS resolved, weaning from mechanical ventilation).[2]
- Case series of 10 patients with severe COVID-19; clinical symptoms improved within 3 days and improvement in lung lesions reported within 7 days[3]
- Clinical trials underway in the US

Adverse Effects:

- No severe adverse effects were reported in case series
- Risks expected to be similar to those of other transfusions
- Transfusion-transmissible infection risk is very low in the US
- Allergic transfusion reactions, transfusion associated circulatory overload (TACO), and transfusion related acute injury (TRALI)
- Theoretical risk of antibody-dependent enhancement (ADE) presumably due to antibodies from previous infection with other coronaviruses
- May lower natural immune response when given for prophylaxis

- Passive antibody therapy by infusion of convalescent plasma may prevent infection or reduce severity of illness[1]
- Used previously for treatment of SARS-CoV-1, MERS, Ebola, and H1N1 influenza
- Most likely to be effective when given as prophylaxis or early in the course of disease
- Clinical trials underway in the US
- NIH guidelines state there are insufficient clinical data to recommend either for or against use of convalescent plasma[4]
- Surviving Sepsis Campaign guidelines suggest against routine use of convalescent plasma in critically ill adults[5]
- The FDA is allowing access through expanded access and single patient emergency protocols[6]

ARDS = acute respiratory distress syndrome

1. E Bloch et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020 April 7 (In press: preview).
2. C Shen et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 March 27 (epub).
3. K Duan et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. Medrxiv 2020 March 16.
4. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed April 28, 2020.
5. W Alhazzani et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19. Crit Care Med 2020 March 27 (epub). Available at: https://journals.lww.com/ccmjournal/abstract/onlinefirst/surviving_sepsis_campaign__guidelines_on_the.95707.aspx. Accessed June 8, 2020.
6. FDA. Recommendations for investigational COVID-19 convalescent plasma. Available at: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed April 14, 2020.

Intravenous Immune Globulin (IVIG)

INTRAVENOUS IMMUNE GLOBULIN (IVIG)
(added 6/8/2020)

Dosage:

- Optimal dosage for COVID-19 unclear
- Phase 3 trial of *Octagam* will use a dosage of 0.5 g/kg IV infusion over 2 hours x 4 days

W Cao et al. Open Forum Infect Dis 2020[1]
Population: Hospitalized patients in China with severe disease and deteriorating course (n = 3)
Design: Case series; patients received IVIg at the start of respiratory distress
Results: all 3 patients had clinical improvement; no fever within 1-2 days, alleviation of breathing difficulties in 3-5 days
Limitations: small case series, 2 patients also received antivirals, 1 received steroids

Xie et al. J Infect 2020[2]
Population: ICU patients with severe or critical illness in Wuhan, China (n=58)
Design: retrospective review of 58 cases
Results: administration of IVIG within 48 hrs of hospital admission was associated with reduced 28-day mortality, shorter hospital stay, and reduced ventilator use compared to administration after 48 hours
Limitation: small retrospective study

Adverse Effects: rarely can case anaphylaxis, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury

- Used for treatment of immune disorders and as an adjunct for treatment of severe pneumonia in influenza patients; modulates immune inflammation, improves passive immunity
- Existing IVIG product unlikely to contain antibodies against SARS-CoV-2
- FDA approved an investigational new drug application (IND) for a phase 3 trial with *Octagam* 10% in COVID-19 patients with severe disease progression (SpO2≤93%, requiring oxygen supplementation)[4]
- Surviving Sepsis Campaign guidelines suggest against routine use of standard IVIG in critically ill adults[5]
- NIH guidelines recommend against use of non-SARS-CoV-2-specific IVIG outside of the context of a clinical trial for treatment of COVID-19; they state this should not preclude use of IVIG when otherwise indicated for treatment of complications arising during the course of COVID-19 illess[6]
- Shortages have been an issue (even prior to COVID-19)

INTRAVENOUS IMMUNE GLOBULIN (IVIG) (CONTINUED)	**Shao et al. 2020[3]** **Population:** Hospitalized severely and critically ill patients (n=325) **Design:** multicenter retrospective cohort study **Results:** ▪ IVIG not associated with improved 28- or 60-day mortality compared to no IVIG in overall cohort ▪ Duration of hospitalization and disease were longer in patients treated with IVIG than in those who were not ▪ In a subgroup analysis, IVIG was associated with reduced 28-day mortality in critically ill patients **Limitation:** not peer reviewed, IVIG group more likely to have coronary heart disease and severe COVID-19

1. W Cao et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis 2020; 7:ofaa102.
2. Y Xie et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infec 2020 April 10 (epub).
3. Shao et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: a multicenter retrospective cohort study. 2020 April 13. Available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3576827. Accessed June 17, 2020.
4. FDA approves Octapharma USA investigational new drug application for severe COVID-19 patients. Press release May 20, 2020. Available at: https://www.octapharma.com/news/press-release/2020/fda-approves-octapharma-usa-investigational-new-drug-application/. Accessed June 8, 2020.
5. W Alhazzani et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19. Crit Care Med 2020 March 27 (epub). Available at: https://journals.lww.com/ccmjournal/abstract/onlinefirst/surviving_sepsis_campaign__guidelines_on_the.95707.aspx. Accessed June 8, 2020.
6. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed June 8, 2020.

Glutathione and N-acetylcysteine

GLUTATHIONE

Dosage: 2 g IV/PO used in case report[1]

N-ACETYLCYSTEINE (NAC; GLUTATHIONE PRECURSOR)
6 g/day IV[2]

(Added 4/28/2020)

No clinical trial results available

Trial recruiting in the US using NAC in severely or critically ill patients[2]

R Horowitz et al. Resp Med Case Rep 2020[1] Case Report

Population: Two patients with COVID-19 pneumonia

Regimen: 2 g IV/PO glutathione

Adverse Effects:
- Nausea, vomiting, other gastrointestinal symptoms, and rash, with or without fever
- Anaphylactoid reactions to IV acetylcysteine, including rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension have occurred.

Pregnancy:
- Acetylcysteine crosses the placenta

- Intracellular anti-oxidant with possible antiviral properties
- One researcher has hypothesized that glutathione deficiency is risk factor for severe COVID-19 illness
- NAC has been proposed for treatment of multiple respiratory conditions and viral illnesses

1. RI Horowitz et al. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: a report of 2 cases. Resp Med Case Rep 2020 April 21 (epub).
2. Memorial Sloan Kettering Cancer Center. A study of N-acetylcysteine in patients with COVID-19 infection. In progress. Available at: https://clinicaltrials.gov/ct2/show/nct04374461?term=acetylcysteine&cond=covid&draw=2&rank=1

Stem Cell Therapy

REMESTEMCEL-L – RYONCIL (MESOBLAST)

(Added 4/28/2020)

- 10 patients with ARDS treated under the FDA compassionate use program with encouraging results
- Randomized clinical trial to be conducted at Mount Sinai in NY
- **Results:** Dyspnea improved within 1 hour of administration

- Risks in patients with COVID-19 not established
- Well tolerated in trials reported by the manufacturer in children with GVHD

- Allogenic stem cell therapy
- Previously studied in children with graft-versus-host-disease (GVHD) after bone marrow transplant; GVHD result of a cytokine storm
- May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease by decreasing production of proinflammatory cytokines, increased production of anti-inflammatory cytokines, and recruitment of anti-inflammatory cells

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Dexamethasone			
DEXAMETHASONE *(updated 6/29/2020)* ▪ 6 mg PO or IV daily x 10 days used in RECOVERY trial	**Horby et al. RECOVERY Trial 2020**[1] **Population:** hospitalized patients in the UK (n=6425) **Design:** ▪ Randomized, controlled, open-label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone ▪ Dexamethasone 6 mg PO or IV once daily x 10 days vs usual care **Results:** 28-day mortality rates (dexamethasone vs usual care) ▪ Overall: 21.6% vs 24.6% (p<0.001) ▪ Patients on invasive mechanical ventilation: 29.0% vs 40.7% (P<0.001) ▪ Oxygen without invasive mechanical ventilation: 21.5% vs 25.0% (p=0.002) ▪ No respiratory support at randomization: 17.0% vs 13.2% (p=0.14) **Limitation:** not yet peer-reviewed	**Adverse Effects:** hyperglycemia, insomnia, adrenal suppression, delirium, depression, mania **Drug Interactions:** ▪ Induces CYP3A4 and P-gp and may decrease concentrations of drugs that are substrates of CYP3A4 or P-gp ▪ Causes hyperglycemia; may decrease the efficacy of antihyperglycemic drugs	▪ Widely available corticosteroid ▪ May modulate immune-mediated lung damage ▪ Authors of RECOVERY trial state that treating 8 ventilated patients or 25 patients requiring oxygen would prevent 1 death[2] ▪ NIH guidelines recommend use of dexamethasone 6 mg daily for up to 10 days mechanically ventilated patients and those who are not mechanically ventilated, but require supplemental oxygen[3] ▪ IDSA guidelines recommend use of dexamethasone for hospitalized patients with severe illness (patients with $SpO_2 \leq 94\%$ on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO)[4] ▪ NIH and IDSA recommend against use of dexamethasone for treatment of COVID-19 in patients who do not require supplemental oxygen[3,4] **Pregnancy:** ▪ Monitor for hypoadrenalism in newborns of mothers who received substantial doses

1. P Horby et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv. 2020 June 22. Available at: https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1. Accessed June 23, 2020.
2. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19. June 16, 2020. Available at: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Accessed June 17, 2020.
3. NIH. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/ Accessed June 29, 2020
4. A Bhimraj et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis 2020 June 25 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
IL-6 Inhibitors			
SARILUMAB – *KEVZARA*[1] (SANOFI/REGENERON) **Dosage:** ▪ No clinical trial data yet ▪ Optimal dosage not established ▪ High and low IV doses are expected to be studied	▪ US-based phase 2 and 3 clinical trials ongoing[2] ▪ Preliminary results have suggested that the drug may have negative or no effects in patients with severe illness (on oxygen therapy, not on ventilator/in ICU), but may be beneficial in critically ill patients (on a ventilator/requiring ICU) *(updated May 4, 2020)* ▪ Phase 3 trials will continue to enroll critical patients only ○ U.S. phase 3 trial in mechanically ventilated patients has been stopped because the trial did not meet primary or key secondary endpoints and negative trends were found in a subgroup of critically ill patients who were not mechanically ventilated at baseline[11] *(updated 7/6/2020)*	**Adverse Effects:** ▪ Neutropenia, thrombocytopenia, serious infections, hypersensitivity reactions including anaphylaxis **Drug Interactions:** ▪ May normalize CYP enzyme formation; could increase metabolism and decrease serum concentrations of drugs with narrow therapeutic indices that are metabolized by CYP isozymes ▪ Hematologic toxicity may be additive with other drugs such as linezolid, clozapine, or azathioprine	▪ Monoclonal antibody that inhibits IL-6 receptors; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-6 inhibitors[3] *(updated 4/28/2020)* **Pregnancy:** ▪ Crosses the placenta, especially in the third trimester, and may affect the immune response in an exposed infant ▪ Parturition is associated with IL-6 increases in the cervix and myometrium; inhibition of IL-6 may lead to possible delays of parturition ▪ Not associated with embryotoxic or teratogenic effects when given in high doses to pregnant monkeys

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB – *ACTEMRA*[4] (GENENTECH) **Dosage:** ▪ Optimal dosage not established ▪ 8 mg/kg (max 400 mg) IV once[5] ▪ Infuse over 1 hour ▪ Optimal timing of administration is unclear	**Zhou et al. Lancet 2020[6]** **Population:** hospitalized patients in China (n=191) **Design:** retrospective study **Results:** elevated levels of IL-6 were associated with severe illness and death **Xu et al 2020[7]** **Population:** hospitalized patients with severe or critical illness and elevated IL-6 levels; (n=20) **Design:** case series; tocilizumab added to standard care **Results:** ▪ improvement in fever (all patients), oxygen requirement (75% of patients), reduction in CRP levels (in 82.4% of patients), lung opacities on CT scan improved (90.5% of patients) **Limitations:** ▪ not peer-reviewed **CORIMUNO-19** *(added 5/4/2020)* **Population:** hospitalized patients in France with moderate to severe illness not requiring ICU care upon admission (n=129) **Design:** open-label'; tocilizumab added to standard care vs standard care alone **Results:** ▪ significantly fewer patients who received tocilizumab died or required ventilation at day 14 **Limitations:** open-label; not yet published	**Adverse Effects:** ▪ Neutropenia, thrombocytopenia, serious infections, hypersensitivity reactions including anaphylaxis **Drug Interactions:** ▪ May normalize CYP enzyme formation; could increase metabolism and decrease serum concentrations of drugs with narrow therapeutic indices that are metabolized by CYP isozymes ▪ Hematologic toxicity may be additive with other drugs such as linezolid, clozapine, or azathioprine	▪ Monoclonal antibody that inhibits IL-6 receptors; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ Surviving Sepsis Campaign guidelines state that there is insufficient evidence to make a recommendation on use of tocilizumab[8] ▪ Infectious Diseases Society of America recommends use only in the context of a clinical trial[9] ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-6 inhibitors[3] *(updated 4/28/2020)* ▪ Randomized, controlled trials are ongoing in the US **Pregnancy:** ▪ Crosses the placenta, especially in the third trimester, and may affect the immune response in an exposed infant ▪ Parturition is associated with IL-6 increases in the cervix and myometrium; inhibition of IL-6 may lead to possible delays of parturition ▪ Increased incidence of abortion/ embryo-fetal death when given to pregnant monkeys during the period of organogenesis

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**Somers et al. 2020[10]** *(added 6/18/2020)* **Population:** hospitalized patients requiring mechanical ventilation (n=154); tocilizumab-treated patients were younger and less likely to have chronic pulmonary disease **Design:** single-center cohort; patients treated with tocilizumab vs patients not treated with tocilizumab **Results:** ▪ tocilizumab was associated with a reduced risk of death (hazard ratio 0.55) ▪ tocilizumab was associated with an increased risk of superinfections (54% in tocilizumab-treated patients vs 25% in tocilizumab-untreated patients) **Limitation:** not peer reviewed		

1. FDA-approved for treatment of rheumatoid arthritis.
2. Clinical trials information available at: https://clinicaltrials.gov/ct2/show/nct04315298?Term=sarilumab&draw=2&rank=4. Accessed March 31, 2020.
3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed April 28, 2020.
4. FDA-approved for chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome, rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis.
5. Experimental dosage used for treatment of COVID-19 in trials; optimal dosage not established.
6. F Zhou et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054.
7. X Xu et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available at: http://chinaxiv.org/abs/202003.00026. Accessed March 31, 2020.
8. W Alhazzani et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19. Crit Care Med 2020 March 27 (epub). Available at: https://journals.lww.com/ccmjournal/abstract/onlinefirst/surviving_sepsis_campaign__guidelines_on_the.95707.aspx. Accessed April 1, 2020.
9. A Bhimraj et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed April 13, 2020.
10. EC Somers et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Medrxiv. 2020 May 29 (preprint). Available at: https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1. Accessed June 29, 2020.
11. Press Release. Regeneron and Sanofi provide update on Kevzara (sarilumab) Phase 3 U.S. trial in COVID-19 patients. Available at: https://www.prnewswire.com/news-releases/regeneron-and-sanofi-provide-update-on-kevzara-sarilumab-phase-3-us-trial-in-covid-19-patients-301087849.html. Accessed July 6, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
IL-1 Receptor Antagonist			
ANAKINRA – *KINERET* (BIOVITRUM AB) *(updated 5/9/2020)* **Dosage:** ▪ Optimal dosage for COVID-19 unknown[1,2,3] ▪ In a trial being conducted by the manufacturer, anakinra is being administered IV at a dosage of 100 mg q6h x 15 days. According to US *Kineret* labeling, the drug is indicated for SC administration.	**Cavalli et al. Lancet Rheum 2020[4]** **Population:** consecutive hospitalized patients with moderate-to-severe ARDS and serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both; not on mechanical ventilation **Design:** retrospective cohort study; single hospital in Itay ▪ Addition of anakinra vs standard treatment (HCQ + LPV/RTV) **Results:** at 21 days ▪ Improved survival with high-dose (5 mg/kg IV bid) anakinra vs standard treatment (90% vs 56%; p=0.009) ▪ Mechanical ventilation-free survival similar between groups (72% vs 50%; p=0.15) ▪ Associated with reduced serum C-reactive protein and improved respiratory function **Limitations:** small, retrospective study	**Adverse Effects:** ▪ Injection-site reactions, infections, neutropenia, thrombocytopenia, hepatic transaminase elevations **Drug Interactions:** ▪ Use with TNF inhibitors or other biologics may increase risk of serious infections and neutropenia and should be avoided	▪ Clinical trials are ongoing[1,2] ▪ IL-1 receptor antagonist; IL-1 mediates inflammatory and immune responses antagonist ▪ May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors[3] *(updated 4/28/2020)* ▪ FDA-approved for treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease. **Pregnancy:** ▪ Not associated with adverse pregnancy outcomes in small retrospective studies in humans or in animal studies

1. Efficacy and safety of emapalumab and anakinra in reducing hyperinflammation and respiratory distress in patients with covid-19 infection. Available at: https://clinicaltrials.gov/ct2/show/nct04324021?term=anakinra&cond=covid&draw=2&rank=1**.** Accessed April 14, 2020.
2. Treatment of COVID-19 patients with anti-interleukin drugs (COV-AID). Available at: https://clinicaltrials.gov/ct2/show/nct04330638**.** Accessed April 14, 2020.
3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/**.** Accessed April 28, 2020.
4. G Cavalli et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheum 2020 May 7 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Janus Kinase (JAK) Inhibitors			
BARICITINIB – *OLUMIANT* (LILLY) **Dosage:** ▪ Optimal dosage for COVID-19 not established ▪ 2 mg PO daily	▪ The manufacturer in an agreement with the National Institute of Allergy and Infectious Diseases (NIAID) is studying baricitinib in hospitalized patients as an arm in NIAID's Adaptive COVID-19 Treatment Trial	**Adverse Effects:** ▪ Nausea is common ▪ Serious, sometimes fatal, infections, including multi-dermatomal herpes zoster and tuberculosis (TB) ▪ Serious, sometimes fatal, thromboembolic events ▪ Malignancy, GI perforation, neutropenia, lymphopenia, anemia, thrombocytosis, and elevations in liver enzymes, creatine phosphokinase levels, and lipid levels have also been reported **Drug Interactions:** ▪ The strong organic anion transporter 3 (OAT3) inhibitor probenecid doubled baricitinib exposure; concurrent use of with strong OAT3 inhibitors is not recommended	▪ FDA-approved for treatment of rheumatoid arthritis ▪ Inhibits JAK enzymes, which mediate signaling of proinflammatory cytokines including IL-6; may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease ▪ NIH recommends against use of JAK inhibitors, except in the context of a clinical trial, because of their broad immunosuppressive effect[1] (updated 4/28/2020) ▪ Should not be used in patients with severe hepatic impairment (Child-Pugh C) or moderate or severe renal impairment (eGFR <60 mL/min/1.73 m2) ▪ Treatment should be withheld if the absolute lymphocyte count falls below 500 cells/mm^3, the absolute neutrophil count falls below 1000 cells/mm^3, or the hemoglobin level falls below 8 g/dL **Pregnancy:** ▪ Administration to pregnant animals resulted in reduced fetal weights, embryolethality, and skeletal malformations

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
RUXOLITINIB – *JAKAFI* (INCYTE/NOVARTIS) **Dosage:** ▪ Optimal dosage not established ▪ 10 mg PO bid x 14 days[2] ▪ Taper dosage when stopping: 5 mg bid x 2 days, then 5 mg once daily x 1 day	▪ Manufacturer is initiating phase III clinical trials in patients with severe COVID-19 to compare ruxolitinib to standard care[3,4]	**Adverse Effects:** ▪ Most common adverse effects include thrombocytopenia, anemia, fatigue, diarrhea, bruising, dizziness, dyspnea, and headache ▪ Severe withdrawal symptoms including a systemic inflammatory response syndrome have been reported when ruxolitinib was stopped **Drug Interactions:** ▪ Strong CYP3A4 inhibitors can increase serum concentrations of ruxolitinib (ketoconazole increased ruxolitinib AUC by 91%) ▪ Concurrent use of ruxolitinib with a strong CYP3A4 inhibitor[5] should be avoided in patients with platelet counts less than 100 X 10^9/L; dosage reductions may be needed for patients with a platelet count ≥100 X 10^9 /L	▪ NIH recommends against use of JAK inhibitors, except in the context of a clinical trial, because of their broad immunosuppressive effect[1] *(updated 4/28/2020)* ▪ *Jakavi* outside the US ▪ FDA-approved for treatment of myelofibrosis ▪ Inhibits JAK1 and 2, which mediate signaling of proinflammatory cytokines including IL-6; may mitigate the effects of cytokines release in response to the virus and limit lung damage in patients with severe disease ▪ Manufacturer initiating an open-label emergency Expanded Access Plan (EAP) in the US ▪ Should be avoided in patients with end stage renal disease (CrCl <15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment or hepatic impairment and a platelet count <100 X 10^9/L **Pregnancy:** ▪ No adequate studies in pregnant women ▪ Administration of ruxolitinib to pregnant animals resulted in an increase in late resorptions and reduced fetal weights

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2. Dosage to be used in clinical trials for COVID-19.
3. Study of the efficacy and safety of ruxolitinib to treat COVID-19 pneumonia. Available at: https://clinicaltrials.gov/ct2/show/nct04331665?term=covid&cond=ruxolitinib&draw=2&rank=1. Accessed April 6, 2020.
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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antimalarials			
CHLOROQUINE[1] **Dosage:** ▪ Optimal dosage not established ▪ Dosages used in COVID-19 clinical trials have varied 500 mg chloroquine phosphate (300 mg chloroquine base) bid x 7-10 days OR 500 mg bid x 2 days, then 500 mg once/day x 12 days[2,3] OR 1 g on day 1, then 500 mg once daily x 4-7 days	▪ Based on *in vitro* data (M Wang et al, Cell Res 2020)[4] ▪ Unpublished clinical data from China[3] in approximately 100 patients suggest more rapid decline in fever, improvement on lung CT scan, shorter time to recovery vs control group **ChloroCovid-19**[5] *(updated 4/30/2020)* **Population:** hospitalized patients with severe illness in Brazil (n=81) **Design:** ▪ parallel, double-blind, randomized, phase IIb ▪ chloroquine high dose (600 mg bid x 10 days) vs low dose (450 mg bid x 1 day, then once/day x 4 days); all patients received azithromycin **Results:** ▪ Trial stopped early because of a higher rate of death and QT interval prolongation in the high-dose chloroquine group ▪ Lethality was 39.0% (16 of 41) in the high-dosage group and 15.0% (6 of 40) in the low-dosage group at day 13 ▪ QTc interval >500 milliseconds occurred in 18.9% (7 of 37) in the high-dose group compared to 11.1% (4 of 36) in the low-dosage group ▪ Respiratory secretion negative in 22.2% (6 of 27) at day 4	**Adverse Effects:** ▪ Retinopathy and other ocular disorders (generally associated with longer use), urticaria, angioedema, tinnitus, reduced hearing, myopathy, muscle atrophy, suppressed tendon reflexes, liver enzyme elevations, hepatitis, GI disturbances, skin reactions, cytopenias, hemolytic anemia (in G6PD-deficient patients), neuropathy, convulsions, extrapyramidal disorders, neuropsychiatric changes, hypotension, cardiomyopathy, hypoglycemia ▪ QT interval prolongation and arrhythmias, including torsades de pointes can occur. Risk is higher in patients with cardiac disease, electrolyte abnormalities, or concurrent use of other QT interval prolonging drugs such as azithromycin.[6-8] The AHA/ACC/HRS recommend the drug be withheld in patients with baseline QT prolongation or if QT interval exceeds 500 msec during treatment. Potassium and magnesium levels should be corrected and other QTc prolonging drugs should be avoided.[7] ▪ Cases (some fatal) of QT interval prolongation, ventricular tachycardia, and ventricular fibrillation have been reported in patients being treated with chloroquine or hydroxychloroquine, alone or in combination with azithromycin or other QTc prolonging drugs, for treatment of COVID-19[9]	▪ *In vitro* activity against SARS-CoV-2, SARS-CoV, and MERS-CoV ▪ FDA issued a Drug Safety Communication warning against use of chloroquine outside of a clinical trial because of the risk of serious cardiac arrhythmias, including QT prolongation; it is not recommended for treatment of outpatients[9] (updated 4/28/2020) ▪ Infectious Diseases Society of America recommends use in the context of a clinical trial[12] ▪ NIH guidelines recommend against use of chloroquine, except in a clinical trial[19] *(updated 6/16/2020)* ▪ Clinical trials evaluating the efficacy and safety of chloroquine for pre-exposure and post-exposure prophylaxis and treatment of mild, moderate, or severe COVID-19 are underway in the US ▪ FDA revoked Emergency Use Authorization that allowed use in some hospitalized patients for whom a clinical trial was not feasible; ongoing analysis indicated that chloroquine and hydroxychloroquine are unlikely to be effective for treatment of COVID-19 and are associated with serious cardiac adverse events; FDA concluded benefit no longer outweighs risk[13] *(updated 6/16/2020)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
CHLOROQUINE[1] (CONTINUED)	**Mehra et al. 2020[22]** *(added 5/26/20) (updated 6/4/2020)* *****Study Retracted[24]***** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** hospitalized patients with COVID-19 who received chloroquine or HCQ with or without a macrolide within 48 hrs of diagnosis; control patients did not receive treatment with these drugs (n = 96,032) **Design:** observational analysis of multinational registry **Results:** ▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group **Limitation:** observational	**Drug Interactions:** ▪ Avoid use with QTc prolonging drugs[6-8] ▪ Substrate of CYP2C8, 2D6, and 3A4, and inhibitor of CYP2D6[10,11] ▪ Use with antihyperglycemic drugs can increase risk of hypoglycemia ▪ Separate from antacids/kaolin by 4 hours ▪ Use with tamoxifen can increase risk of ocular toxicity and should be avoided ▪ FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[26] *(added 6/18/2020)*	**Pregnancy:** ▪ Accumulates in fetal ocular tissues and is retained there for months after elimination from remainder of body ▪ Chloroquine has been used safely in pregnant women for treatment and prophylaxis of malaria
HYDROXYCHLOROQUINE (HCQ)[1] – GENERICS *PLAQUENIL* (CONCORDIA) **Dosage:** ▪ Optimal dosage not established ▪ Dosages used in COVID-19 clinical trials have varied	**P Gautret et al. Int J Antimicrob Agents 2020[14]** **Population:** hospitalized patients; varying severity of illness (n=42) **Design:** ▪ open-label, observational ▪ HCQ + azithromycin vs HCQ vs standard care **Results:** ▪ HCQ-treated patients had more rapid viral clearance vs controls	**Adverse Effects:** ▪ Better tolerated than chloroquine ▪ Retinopathy and other ocular disorders (sometimes irreversible, but generally associated with longer use), serious cardiomyopathy, worsening of psoriasis and porphyria, proximal myopathy, neuropathy, suicidality, hypoglycemia ▪ QT interval prolongation and arrhythmias, including torsades de pointes can occur.	▪ *In vitro* activity against SARS-CoV-2 ▪ Weak data in COVID-19 in humans ▪ The FDA issued a Drug Safety Communication warning against use of hydroxychloroquine outside of a clinical trial because of the risk of serious arrythmias, including QT prolongation it; is not recommended for treatment of outpatients[9] (updated 4/28/2020)

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED) ▪ Most frequently used dosage in the US has been 400 mg PO bid on day 1, then 200 mg PO bid x 4 days[2]	▪ addition of azithromycin to HCQ (n=6) resulted in a more rapid decrease in viral load compared to treatment w/ HCQ alone **Limitations:** ▪ not randomized or double-blind, some dropouts not included in trial results ▪ International Society of Antimicrobial Chemotherapy states concerns about the paper **<u>Z Chen et al. 2020</u>[15]** **Population:** hospitalized patients w/ pneumonia; mild illness (n=62) **Design:** ▪ randomized, parallel-group ▪ hydroxychloroquine 200 mg bid vs standard care **Results:** ▪ shortened duration of fever and cough ▪ pneumonia improvement on chest CT in 80.6% of patients w/ HCQ vs 54.8% w/ standard care ▪ 4 patients in control group progressed to severe illness vs none with HCQ **Limitations:** published online ahead w/o peer review **<u>M Mahevas et al. 2020</u>[16]** **Population:** hospitalized patients with pneumonia requiring oxygen ≥2 L (n=181)	Risk is higher in patients with pre-existing cardiac disease, electrolyte abnormalities or concurrent use of other QT interval prolonging drugs such as azithromycin. EKG monitoring recommended.[6-8] The AHA/ACC/HRS recommend use be avoided in patients with baseline QT prolongation or if QT interval exceeds 500 msec during treatment. Potassium and magnesium levels should be corrected and other QTc prolonging drugs should be avoided.[7] ▪ Cases (some fatal) of QT interval prolongation, ventricular tachycardia, and ventricular fibrillation have been reported in patients being treated with chloroquine or hydroxychloroquine, alone or in combination with azithromycin or other QTc prolonging drugs, for treatment of COVID-19[8] ▪ In a cohort of 84 patients with COVID-19 who were treated with hydroxychloroquine/azithromycin, QTc was significantly prolonged; in 9 (11%) patients, QTc was prolonged to >500 ms[18] **Drug Interactions:** ▪ Avoid use with other QT interval-prolonging drugs. Concurrent use with azithromycin can cause additive effects on the QT interval; avoid coadministration in patients at high risk of QT interval prolongation; ECG monitoring, correction of electrolyte abnormalities, and	▪ Infectious Diseases Society of America recommends use in the context of a clinical trial[12] ▪ NIH guidelines recommend against use of hydroxychloroquine, except in a clinical trial[19] *(updated 6/16/2020)* ▪ NIH recommends against the use of hydroxychloroquine plus azithromycin, except in the context of a clinical trial, because of the potential for toxicities[19] (updated 4/28/2020) ▪ Clinical trials evaluating the efficacy and safety of hydroxychloroquine for pre-exposure and post-exposure prophylaxis and treatment of mild, moderate, or severe COVID-19 are underway in the US ▪ FDA revoked Emergency Use Authorization that allowed use in some hospitalized patients for whom a clinical trial was not feasible; ongoing analysis indicated that chloroquine and hydroxychloroquine are unlikely to be effective for treatment of COVID-19 and are associated with serious cardiac adverse events; FDA concluded benefit no longer outweighs risk[13] *(updated 6/16/2020)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**Design:** ▪ Retrospective; HCQ 600 mg/day within 48 hrs of admission vs no HCQ **Results:** ▪ Transferred to ICU or died w/in 7 days: 20.2% HCQ vs 22.1% w/o HCQ (no significant difference) **Limitations:** not randomized or peer reviewed **J Magagnoli et al 2020[17]** *(updated 4/28/2020)* **Population:** hospitalized male patients in VA medical centers across the US (n=368) **Design:** ▪ Retrospective; HCQ vs HCQ plus azithromycin vs no HCQ **Results:** ▪ No significant difference in the rate of mechanical ventilation between groups (13.3% HCQ, 6.9% HCQ + azithromycin, and 14.1% no HCQ) ▪ Compared to no HCQ, rates of death higher in the HCQ group, but not the HCQ + azithromycin group (11.4% no HCQ vs 27.8% with HCQ and 22.1% with HCQ + azithromycin) **Limitations:** retrospective, not peer reviewed	avoidance of other QT prolonging agents is recommended if coadministered[6-8] ▪ May inhibit CYP2D6 and may be metabolized by CYP2C8, 2D6, and 3A4 to some extent; less likely to cause CYP-related interactions than chloroquine ▪ Separate from antacids/kaolin by 4 hours ▪ May increase digoxin levels ▪ May impair activity of antiepileptic drugs ▪ FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended[26] *(added 6/18/2020)*	**Pregnancy:** ▪ No evidence of increased rate of birth defects in pregnant women ▪ Embryonic deaths and ocular malformations have occurred in pregnant rats

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**J Geleris et al. NEJM 2020[20]** *(added 5/9/2020)* **Population:** consecutive hospitalized patients (n=1376 patients in analysis) **Design:** observational; single medical center in New York City; median follow-up 22.5 days **Results:** ▪ 811 (58.9%) patients treated with HCQ ▪ HCQ-treated patients had more severe illness than those who were not treated with the drug ▪ No significant association between HCQ use and intubation or death (HR 1.04; 95% CI 0.82-1.32) **Limitations:** observational data **W Tang et al. BMJ 2020[21]** *(added 5/18/20)* **Population:** hospitalized patients, mostly mild to moderate disease (n=150) **Design:** open-label HCQ 1200mg x 3 days, then 800 mg/day x2-3 weeks vs standard care **Results:** ▪ No significant difference in probability of negative conversion ▪ Adverse effects more common with HCQ (mainly diarrhea) **Limitations:** open label, tx initiated late, confounding tx allowed		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**Mehra et al. Lancet 2020[22]** *(added 5/26/20)* *(updated 6/4/2020)* ***Study Retracted[24]*** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** hospitalized patients with COVID-19 who received chloroquine or HCQ with or without a macrolide within 48 hrs of diagnosis; control patients did not receive treatment with these drugs (n = 96,032) **Design:** observational analysis of multinational registry **Results:** ▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group **Limitation:** observational		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**<u>WHO Solidarity Trial 2020</u>[23]** *(updated 6/20/2020)* ▪ HCQ arm stopped based on data from the Solidarity trial, the RECOVERY trial, and a Cochrane review of other HCQ evidence ▪ Data showed no reduction of mortality with HCQ **<u>RECOVERY Trial 2020</u>** *(added 6/20/2020)* **Population:** hospitalized adults in the UK (n=4674) **Design:** randomized controlled trial; HCQ vs usual care **Results**: ▪ 28-day mortality was not significantly different between patients treated with HCQ and those who received usual care (25.7% vs 23.5%) ▪ Enrollment in the HCQ arm of the trial has been stopped **Limitations**: data not yet published		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	S Arshad et al. Int J Infect Dis 2020[28] *(added July 7, 2020)* **Population:** Consecutive hospitalized patients in a hospital system in Michigan (n=2541) **Design:** Multi-center, retrospective observational study comparing hydroxychloroquine alone or with azithromycin, azithromycin alone or neither **Results:** ▪ in-hospital mortality was 20.1% with hydroxychloroquine + azithromycin, 13.5% with hydroxychloroquine, 22.4% with azithromycin, and 26.4% with neither drug (p<0.001) ▪ 82% of patients received hydroxychloroquine within 24 hours of admission **Limitations:** retrospective, observational data **PROPHYLAXIS TRIALS:** **DR Boulware et al NEJM 2020[25] (prophylaxis)** *(added 6/4/2020)* **Population:** adults with household or occupational exposure to an individual with confirmed COVID-19 at a distance <6 feet for >10 mins with no mask or eye shield (high-risk) or with a mask but no eye shield (moderate-risk) (n = 821) **Design:** randomized, double-blind, placebo-controlled trial in the US and Canada		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	▪ **Prophylaxis** given within 4 days after exposure ▪ HCQ (800 mg x 1, then 600 mg in 6 to 8 hrs, then 600 mg daily x 4 days) vs placebo **Results:** ▪ 87.6% had a high-risk exposure ▪ New illness compatible with COVID-19 within 14 days was similar between the 2 groups (11.8% HCQ vs 14.3% placebo; p=0.35) ▪ Patient-reported adherence to study drug regimen was lower in HCQ group (75.4% with HCQ vs 82.6% with placebo; p=0.01) ▪ Adverse effects occurred more often with HCQ (GI effects most common) ▪ No arrhythmias or deaths reported **Limitations:** endpoint did not require laboratory-confirmed COVID-19; study population generally younger and healthier than those at most risk for COVID-19 **N White and W Schilling et al (COPCOV trial)**[27] *(added July 1, 2020)* **(prophylaxis)** **Population:** Healthcare workers and staff who have close contact with COVID-19 patients (anticipated enrollment is 40,000+ subjects) **Design:** ▪ Randomized, double-blind, placebo-controlled, multi-center prophylaxis trial ▪ Chloroquine/hydroxychloroquine vs placebo **Results:** trial enrolling as of July 2020		

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DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Macrolide Antibiotic			
AZITHROMYCIN – GENERICS *ZITHROMAX* (PFIZER)[1] **Dosage:** ▪ Optimal dosage not established 500 mg on day 1, then 250 mg once/day on days 2-5[2] ▪ In addition to hydroxychloroquine	**P Gautret et al. Int J Antimicrob Agents 2020[3]** ▪ Addition of azithromycin to hydroxychloroquine (n=6) resulted in a more rapid decrease in viral load compared to hydroxychloroquine treatment alone in one open-label trial in France (see hydroxychloroquine above)	**Adverse Effects:** ▪ GI disturbances, headache, dizziness, hepatotoxicity, QT prolongation[4] **Drug Interactions:** ▪ Use with other drugs that prolong the QT interval (such as chloroquine and hydroxychloroquine) can result in additive effects; avoid coadministration in patients at high risk of QT interval prolongation; ECG monitoring, correction of electrolyte abnormalities, and avoidance of other QT prolonging agents is recommended if coadministered[4-6] ▪ In a cohort of 84 patients with COVID-19 who were treated with hydroxychloroquine/azithromycin, QTc was significantly prolonged; in 9 (11%) patients, QTc was prolonged to >500 ms[7] ▪ May increase the risk of toxicity with digoxin, cyclosporine, tacrolimus	▪ *In vitro* activity against some viruses (influenza A H1N1 and Zika); no data on its activity against SARS-CoV-2 ▪ Minimal data supporting efficacy in COVID-19 in humans and cardiac toxicity can occur when used with chloroquine/hydroxychloroquine ▪ Infectious Diseases Society of America recommends use only in the context of a clinical trial[8] ▪ NIH recommends against the use of hydroxychloroquine plus azithromycin, except in the context of a clinical trial, because of the potential for toxicities (updated 4/28/2020) ▪ Some evidence of immunomodulatory and anti-inflammatory activity; it has been used as adjunctive treatment for other respiratory conditions (such as COPD) **Pregnancy:** ▪ No evidence of fetal harm

1. FDA-approved for other indications.
2. Experimental dosage used for treatment of COVID-19 in trials, but optimal dosage not yet established.
3. P Gautret 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 March 20 (epub).
4. RL Woosley and KA Romero. QT drugs list. Available at: www.crediblemeds.org. Accessed March 31, 2020.
5. DN Juurlink. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ 2020 April 8 (epub).
6. DM Roden et al. Drug interactions on QTc in exploratory COVID-19 treatment. Circulation 2020 April 8 (epub).
7. E Chorin et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020 April 24 (epub).
8. A Bhimraj et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed April 13, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HIV Protease Inhibitors			
ATAZANAVIR[1] (ATV) – *REYATAZ* (BMS) AND GENERICS **Dosage:** ▪ Optimal dosage/duration not established ▪ 300-400 mg PO once/day[2]	▪ Predicted to inhibit SARS-CoV-2 replication[3,4] ▪ No clinical trial data available	**Adverse Effects:** ▪ Nausea, diarrhea, asymptomatic indirect hyperbilirubinemia, rash, nephrolithiasis, cholelithiasis, PR interval prolongation **Drug Interactions:** ▪ Substrate of CYP3A4 and inhibitor of CYP3A4 and CYP2C8[5] ▪ Use of drugs that increase gastric pH, such as PPIs, H2-antihistamines, and antacids may decrease absorption of atazanavir; administer atazanavir 2 hours before or 10 hours after an H2-antihistimine; consider avoiding use of PPIs	▪ No clinical trials available evaluating use of atazanavir for COVID-19 ▪ Available in powder form or capsules can be opened for administration via enteral tube ▪ NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6] **Pregnancy:** ▪ Does not appear to increase the risk of major birth defects
DARUNAVIR/COBICISTAT[1] - *PREZCOBIX* (JOHNSON & JOHNSON) **Dosage:** 800/150 mg PO once/day x 5 days[7]	**Shanghai Public Health Clinical Center (SPHCC)[8,9]** **Population:** hospitalized patients (n=30) **Design:** ▪ randomized, open label ▪ darunavir/cobicistat 800/150 mg once/day x 5 days vs standard care **Results:** ▪ darunavir/cobicistat was **not** effective	**Adverse Effects:** ▪ Nausea, diarrhea, increased transaminases, headache, rash, severe skin reactions (including Stevens-Johnson syndrome) **Drug Interactions:** ▪ Substrate and inhibitor of CYP3A4 and CYP2D6[5]	▪ An initial laboratory study had suggested darunavir (at exposures higher than those achieved in humans) may be effective against SARS-CoV-2 ▪ No evidence that darunavir is effective for treatment of COVID-19 ▪ NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6] **Pregnancy:** ▪ Not recommended for use in pregnant women

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LOPINAVIR/RITONAVIR[1] (LPV/RTV) – *KALETRA* (ABBVIE) **Dosage:** ▪ Optimal dosage/duration not established ▪ Dosages/duration/ concomitant drugs used in COVID-19 clinical trials have varied ▪ 400/100 mg PO bid[2] ▪ With or without food ▪ Tablets should not be crushed (decrease exposure)	**B Cao et al. NEJM 2020[10]** **Population:** ▪ hospitalized patients w/ pneumonia, SaO_2 ≤94% or PaO_2:FiO_2 ≤300 mm Hg (n=199) ▪ median time from symptom onset to randomization was 13 days **Design:** ▪ randomized, open-label vs standard care **Results:** ▪ no statistically significant difference in time to clinical improvement (median of 16 days in both groups), time to discharge (median 12 days with LPV/RTV vs 14 days with standard care), mortality (19.2% vs 25.0%), or viral load reduction **Limitations:** ▪ not blinded ▪ treatment started long after symptom onset	**Adverse Effects:** ▪ Diarrhea, nausea, vomiting, headache, asthenia, hepatoxicity, pancreatitis, PR and QT interval prolongation **Drug Interactions:** ▪ Substrate and inhibitor of CYP3A4[5] ▪ Avoid use with other PR or QT interval-prolonging drugs[11]	▪ *In vitro* activity against SARS-CoV, and MERS-CoV; data in SARS-CoV-2 limited ▪ Society of Critical Care Medicine recommends against use of LPV/RTV in critically ill patients[12] ▪ Infectious Diseases Society of America recommends use only in the context of a clinical trial[13] ▪ NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data[6] **Pregnancy:** ▪ No association with teratogenic effects; may be associated with preterm delivery

1. FDA-approved for other indications.
2. Dosage for treatment of COVID-19 not established.
3. BR Beck et al. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Computational and Structural Biotechnology Journal 2020; 18:784.
4. YC Chang et al. Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking. Available at: file:///C:/Users/smorey/Downloads/preprints202002.0242.v1.pdf. Accessed April 12, 2020.
5. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf.
6. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed April 28, 2020.
7. Dosage used for treatment of COVID-19 in trials; optimal dosage not established.
8. Johnson & Johnson. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. Available at: https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus. Accessed March 31, 2020.
9. Efficacy and safety of darunavir and cobicistat for treatment of pneumonia caused by 2019-nCoV (DACO-nCoV). Available at: https://clinicaltrials.gov/ct2/show/study/NCT04252274. Accessed March 31, 2020.
10. B Cao et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382:1787.
11. RL Woosley and KA Romero. QT drugs list. Available at www.crediblemeds.org. Accessed March 31, 2020.
12. W Alhazzani et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19. Crit Care Med 2020 March 27 (epub). Available at: https://journals.lww.com/ccmjournal/Abstract/onlinefirst/Surviving_Sepsis_Campaign__Guidelines_on_the.95707.aspx. Accessed April 13, 2020.
13. A Bhimraj et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available At: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed April 13, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Interferon Beta and Ribavirin			
INTERFERON BETA-1B – ***BETASERON*** ***EXTAVIA*** **RIBAVIRIN –** ***REBETOL*****, AND GENERICS** *(added 5/14/2020)* **Dosage:** ▪ Optimal dosage unknown ▪ Dosage used in clinical trial: **Interferon beta-1b**: 1 mL on alternate days x 1-3 doses depending on day of initiation **Ribavirin**: 400 mg q12h x 14 days	**Hung et al. Lancet 2020[1]** **Population:** hospitalized patients with symptom duration ≤14 days (n=127) **Design:** ▪ prospective, randomized, open-label, multi-center ▪ LPV/RTV + ribavirin + interferon beta-1b vs LPV/RTV x 14 days ▪ Treatment started within 48 hrs of admission **Results:** ▪ Time to negative nasopharyngeal swab shorter with triple combination vs LPV/RTV (7 vs 12 days; p=0.0010) ▪ Time to alleviation of symptoms: 4 days with combination vs 8 days with LPV/RTV (p<0.0001 **Limitations:** patients presenting ≥7 days from symptom onset did not receive interferon due to concerns about proinflammatory effects; no critically ill patients included	**Adverse Effects:** ▪ Hung et al trial found no difference in adverse events between 2 groups ▪ **Interferon:** injection-site reactions, flu-like symptoms, depression, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia ▪ **Ribavirin:** hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, rash, conjunctival irritation, neuropsychologic symptoms **Drug Interactions:** ▪ **Ribavirin:** may decrease anticoagulant effect of warfarin, increase concentrations of azathioprine, increased risk of hepatic decompensation and lactic acidosis with NRTIs, additive myelosuppression with interferons, linezolid, clozapine, adalimumab	▪ *In vitro* activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies[2] ▪ Society of Critical Care Medicine recommends against use of LPV/RTV in critically ill patients and states the evidence is insufficient to recommend interferons or ribavirin[3] ▪ NIH guidelines recommend against use of interferons because of lack of efficacy in other coronavirus infections and toxicity[4] ▪ If administered, should be given early in course of disease **Pregnancy:** ▪ **Interferon:** may cause fetal harm, based on data from animal studies **Ribavirin:** ▪ contraindicated in pregnant women and in men whose partners are pregnant ▪ pregnancy should be avoided for 6 months after treatment in women who received the drug and in women whose partners received the drug

1. IFN Hung et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020; 396: 1695.
2. E Sallard et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 2020 Available at: https://doi.org/10.1016/j.antiviral.2020.104791. Accessed May 14, 2020.
3. W Alhazzani et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19. Crit Care Med 2020 March 27 (epub). Available at: https://journals.lww.com/ccmjournal/Abstract/onlinefirst/Surviving_Sepsis_Campaign__Guidelines_on_the.95707.aspx. Accessed May 14, 2020.
4. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed May 14, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antiparasitic			
IVERMECTIN – *STROMECTOL* (MSD) **Dosage:** ▪ Dosage for COVID-19 not established 200-400 mcg/kg/dose PO[1]	▪ No data on its efficacy for treatment of COVID-19 ▪ Inhibits SARS-CoV-2 *in vitro*; ~5000-fold reduction in viral RNA in cell culture 48 hours after a single treatment[2]	**Adverse Effects:** ▪ Generally well tolerated when used for treatment of lice; diarrhea has occurred ▪ Diarrhea, nausea, dizziness, pruritis, dermatologic reactions, lymphadenitis, arthralgia, and fever have been reported when used for treatment of onchocerciasis **Drug Interactions:** ▪ Azithromycin may increase serum concentrations of ivermectin	▪ FDA-approved for treatment of intestinal strongyloidiasis and onchocerciasis; used off-label for a variety of other parasitic infections including lice and scabies ▪ Inhibited SARS-CoV-2 *in vitro*; may inhibit nuclear transport activity ▪ Clinical data on its efficacy for treatment of COVID-19 are needed **Pregnancy:** ▪ Limited data available in pregnant women

1. Dosage for other indications. For some indications only a single dose is required, but for others the dose may need to be repeated 2-3 times.
2. L Caly et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020 April 3 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Colchicine			
COLCHICINE *(Added 7/1/2020)* **Dosage:** ▪ Optimal dosage in patients with COVID-19 is unclear	**GRECCO-19 trial[1]** **Population:** Hospitalized patients (n=105) **Design:** ▪ Randomized, open-label trial in Greece ▪ Colchicine plus standard of care vs standard of care alone x 3 weeks **Results:** ▪ Differences in inflammatory biomarkers (high sensitivity cardiac troponin, C-reactive protein) were not statistically significant between groups ▪ The clinical primary endpoint (time from baseline to clinical deterioration, defined as a 2-grade increase on a 7 point scale) occurred in 7 patients (14.0%) in the control group and in 1 patient (1.8%) in the colchicine group (p = 0.02) **Limitations:** ▪ Small, open-label trial ▪ Almost all patients also received treatment with hydroxychloroquine and azithromycin or lopinavir/ritonavir	**Adverse Effects:[2]** ▪ Diarrhea, nausea, and vomiting are common with use of colchicine. ▪ Blood dyscrasias have been reported. ▪ Neuromyopathy is rare; it typically occurs in elderly patients or in those with hepatic or renal impairment. ▪ Overdosage of colchicine can be fatal. **Drug Interactions:** ▪ Substrate of CYP3A4 and the efflux transporter P-glycoprotein (P-gp); fatalities have been reported rarely in patients taking colchicine with a strong CYP3A4 inhibitor such as clarithromycin or a strong P-gp inhibitor such as cyclosporine ▪ Dosage should be reduced when colchicine is taken concurrently with or within 2 weeks after a CYP3A4 or P-gp inhibitor ▪ Myopathy and rhabdomyolysis have occurred in patients taking colchicine with a statin or a fibrate	▪ Colchicine has anti-inflammatory properties ▪ More trials are ongoing to evaluate the efficacy of colchicine for treatment of COVID-19 **Pregnancy:** ▪ No adequate studies in pregnant women ▪ Embryofetal toxicity and teratogenicity and altered postnatal development reported in animal studies

1. SG Deftereos et al. Cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with Coronavirus Disease 2019. The GRECCO-19 randomized clinical trial. JAMA Netw Open 2020; 3:e2013136.
2. Drugs for gout. Med Lett Drugs Ther 2019; 61:33.
3. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors			
ALOGLIPTIN – *NESINA* **LINAGLIPTIN – *TRADJENTA*** **SAXAGLIPTIN – *ONGLYZA*** **SITAGLIPTIN – *JANUVIA*** *(Added 5/12/2020)* **Dosage:** ▪ Optimal dosage in patients with COVID-19 is unclear ▪ Dosage adjustments are needed for reduced renal function Usual dosage for treatment of type 2 diabetes: ▪ Alogliptin: 25 mg PO once/day ▪ Linagliptin: 5 mg PO once/day ▪ Saxagliptin: 2.5-5 mg PO once/day ▪ Sitagliptin: 100 mg PO once/day	▪ Clinical trials with linaglipatin in patients with type 2 diabetes and mild or moderate COVID-19 are expected to begin to determine if use of the drug can improve glucose control and reduce the severity of COVID-19[1,2]	**Adverse Effects:** ▪ Acute pancreatitis, fatal hepatic failure, possible worsening of heart failure, possible severe and disabling joint pain **Drug Interactions:** ▪ Strong P-glycoprotein or CYP3A4 inducers[5] can decrease serum concentrations of linagliptin; concurrent use should be avoided if possible ▪ Strong CYP3A4/5 inhibitors[5] can increase saxagliptin concentrations; the dose of saxagliptin should not exceed 2.5 mg when used in combination with a CYP3A4/5 inhibitor ▪ Sitagliptin may increase digoxin concentrations; monitor patients taking digoxin	▪ Hypothesized that inhibition of DPP-4 may prevent infection with or progression of COVID-19 ▪ Mechanism not established, but it has been suggested that DPP-4 may be involved in SARS-CoV-2 cell adhesion and DPP-4 inhibitors may have effects on inflammation[3,4] **Pregnancy:** ▪ Limited data on use during pregnancy; insulin is generally preferred in pregnant women

1. G Iacobellis et al. Effects of DPP4 Inhibition on COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04341935?term=dpp&cond=COVID&draw=2&rank=1. Accessed May 12, 2020.
2. Ran Abuhasira et al. Efficacy and safety of dipeptidyl peptidase-4 inhibitors in diabetic patients with established COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04371978?term=dpp&cond=COVID&draw=2&rank=2. Accessed May 12, 2020.
3. R Strollo and P Pozzilli. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes Metab Res Rev 2020 Apr 26 (epub).
4. SR Bornstein et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020 April 23 (epub).
5. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors			
DAPAGLIFLOZIN – *FARXIGA* (ASTRAZENECA) *(Updated 4/28/2020)* **Dosage:** ▪ 10 mg once/day[1]	▪ Phase III trial (DARE-19) ongoing in the US and Europe in hospitalized patients with cardiovascular (CV), metabolic, or renal risk factors[1]	**Adverse Effects:** ▪ Genital mycotic and urinary tract infections, acute kidney injury, volume depletion, hypotension, and ketoacidosis **Drug Interactions:** ▪ Metabolized primarily by UGT1A9; mefenamic acid *(Ponstel)*, a UGT1A9 inhibitor, increased dapagliflozin AUC by about 50%, but dapagliflozin dosage reduction not needed ▪ Taking dapagliflozin with insulin or a sulfonylurea increases the risk of hypoglycemia	▪ Some experts have advised that SGLT2 inhibitors be stopped in hospitalized COVID-19 patients because of in increased risk of DKA and have concerns with the conduction of the DARE-19 trial[2] ▪ SGLT2 inhibitors have been shown to have beneficial effects in patients with cardiovascular and renal comorbidities not infected with COVID-19; hypothesized that they may also have protective effects in patients with COVID-19[1] ▪ Mechanism not established, but SGLT2 inhibitors may have favorable effects on mechanisms involved in respiratory failure, sepsis, and multi-organ failure/cytokine storm[1] **Pregnancy:** ▪ Not recommended during the second and third trimester; adverse renal effects have been reported in animal studies

1. Dapagliflozin in respiratory failure in patients with COVID-19 (DARE-19). Available at: https://clinicaltrials.gov/ct2/show/nct04350593?term=farxiga&cond=covid&draw=2&rank=1. Accessed April 29, 2020.
2. ME Tucker et al. New study of diabetes drug for COVID-19 raises eyebrows. Medscape. Available at: https://www.medscape.com/viewarticle/929716#vp_2. Accessed April 28, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
H2-Receptor Antagonists (H2RAs)			
FAMOTIDINE – *PEPCID* (VALEANT) *(Updated 6/5/2020)* **Dosage:** ▪ Clinical trial administering high-dose IV treatment (120 mg IV q8h)	▪ Ongoing trial in New York ▪ Review of patient records from China suggested that use of famotidine was associated with a lower death rate compared to those not taking the drug (Science April 26, 2020) **DE Freedberg et al. Gastroenterology 2020[1]** *(updated 6/5/2020)* **Population:** hospitalized, non-intubated, non-ICU (n=1620) **Design:** Retrospective cohort, famotidine vs no famotidine **Results:** ▪ Reduced risk for death or intubation (adjusted HR 0.42) ▪ PPI use not associated with lower risk ▪ 5.1% of patients were given famotidine within 24 hours of admission **Limitations:** observational, retrospective, single center, not peer reviewed **T Janowitz et al. Gut 2020[2]** *(added 6/5/2020)* **Population:** non-hospitalized patients (n=10) **Design:** case series; self-administered famotidine (80 mg tid x 11 days most commonly used)	**Adverse Effects:** ▪ Hepatitis, hematologic toxicity, and CNS effects such as headache, lethargy, depression, and cognitive impairment have occurred **Drug Interactions:** ▪ May decrease serum concentrations of drugs that require gastric acidity for absorption	▪ Mechanism not established; computer simulation suggested famotidine may inhibit an enzyme required for replication of the virus ▪ Concerns about use in patients with renal impairment (especially at high doses) **Pregnancy:** ▪ No adequate data in pregnant women; no evidence of risk in animal studies

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
FAMOTIDINE (CONTINUED)	**Results:** ▪ combined symptom score improved significantly within 24 hrs of famotidine ▪ symptoms (cough, shortness of breath, fatigue, headache, anosmia) were scored on a 4-point ordinal scale ▪ no patients were hospitalized ▪ time from onset of symptoms to start of treatment ranged from 2 to 26 days **Limitations:** case series (small number of patients, no placebo group)		

1. DE Freedberg et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. Gastroenterology 2020 (journal pre-proof).
2. T Janowtiz et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. Gut 2020 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Vitamins			
ASCORBIC ACID – GENERICS **Dosage:** ▪ Optimal dosage not established 12 g IV q12h x 7 days (infused at a rate of 12 ml/hr)[1]	▪ Trials in China and Italy of high-dose ascorbic acid in patients with severe COVID-19-associated pneumonia are ongoing ▪ The results of these trials have not been published to date	**Adverse effects:** ▪ Large doses can acidify the urine, causing cysteine, urate, or oxalate stones; prolonged administration of high IV doses can cause oxalate nephropathy ▪ Nausea, vomiting, diarrhea, dizziness, and flushing can occur **Drug Interactions:** ▪ May decrease serum concentrations of amphetamines ▪ May decrease the efficacy of bortezomib (*Velcade*, and generics) and cyclosporine ▪ May cause deferoxamine (*Desferal*) toxicity and left ventricular dysfunction; avoid oral doses >200 mg/day	▪ Antioxidant properties may protect host cells against infection-induced oxidative stress; may boost host defenses against infection ▪ Infection may reduce vitamin C concentrations ▪ In the CITRIS-ALI trials, a 50 mg/kg dose q6h x 4 days did not significantly improve organ dysfunction or inflammation markers in patients with sepsis and ARDS[2] **Pregnancy:** ▪ No data are available in pregnant women
1. Randomized, controlled trial beginning. Https://clinicaltrials.gov/ct2/show/nct04264533. 2. AA Fowler et al. The CITRIS-ALI randomized clinical trial. JAMA 2019; 322:1261.			
ZINC – ZINC SULFATE **Dosage:** ▪ Optimal dosage not established 220 mg daily x 5 days[1]	▪ No data on its efficacy for treatment of COVID-19 ▪ Has impaired replication of SARS-CoV i*n vitro*[2] ▪ A trial in Turkey is evaluating use of zinc plus vitamins A, C, and D in combination with hydroxychloroquine for prevention of COVID-19 infection[3]	**Adverse Effects:** ▪ Bad taste and nausea ▪ Irreversible anosmia when administered intranasally ▪ GI symptoms have occurred with high doses **Drug Interactions:** ▪ Zinc can interfere with absorption of many drugs including fluoroquinolones	▪ Impairs replication of some RNA viruses including SARS-CoV *in vitro*; no data on the activity of zinc against SARS-CoV-2 ▪ Chloroquine/hydroxychloroquine may increase cellular uptake of zinc by SARS-CoV-2[4] **Pregnancy:** ▪ Limited data on the safety of doses higher than the recommended daily allowance in pregnant women
1. Dosage regimen tried for treatment of covid-19; effective dosage has not been established in clinical trials. 2. Aj te velthuis et al. Zn2+ inhibits coronavirus and arterivirus rna polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. Plos pathog 2010; 6: e1001176. 3. Prophylaxis using hydroxychloroquine plus vitamins-zinc during covid-19 pandemia. Available at: https://clinicaltrials.gov/ct2/show/nct04326725. **ACCESSED APRIL 9, 2020.** 4. X xue j et al. Chloroquine is a zinc ionophore. Plos one 2014; 9:e109180.			

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
VITAMIN D **Dosage:** ▪ Dosage in patients with COVID-19 not established ▪ 400-800 IU/day (recommended daily allowance for most people) ▪ Serum 25(OH)D 20 to 30 ng/mL: 800-2000 IU/day ▪ Serum 25(OH)D <20 ng/mL: may need 50,000 IU/week	▪ Limited data from observational studies (that have not been peer-reviewed) suggests there is an association between vitamin D levels and severity of COVID-19 illness; people with vitamin D deficiency may be at higher risk of more severe disease[1,2] ▪ Earlier meta-analysis of randomized trials in patients with respiratory tract infections (non-COVID-19) found vitamin D supplementation associated with reduced risk of respiratory tract infections[3] ▪ Earlier randomized, double-blind trial of critically ill (non-COVID-19) patients found no significant effect of vitamin D administration on 90-day mortality vs placebo[4]	▪ Excessive doses could cause toxicity (hypercalciuria, hypercalcemia, nausea, vomiting, anorexia, constipation, dehydration, fatigue, irritability, confusion, weakness) ▪ Metabolism of vitamin D altered in patients with chronic kidney disease	▪ Vitamin D plays an important role in immune function ▪ Limited data in COVID-19 and other serious illness ▪ NICE guidance states that there is no evidence to support use of vitamin D supplements to prevent or treat COVID-19[5] *(added 6/30/2020)* ▪ An expert consensus paper states that vitamin D supplements have not been shown to prevent or treat COVID-19 and strongly cautions against use of high doses of vitamin D; avoidance of vitamin D deficiency is recommended[6] *(added 6/17/2020)* ▪ Some sources of vitamin D include exposure to sunlight, fortified cereals and dairy products, fatty fish

1. M Alipio. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-19). SSRN 2020 April 9. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3571484. Accessed May 12, 2020.
2. A Daneshkhah et al. The possible role of vitamin D in suppressing cytokine storm associated mortality in COVID-19 patients. MedRxiv 2020 April 30. Available at: https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v3. Accessed May 12, 2020.
3. AR Martineau et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. Br Med J 2017; 356:i6583.
4. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med 2019; 381:2529.
5. NICE Guidance. COVID-19 rapid evidence summary: vitamin D for COVID-19. Available at: https://www.nice.org.uk/advice/es28/chapter/Key-messages. Accessed June 30, 2020.
6. SA Lanham-New et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutrition, Prevention & Health 2020 April 30 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
OTC Products			
Nasal Saline Irrigation			
NASAL SALINE IRRIGATION – (NETI POT OR SINUS RINSE SQUEEZE BOTTLE) **Dosage:** Multiple times per day	▪ No data for treatment or prevention of COVID-19 ▪ Open-label, randomized trial in 61 patients with viral upper respiratory tract infections (including rhinovirus and coronavirus), hypertonic nasal saline irrigation shortened the duration of illness, lowered transmission to household contacts, and reduced viral shedding[1]	**Adverse Effects:** ▪ Minor nasal discomfort or irritation ▪ Sterile, distilled, or boiled (and cooled) tap water should be used to prevent bacterial or protozoal infection[2]	▪ No evidence that regular nasal saline irrigation can prevent or treat COVID-19 infection ▪ Some limited evidence that nasal irrigation with hypertonic saline can shorten the duration of the common cold ▪ Hypothesized mechanism is cellular use of chloride ions to produce hypochlorous acid (HOCL), which has antiviral effects[1]

1. S Ramalingam et al. A pilot, open labelled, randomised controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. Sci Rep 2019; 9:1015.
2. FDA. Is rinsing your sinuses with Neti Pots safe? Available at: https://www.fda.gov/consumers/consumer-updates/rinsing-your-sinuses-neti-pots-safe. Accessed March 31, 2020.

Melatonin			
MELATONIN – GENERICS **Dosage:** ▪ Optimal dosage not established 5-10 mg/day PO[1]	▪ No data available on use of melatonin for treatment of COVID-19 ▪ Based on data suggesting melatonin may be helpful in acute lung injury/acute respiratory distress syndrome caused by other pathogens[2]	**Adverse effects:** ▪ Well tolerated; dizziness, headache, nausea, and sleepiness can occur **Drug Interactions:** ▪ May decrease the antihypertensive effects of calcium channel blockers ▪ Melatonin is a substrate of CYP1A2; inducers of CYP1A2 may decrease melatonin concentrations and inhibitors of CYP1A2 may increase melatonin concentrations[3]	▪ May have anti-viral and anti-inflammatory effects; could decrease serum levels of inflammatory cytokines ▪ Has been used in critical care patients (not COVID-19) to reduce vessel permeability, anxiety, sedation use, and improving sleeping quality[2] **Pregnancy:** ▪ Limited data on the safety of melatonin use during pregnancy

1. Dosage used for reduction of pro-inflammatory cytokines in studies for other indications. Optimal dosage for use in patients with COVID-19 unknown.
2. R Zhang et al. COVID-19: melatonin as a potential adjuvant treatment. Life Sci 2020; 250:117583.
3. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2019 November 6 (epub). Available at: medicalletter.org/downloads/cyp_pgp_tables.pdf.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Benzalkonium Chloride			
BENZALKONIUM CHLORIDE (added 5/9/2020) **Dosage:** ▪ Topical use ▪ Available OTC in hand sanitizer formulations and an intranasal formulation	▪ The manufacturer of a nasal formulation of 0.13% benzalkonium chloride *(NanoBio Protect)* states the product has been shown to kill SARS-CoV-2 in *in vitro* studies conducted by Public Health England; published data are not yet available[1] ▪ Previous studies have reported that 0.05-0.2% benzalkonium chloride formulations were less effective than alcohol-based disinfectants against other coronaviruses[2]	**Adverse Effects:** ▪ Irritation, burning or stinging, hypersensitivity reactions	▪ No clinical data demonstrating efficacy of a nasal formulation of benzalkonium chloride for prevention of COVID-19 infection ▪ The CDC recommends alcohol-based hand sanitizers containing 80% ethanol or 75% isopropanol[3]

1. Press Release. Available at: https://www.bluewillow.com/%ef%bb%bf%ef%bb%bfnanobio-protect-over-the-counter-nasal-antiseptic-kills-covid-19-virus-in-lab-tests/. Accessed May 6, 2020.
2. G Kampf et al. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020; 104:246.
3. CDC. Hand hygiene recommendations. Guidance for healthcare providers about hand hygiene and COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/hand-hygiene.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fhand-hygiene-faq.html#references. Accessed May 6, 2020.

CONCOMITANT DRUGS

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Renin-Angiotensin System (RAS) Inhibitors			
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS ▪ Benazepril (*Lotensin*, and generics) ▪ Captopril (generic) ▪ Enalapril (*Vasotec*, and others) ▪ Fosinopril (generic) ▪ Lisinopril (*Zestril*, *Prinivil*, and others) ▪ Moexipril (generic) ▪ Perindopril (generic) ▪ Quinapril (*Accupril*, and generics) ▪ Ramipril (*Altace*, and generics) ▪ Trandolapril (generic) **ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)** ▪ Azilsartan (*Edarbi*) ▪ Candesartan (*Atacand*, and generics) ▪ Eprosartan (*Teveten* and generics) ▪ Irbesartan (*Avapro*, and generics) ▪ Losartan (*Cozaar*, and generics) ▪ Olmesartan (*Benicar*, and generics) ▪ Telmisartan (*Micardis*, and generics) ▪ Valsartan (*Diovan*, and generics)	▪ Increased risk of severe COVID-19 in patients with cardiovascular disease ▪ ACE inhibitors and ARBs increase expression of ACE2 by epithelial cells in the lung, and pathogenic coronaviruses such as SARS-CoV-2 enter these cells via ACE2 receptors[1] ▪ Some researchers have suggested that this increase in risk may be due to use of ACE inhibitors or ARBs in patients with diabetes, hypertension, or heart failure ▪ Others have suggested, however, that ACE2 may protect against lung injury in coronavirus infection and that taking an ACE inhibitor or an ARB might be beneficial[2,3]	**P Zhang et al. Circ Res 2020[4]** **Population:** ▪ hospitalized patients w/ hypertension (n=1128) ▪ 188 taking an ACE inhibitor or ARB **Design:** ▪ retrospective, multi-center **Results:** ▪ all-cause mortality was lower in patients taking an ACE inhibitor or ARB compared to those not taking an ACE inhibitor or ARB (3.7% vs 9.8%) ▪ adjusted HR 0.37 (95% CI, 0.15-0.89; P = 0.03) in a propensity score-matched analysis **Limitations:** retrospective **J Li et al. JAMA Cardiol 2020[5]** **Population:** hospitalized patients (n = 1178); 362 patients with hypertension, 115 taking an ACE inhibitor or ARB **Design:** retrospective, single-center **Results:** percentage of patients taking an ACE inhibitor or ARB was similar between patients with (32.9%) and without (30.7%) severe infection and between survivors (33.0%) and non-survivors (27.3%) **Limitations:** no adjustment for confounding factors	▪ Multiple medical organizations, including the NIH, have advised against stopping or starting these drugs to prevent or treat COVID-19 infection[3,10,11] ▪ Patients who are taking an ACE inhibitor or an ARB and subsequently develop COVID-19 should continue to take the drug[3,10] ▪ Some evidence from retrospective trials suggesting that use of an ACE inhibitor or an ARB in patients with hypertension who were hospitalized for COVID-19 was associated with similar or lower mortality rates compared to patients who were not taking a drug from either class prior to infection.[4,5,6] ▪ Prospective randomized-controlled trials evaluating these drugs in patients hospitalized for COVID-19 are in progress. ▪

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**DM Bean et al. 2020[6]** **Population:** hospitalized patients (n=205) **Design:** retrospective, single-center **Results:** Lower rate of death or transfer to the ICU within 7 days of symptom onset in patients on an ACE inhibitor (OR 0.29) **Limitations:** small sample size, not peer reviewed **Mancia et al. NEJM 2020[7]** **Population:** 6272 case patients with COVID-19; 30,759 controls **Design:** population-based case-control study in Italy **Results:** ▪ use of ACE inhibitors or ARBs was not associated with COVID-19 among case patients (adjusted OR for ACE inhibitors 0.96 [CI 0.87-1.07] and for ARBs 0.95 [CI 0.86-1.05]) ▪ no association between use of ACE inhibitors or ARBs and severe or fatal disease (adjusted OR for ACE inhibitors 0.91 [CI 0.69-1.21] and for ARBs 0.83 [CI 0.63-1.10]) **Limitations:** observational data **Mehra et al. NEJM 2020[8]** *(updated 6/4/2020)* ***Study Retracted[12]*** ▪ *Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available* **Population:** 8910 hospitalized patients in Asia, Europe, and North America **Design:** observational; data collected from an international registry	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Results:** Use of ACE inhibitors or ARBs was not found to be associated with an increased risk of in-hospital death **Limitations:** observational data **Reynolds et al. NEJM 2020[9]** **Population:** 12,954 patients tested for COVID-19 in a New York City health system **Design:** observational; data obtained from electronic medical records **Results:** ▪ 5894 (46.8%) were positive; 1002 of them (17.0%) had severe illness ▪ ACE inhibitors, ARBs, or other antihypertensive drug classes (beta-blockers, calcium channel blockers, thiazide diuretics) were not associated with an increased risk of COVID-19 infection or of severe illness **Limitations:** observational data	

1. L Fang et al. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020 March 11 (epub).
2. MA Sparks et al. The coronavirus conundrum: ACE2 and hypertension edition. Available at: http://www.nephjc.com/news/covidace2. Accessed April 30, 2020.
3. M Vaduganathan et al. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. N Engl J Med 2020 March 30 (epub).
4. P Zhang et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020 April 17 (epub).
5. J Li et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol 2020 April 23 (epub).
6. DM Bean et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-COVID-19 infection in a multisite UK acute hospital trust. Medrxiv 2020 April 11 (preprint).
7. G Mancia et al. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med 2020 May 1 (epub).
8. MR Mehra et al. Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020 May 1 (epub).
9. HR Reynolds et al. Renin–angiotensin–aldosterone system inhibitors and risk of COVID-19. N Engl J Med 2020 May 1 (epub).
10. ACC. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Available at: https://bit.ly/2uimyt6. Accessed May 4, 2020.
11. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed May 4, 2020.
12. MR Mehra et al. Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020 June 4 (epub).

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)			
NSAIDS (E.G., IBUPROFEN, NAPROXEN)	▪ The Health Minister of France has warned that use of NSAIDs such as ibuprofen (*Advil*, *Motrin*, and others) to reduce fever in patients with COVID-19 increases the risk of severe adverse events and recommended use of acetaminophen (*Tylenol*, and others) instead[1]	▪ No convincing evidence that NSAIDs are especially dangerous for patients with COVID-19,[2] but they can cause GI bleeding, fluid retention, and renal dysfunction in any patient, which can be dangerous for the critically ill ▪ Acetaminophen is an effective antipyretic alternative to an NSAID and in recommended doses is less likely than an NSAID to cause serious adverse effects in most patients	▪ Use of an NSAID or acetaminophen for continual fever suppression may reduce the immune response and prolong viral shedding ▪ NIH guidelines recommend that antipyretic strategies (e.g., with acetaminophen or NSAIDs) should not differ between patients with or without COVID-19[3] ▪ Patients who are taking NSAIDs for other indications should not stop taking them[3]

1. M Day. COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020; 368:m1086.
2. FDA. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. Available at: https://bit.ly/3dnggwx. Accessed May 4, 2020.
3. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed May 4, 2020.

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