The Medical Letter®
on Drugs and Therapeutics

Treatments Considered for COVID-19 (Updated August 27, 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.

Table of Contents

INVESTIGATIONAL DRUGS ..... - 4 -

Antivirals ..... - 4 -

FAVIPIRAVIR

REMDESIVIR

Convalescent Plasma ..... - 11 -

Intravenous Immune Globulin (IVIG) ..... - 14 -

Monoclonal Antibody ..... - 16 -

LY-CoV555

Glutathione and N-acetylcysteine ..... - 17 -

Stem Cell Therapy ..... - 18 -

MESENCHYMAL STEM CELL THERAPY

Oleandrin ..... - 19 -

OLEANDRIN

REPURPOSED DRUGS ..... - 20 -

Corticosteroids (systemic) ..... - 20 -

Inhaled Corticosteroids ..... - 22 -

IL-6 Inhibitors ..... - 23 -

SARILUMAB

TOCILIZUMAB

IL-1 Receptor Antagonist ..... - 27 -

ANAKINRA

Janus Kinase (JAK) Inhibitors ..... - 29 -

BARICITINIB

RUXOLITINIB

TNF Inhibitors ..... - 31 -

TNF INHIBITORS

Anti-CD6 Monoclonal Antibody ..... - 32 -

ITOLIZUMAB

Antimalarials ..... - 33 -

CHLOROQUINE

HYDROXYCHLOROQUINE

Macrolide Antibiotic ..... - 46 -

AZITHROMYCIN

HIV Protease Inhibitors ..... - 51 -

ATAZANAVIR

DARUNAVIR/COBICISTAT

LOPINAVIR/RITONAVIR

Interferon Beta and Ribavirin ..... - 54 -

Antiparasitic ..... - 56 -

IVERMECTIN

Bradykinin Inhibitor ..... - 57 -

ICATIBANT

Colchicine ..... - 58 -

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors ..... - 59 -

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors ..... - 60 -

H2-Receptor Antagonists (H2RAs) ..... - 61 -

FAMOTIDINE

Vitamins ..... - 64 -

ASCORBIC ACID

ZINC

VITAMIN D

THIAMINE

Nasal Saline Irrigation ..... - 68 -

Melatonin ..... - 68 -

Benzalkonium Chloride ..... - 69 -

CONCOMITANT DRUGS ..... - 70 -

Renin-Angiotensin System (RAS) Inhibitors ..... - 70 -

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) ..... - 76 -

Proton Pump Inhibitors (PPIs) ..... - 77 -

Biguanide ..... - 78 -

METFORMIN

VACCINES ..... - 79 -

Adenovirus-Vectored Vaccines ..... - 79 -

CHIMPANZEE ADENOVIRUS-VECTORED COVID-19 (ChAdOx1 nCoV-19) VACCINE

RECOMBINANT ADENOVIRUS TYPE-5 (Ad5)-VECTORED COVID-19 VACCINE

ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)

mRNA Vaccines ..... - 81 -

mRNA-1273

BNT162b1 and BNT162b2

Adjuvanted Recombinant Nanoparticle Vaccine ..... - 83 -

NVX-CoV2373

Inactivated Vaccine ..... - 84 -

Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain)

INVESTIGATIONAL DRUGS

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antivirals			
FAVIPIRAVIR – *AVIGAN* (FUGIFILM) *(updated 8/9/2020)* **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 **Ivashchenko et al. Clin Infect Dis 2020**[5] *(added 8/9/2020)* **Population:** hospitalized patients with moderate COVID-19 pneumonia in	**Adverse Effects:** ▪ Elevated LFTs, diarrhea, nausea, vomiting, chest pain 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 ▪ Russian Ministry of Health granted conditional marketing authorization for favipiravir (*Avifavir*) *(added 8/9/2020)* ▪ 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

Russia; 25% on supplemental oxygen and 75% on ambient air (n=60)
Design: adaptive, multicenter, randomized, open-label trial; results from 60 patients in phase II trial presented

- Favipiravir 1600 mg BID on day 1, then 600 mg bid days 2-14, favipiravir 1800 mg BID on day 1, then 800 mg bid days 2-14, or standard of care (75% received hydroxychloroquine or chloroquine)
- Mean 6.7 days from start of symptoms

Results:

- Viral clearance (2 negative PCR tests with at least a 24-hour interval) was achieved by day 5 in 62.5% of patients taking favipiravir vs 30.0% of those who received standard of care (p=0.018)
- Viral clearance by day 10 was achieved in 92.5% of favipiravir-treated patients vs 80.0% on standard of care (p=0.155)

Limitations: interim results

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.
5. AA Ivashchenko et al. Avifavir for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. Clin Infect Dis 2020 August 9 (epub).

REMDESIVIR –
***VEKLURY* (GILEAD)**

(updated 8/23/2020)

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 or until hospital discharge[7]

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, hypokalemia, headache, 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] and inhibitors of these enzymes/transporters could potentially increase the risk of toxicity such as hepatotoxicity[14]
- 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
- Because remdesivir supply is limited, NIH guidelines recommend remdesivir be prioritized for hospitalized patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)[7] *(updated 7/25/2020)*
- NIH guidelines state a recommendation cannot be made for or against remdesivir in patients on high-glow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO because there is uncertainty regarding benefits of remdesivir in these patients[7] *(added 7/25/2020)*
- 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)*
- 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

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	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] ▪ An editorial in NEJM suggests priority be given to a 5-day course of remdesivir for patients at early stages of severe disease[10] ▪ The manufacturer has initiated a phase 1a trial of an inhaled, nebulized solution of remdesivir in healthy volunteers; this trial is intended to form the basis for further clinical studies of this formulation in outpatients with COVID-19[13] *(added 7/9/2020)* ▪ Gilead filed with the FDA for approval of remdesivir for COVID-19 *(added 8/19/2020)* **Pregnancy:** ▪ No data are available in pregnant women

REMDESIVIR (CONTINUED)	**Spinner et al. JAMA 2020[11,16]** *(updated 8/23/2020)* **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:** ▪ median duration of symptoms before day 1 was 8 days in the remdesivir groups and 9 days in the standard care group ▪ median duration of treatment was 5 days in the 5-day group and 6 days in the 10-day group ▪ on day 11, the odds of a better clinical status distribution on a 7-point ordinal scale was significantly higher in those treated with remdesivir for 5 days than with standard care (OR 1.65; 95% CI 1.09-2.48; p=0.02); clinical importance unclear ▪ treatment with remdesivir x 10 days did not reach statistical significance **Limitations:** open-label; median symptom duration at start of trial was 8 days; only 38% of remdesivir 10-day group received the drug for 10 days **Olender et al. Clin Infect Dis 2020[15]** *(added 7/31/2020)* **Population:** hospitalized adults with severe COVID-19 (oxygen saturation ≤94% on room air or requiring supplemental oxygen and pulmonary infiltrates) (n=312 remdesivir; n=818 non-remdesivir) **Design:** comparative analysis of 2 ongoing studies

REMDESIVIR (CONTINUED)	▪ a randomized, open-label phase 3 trial comparing 2 courses of remdesivir and a retrospective cohort study in patients receiving standard-of-care **Results:** ▪ 74.4% of remdesivir-treated patients recovered at day 14 vs 59.0% of non-remdesivir-treated patients (adjusted OR 2.03; p<0.001) ▪ 7.6% of remdesivir-treated patients died vs 12.5% in non-remdesivir-treated patients (adjusted OR 0.38; p=0.001) **Limitations:** comparative analysis of interim data sponsored by manufacturer **Inhaled Remdesivir** *(added 7/9/2020)* ▪ The manufacturer has initiated a phase 1a trial evaluating remdesivir in an inhaled, nebulized formulation in healthy volunteers[13] **NIH Adaptive COVID-19 Treatment Trial 3 (ACTT 3)** *(added 8/9/2020)* ▪ A randomized, double-blind trial comparing remdesivir plus interferon beta 1a to remdesivir alone has begun ▪ Expected to enroll >1000 adults

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 July 20, 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. CD Spinner et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. A randomized clinical trial. JAMA 2020 August 21 (epub).
12. FDA. Remdesivir by Gilead 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.
13. Gilead Sciences statement on the initiation of clinical testing of an inhaled solution of remdesivir for potential outpatient treatment of COVID-19. July 8, 2020. Available at: https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-initiation-of-clinical-testing-of-an-inhaled-solution-of-remdesivir-for-potential-outpatient-treatment-of-covid19. Accessed July 9, 2020.
14. E Leegwater et al. Drug-induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors. Clin Infect Dis 2020 June 28; ciaa883.
15. SA Olender et al. Remdesivir for severe COVID-19 versus a cohort receiving standard of care. Clin Infect Dis 2020 July 24 (epub).
16. EK McCreary and DC Angus. Efficacy of remdesivir in COVID-19. JAMA 2020 August 21 (epub).

Convalescent Plasma

CONVALESCENT PLASMA

(updated 8/23/2020)

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]

Li et al. JAMA 2020[7] *(added 8/16/2020)*
Population: hospitalized patients in China with severe or life-threatening COVID-19 (n=103)
Design: open-label, multicenter, randomized trial
- Convalescent plasma plus standard treatment vs standard treatment alone
- Plasma units with an S-RBD–specific IgG titer of at least 1:640 were used
- Median time from symptom onset to randomization: 30 days

Results:
- Trial stopped early
- Clinical improvement within 28 days occurred in 51.9% of patients treated with convalescent plasma vs 43.1% of those given standard treatment alone, not a statistically significant difference (p=0.26)
- In those with severe disease, clinical improvement occurred in 91.3% with convalescent plasma vs 68.2% with standard care alone (p-0.03) and in

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]

- FDA issued an Emergency Use Authorization for convalescent plasma[6,9] (*added 8/19/2020*)

those with life-threatening disease in 20.7% vs 24.1% (p=0.83)
- 28-day mortality was 15.7% with convalescent plasma vs 24.0% with standard care (p=0.30)
- Negative conversion rate of viral PCR at 72 hours was 87.2% with convalescent plasma vs 37.5% with standard care (p<0.001)

Limitations: trial stopped early before full enrollment reached

MJ Joyner et al MedRxiv 2020[8]
(added 8/17/2020)

Population: hospitalized patients in the US with severe or life-threatening acute COVID-19 respiratory syndrome (n=35,322)

Design: open-label exploratory analysis of patients who received convalescent plasma through an Expanded Access Program in the US

Results:
- 52.3% of patients in ICU; 27.5% on mechanical ventilation
- 7-day mortality rate 8.7% in patients transfused ≤ 3 days of diagnosis and 11.9% in patients transfused ≥ 4 days after diagnosis (p<0.001); 30-day mortality was 21.6% vs 26.7% (p<0.0001)
- 7-day mortality was 8.9% with high IgG plasma, 11.6% with medium IgG plasma, and 13.7% with low IgG plasma

Limitations: observational, not peer reviewed; authors state efficacy signals are preliminary

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.
7. L Li et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. A randomized clinical trial. JAMA 2020; 324:460.
8. MJ Joyner et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. MedRxiv 2020 August 12. Available at: https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1.full.pdf. Accessed August 17, 2020.
9. FDA. Convalescent plasma Emergency Use Authorization (EUA) letter. Available at: https://www.fda.gov/media/141477/download. Accessed August 23, 2020.

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]
- NIH guidelines state there are insufficient data to recommend for or against use of SARS-CoV-2 immunoglobulins[6] *(added 7/22/2020)*
- 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 July 22, 2020.

Monoclonal Antibody

LY-CoV555

(Eli Lilly/AbCellera)

(added 8/17/2020)

NIH ACTIV-2[1]

- Phase 2 trial
- Expected to enroll 200 outpatients with mild to moderate COVID-19 symptoms for < 10 days
- LY-CoV555 vs placebo

NIH ACTIV-3[1]

- Phase 3 study; LY-CoV555 vs placebo
- Expected to enroll 300 hospitalized patients with mild to moderate COVID-19 with < 13 days of symptoms

- Phase 3 trial of LY-CoV555 antibody for prophylaxis of COVID-19 in nursing home residents ongoing

- LY-CoV555 is an investigational monoclonal antibody for treatment of COVID-19
- The antibody was discovered in a blood sample from a recovered COVID-19 patient
- Administered IV

1. NIH. NIH launches clinical trial to test antibody treatment in hospitalized COVID-19 patients. Available at: https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trial-test-antibody-treatment-hospitalized-covid-19-patients. Accessed August 17, 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

MESENCHYMAL STEM CELL THERAPY
(updated 7/21/2020)

Remestemcel-L *(Ryoncil)*

- 10 patients with ARDS treated with remestemcel-L 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

Leng et al. Aging Dis 2020[1] *(updated 7/21/2020)*

Population: hospitalized patients with COVID-19 pneumonia in China (n=10)
Design: pilot trial; 7 patients (1 critical, 4 severe, 2 common-type illness)treated with mesenchymal stem cells and 3 (severe illness) treated with placebo
Results:

- pulmonary function and symptoms improved within 2 days of transplantation
- All patients in the treatment group recovered

Limitation: small pilot study

Adverse Effects:

- Risks in patients with COVID-19 not established
- Possible product contamination, infusion site reactions, thrombosis, infection, tumor growth
- Remestemcel-L well tolerated in trials reported by the manufacturer in children with GVHD

Pregnancy:

- There are inadequate data on the use of stem cell therapies in pregnant women

- 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
- FDA granted an investigational new drug (IND) application for use of remestemcel-L (*Ryoncil* - Mesoblast), an allogenic mesenchymal stem cell therapy, to treat patients with ARDS caused by COVID-19[2] *(updated 7/21/2020)*
- FDA approved an expanded access protocol for compassionate use of remestemcel-L in children with multisystem inflammatory syndrome associated with COVID-19[3] *(updated 7/21/2020)*
- NIH guidelines recommend against use of mesenchymal stem cells, except in a clinical trial[4] *(updated 7/21/2020)*
- FDA has warned about safety concerns with use of unapproved or illegal stem cell therapies[5] *(updated 7/21/2020)*

1. Z Leng et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216.
2. Press Release. GlobeNewswire. FDA clears investigational new drug application for mesoblast to use remestemcel-L in patients with acute respiratory distress syndrome caused by COVID-19. Available at: https://www.globenewswire.com/news-release/2020/04/06/2011944/0/en/FDA-CLEARS-INVESTIGATIONAL-NEW-DRUG-APPLICATION-FOR-MESOBLAST-TO-USE-REMESTEMCEL-L-IN-PATIENTS-WITH-ACUTE-RESPIRATORY-DISTRESS-SYNDROME-CAUSED-BY-COVID-19.html. Accessed July 21, 2020.
3. Press Release. BioSpace. Expanded Access Protocol initiated for compassionate use of remestemcel-L in children with multisystem inflammatory syndrome associated with COVID-19. Available at: https://www.biospace.com/article/releases/expanded-access-protocol-initiated-for-compassionate-use-of-remestemcel-l-in-children-with-multisystem-inflammatory-syndrome-associated-with-covid-19-/. Accessed July 21, 2020.
4. 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 July 21, 2020.
5. FDA. FDA warns about stem cell therapies. Available at: https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies. Accessed July 21, 2020.

Oleandrin

OLEANDRIN

(added 8/19/2020)

- No published *in vivo* data on use of oleandrin for treatment or prevention of COVID-19
- An *in vitro* study (not peer reviewed) suggested that oleandrin may inhibit SARS-CoV-2 replication[1]

Adverse Effects:

- Toxicity includes nausea, vomiting, abdominal pain, diarrhea (possibly bloody stools), anorexia, arrhythmias, drowsiness, tremors, seizures, coma, death
- Toxicity occurs several hours after ingestion

- There are no available data to support use of oleandrin for COVID-19 and it can have serious, life-threatening toxicity; avoid use
- Toxic cardiac glycoside from the *Nerium oleander* plant
- All parts of the oleander plant are toxic; it is responsible for cases of accidental poisoning worldwide

1. KS Plante et al. Prophylactic and therapeutic inhibition of in vitro SARS-CoV-2 replication by oleandrin. BioRxiv 2020 July 15. Available at: https://www.biorxiv.org/content/10.1101/2020.07.15.203489v1.full.pdf. Accessed August 19, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Corticosteroids (systemic)			
DEXAMETHASONE *(updated 7/27/2020)* ▪ 6 mg PO or IV daily x 10 days used in RECOVERY trial	**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 (n=2104) x 10 days vs usual care (n=4321) **Results:** 28-day mortality rates (dexamethasone vs usual care) ▪ Overall: 22.9% vs 25.7% (p<0.001) ▪ Patients on invasive mechanical ventilation: 29.3% vs 41.4% (rate ratio 0.64; 95% CI 0.51-0.81) ▪ Oxygen without invasive mechanical ventilation: 23.3% vs 26.2% (rate ratio 0.82; 95% CI 0.72-0.94) ▪ No respiratory support at randomization: 17.8% vs 14.0% (rate ratio 1.19; 95% CI 0.91-1.55) **Limitation:** preliminary results; open-label study	**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	▪ Anti-inflammatory effects 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 in mechanically ventilated patients and those who are not mechanically ventilated but require supplemental oxygen[3] ▪ IDSA guidelines recommend use of dexamethasone (or methylprednisolone or prednisone if dexamethasone is not available) 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] ▪ NIH guidelines state it is unknown whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone have benefits similar to those of dexamethasone in patients with COVID-19[3] *(added 7/20/2020)*

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
DEXAMETHASONE (continued)	**Keller et al. J Hosp Med 2020[5]** *(added 7/27/2020)* **Population:** hospitalized patients in NYC (n=1806) **Design:** observational study ▪ patients treated with steroids within 48 hrs of admission (n=148) compared to those who did not receive steroid treatment **Results:** ▪ patients in the steroid group were more likely to have COPD, asthma, rheumatoid arthritis, or lupus, or to have taken steroids in the year before admission than those in the control group ▪ overall, early use of glucocorticoids was not associated with mortality or mechanical ventilation ▪ in patients with CRP ≥ 20 mg/dL, glucocorticoid treatment was associated with a significant reduction in risk of mortality or mechanical ventilation ▪ in those with CRP < 10 mg/dL, glucocorticoid use was associated with a significant increase in the risk of mortality or mechanical ventilation **Limitations:** observational data		**Pregnancy:** ▪ NIH recommends use of dexamethasone in pregnant women with COVID-19 who are mechanically ventilated or who require supplemental oxygen but are not mechanically ventilated[3] *(added 7/20/2020)* ▪ Monitor for hypoadrenalism in newborns of mothers who received substantial doses

1. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. N Engl J Med 2020 July 17 (epub).
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 July 20, 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).
5. MJ Keller et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. J Hosp Med 2020 July 22 (epub).

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Inhaled Corticosteroids			
INHALED CORTICOSTEROIDS (ICSs) *(added 7/30/2020)* ▪ **Ciclesonide *(Alvesco)*** ▪ **Budesonide *(Pulmicort Flexhaler)***	**Iwabuchi et al. J Infect Chemother 2020[1]** **Population:** hospitalized patients with poor oxygenation and CT findings in Japan (n=3) **Design:** case series: all given inhaled ciclesonide **Results:** favorable outcomes in all **Limitations:** cases series of 3 patients **Schultze et al. medRxiv 2020[2]** **Population:** asthma (n=817,973) and COPD (n=148,588) patients in the UK **Design:** cohort study using linked electronic health records (OpenSAFELY platform); compared patients using an ICS to those taking other drugs for COPD/asthma **Results:** ▪ COPD: risk of death higher in patients using ICSs than in those use a long-acting beta agonist and a long-acting muscarinic antagonist (adjusted HR = 1.38; 95% CI 1.08-1.75) ▪ Asthma: risk of death higher in patients using ICSs than in those using only a short-acting beta agonist (adjusted HR = 1.52; 95% CI 0.82-1.49) **Limitations:** observational; not peer reviewed; possible confounding	**Adverse Effects:** ▪ local adverse effects include oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm ▪ high doses may cause HPA axis suppression, changes in bone density, and development of cataracts or glaucoma ▪ increases the risk of pneumonia in patients with COPD ▪ rinse mouth after use to reduce the risk of local adverse effects **Drug Interactions:** ▪ Significant drug interactions less likely with inhaled corticosteroids than with systemic formulations ▪ Strong CYP3A4 inhibitors may increase serum concentrations of inhaled corticosteroids	▪ Hypothesized that inhaled corticosteroids delivered to the lungs may inhibit adhesion and inflammatory effects of cytokines released in response to the virus ▪ Ciclesonide may have anti-viral activity against SARS-CoV-2[3] ▪ NIH guidelines recommend that patients with COVID-19 who are using inhaled corticosteroids for treatment of asthma or COPD should not discontinue treatment[4] ▪ No data available on use of inhaled corticosteroids for treatment of COVID-19 from randomized controlled trials **Pregnancy:** ▪ Low-to-moderate doses appear to be safe for use during pregnancy[5]

1. K Iwabuchi et al. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: report of three cases. J Infect Chemother 2020 26:625.
2. A Schultze et al. Inhaled corticosteroid use and risk COVID-19 related death among 966,461 patients with COPD or asthma: an OpenSAFELY analysis. MedRxiv 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.06.19.20135491v1. Accessed July 30, 2020.
3. S Jeon et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother 2020; 64:e00819-20.
4. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 30, 2020.
5. Drugs for asthma. Med Lett Drugs Ther 2017; 59:139.

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; updated 7/14/2020)* **Population:** hospitalized patients requiring mechanical ventilation (n=154) ▪ tocilizumab-treated patients were younger (55 yrs vs 60 yrs), less likely to have chronic pulmonary disease (10% vs 28%), and had lower D-dimer values at intubation (median 2.4 vs 6.5 mg/dL) **Design:** single-center cohort; patients treated with tocilizumab vs patients not treated with tocilizumab **Results:** median follow-up 47 days ▪ tocilizumab associated with a reduced risk of death (hazard ratio 0.55; 95% CI 0.33,0.90) ▪ tocilizumab associated with an increased risk of superinfections (54% vs 26%; p<0.001) ▪ no significant difference in 28-day case fatality rate in patients treated with tocilizumab who had superinfections vs those who did not (22% vs15%; p=0.42) **Limitation:** observational data **COVACTA 2020[12]** *(added 8/16/2020)* **Population:** hospitalized patients with severe COVID-19 pneumonia (n=450) **Design:** randomized, double-blind, placebo-controlled ▪ IV tocilizumab plus standard of care vs placebo plus standard of care		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TOCILIZUMAB (CONTINUED)	**Results:** ▪ No significant difference between tocilizumab and placebo in the primary endpoint of clinical status on a 7-point scale at week 4 ▪ No difference between groups in percentage of patients who died by week 4 (19.7% tocilizumab vs 19.4% placebo) **Limitations:** not yet published		

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. Clin Infect Dis 2020 July 11 (epub):ciaa954.
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.
12. Press Release. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 associated pneumonia. Available at: https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed August 16, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
IL-1 Receptor Antagonist			
ANAKINRA – *KINERET* (BIOVITRUM AB) *(updated 7/27/2020)* **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 **Cauchois et al. Proc Natl Acad Sci U S A 2020[5]** *(added 7/27/2020)* **Population:** hospitalized patients in France with hypoxemic pneumonia or ARDS (n=22) **Design:** retrospective ▪ anakinra plus standard care compared to standard care alone ▪ anakinra dosage: 300 mg IV x 5 days, then tapered to 200 mg/d x 2 days, then 100 mg x 1 day	**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

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
ANAKINRA (continued)	**Results:** ▪ compared to standard care alone, all anakinra-treated patients had clinical improvement ($p<0.01$), decreases in oxygen requirements ($p<0.05$), and more days off invasive mechanical ventilation ($p<0.06$) ▪ there were no deaths in the anakinra group and 1 death in the standard care group ▪ significant reduction of fever and CRP by day 3 with anakinra **Limitations:** small retrospective study		

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).
5. R Couchois et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A 2020 July 22 (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

1. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed April 28, 2020.
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.
4. Treatment of SARS caused by COVID-19 with ruxolitinib. Available at: https://clinicaltrials.gov/ct2/show/nct04334044?term=covid&cond=ruxolitinib&draw=2&rank=2. Accessed April 6, 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.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
TNF Inhibitors			
TNF INHIBITORS *(added 7/29/2020)* ▪ Optimal dosage for treatment of COVID-19 not established ▪ Adalimumab *(Humira)* ▪ Certolizumab pegol *(Cimzia)* ▪ Infliximab (*Remicade*, and biosimilars) ▪ Etanercept *(Enbrel)* ▪ Golimumab *(Simponi)*	**Brenner et al. Gastroenterology 2020**[1] **Population**: patients with inflammatory bowel disease (IBD) and COVID-19 (525 cases) **Design:** international (33 countries) registry to monitor outcomes of IBD patients with COVID-19 (Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) **Results:** ▪ 31% hospitalized and 3% died ▪ Risk factors for severe COVID-19 included corticosteroid and sulfasalazine or 5-aminosalicylate use, but not TNF-inhibitor use **Limitations:** observational data **Gianfrancesco et al. Ann Rheum Dis 2020**[2] **Population**: patients with rheumatic disease and COVID-19 (600 cases) **Design:** international (40 countries) case series from the C19-GRA registry **Results:** ▪ 46% hospitalized and 9% died ▪ Risk factors for hospitalization included corticosteroid use (prednisone dose ≥ 10 mg/day); TNF-inhibitor use was associated with reduced odds of hospitalization **Limitations:** observational data	**Adverse Effects:** ▪ Injection-site reactions or infusion reactions (fever, urticaria, dyspnea, hypotension) ▪ Cytopenias; malignancies, especially lymphomas, have been reported, but a cause-and-effect relationship has not been established ▪ Increased risk of infections, including reactivated and disseminated tuberculosis, invasive or disseminated fungal infection, and other opportunistic infections; reactivation of HBV ▪ Rarely induces or exacerbates heart failure or induces a reversible lupus-like syndrome ▪ Demyelinating conditions, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome have been reported **Drug Interactions:** ▪ Concomitant administration of a TNF inhibitor with another biologic agent may increase the risk of serious infections and neutropenia ▪ Patients being treated with TNF inhibitors should not receive live vaccines	▪ Patients with COVID-19 have been found to have increased levels of inflammatory cytokines including TNF ▪ TNF-inhibitors may mitigate the effects of cytokines released in response to the virus ▪ No clinical trial data yet available on efficacy of TNF inhibitors in patients with COVID-19 **Pregnancy:** ▪ Generally considered safe for use during pregnancy ▪ Placental transfer of anti-TNF antibodies is higher in the late second and third trimesters, especially with infliximab, adalimumab, and golimumab

1. EJ Brenner et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology 2020 July 8 (epub).
2. M Gianfrancesco et al. Characteristics associated with hospitalization for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020; 79:859.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Anti-CD6 Monoclonal Antibody			
ITOLIZUMAB *(added 7/16/2020)* ▪ Optimal dosage for treatment of COVID-19 not established ▪ Formulation: 25 mg/5 mL vials for injection were approved for emergency use in India	**Biocon Trial – 2020**[1] **Population:** hospitalized patients with moderate to severe ARDS in 4 hospitals in India (n=30) **Design:** Randomized, controlled, open-label trial ▪ 20 patients randomized to itolizumab plus best supportive care and 10 patients randomized to best supportive care **Results:** ▪ at one month, no deaths occurred in patients treated with itolizumab and 3 deaths occurred in patients treated with supportive care alone ▪ reductions in IL-6 and TNF-α were reported in itolizumab-treated patients **Limitation:** trial results not yet published	**Adverse Effects:** ▪ Infusion reactions including nausea, rash, urticaria, flushing, cough, wheezing, dyspnea, dizziness, headache; diarrhea ▪ Increased risk of infections **Drug Interactions:** ▪ Live vaccines should be avoided	▪ Approved in India for emergency use in COVID-19 patients; also approved in India for psoriasis ▪ Not available in the US ▪ Anti-CD6 IgG1 monoclonal antibody that binds to the CD6 receptor and blocks activation of T lymphocytes; may mitigate the effects of cytokines released in response to the virus **Pregnancy:** ▪ No adequate data on use in pregnant women ▪ Crosses the placenta

1. Equillium. Press Release. Clinical trial shows itolizumab reduced mortality in patients hospitalized with COVID-19. Available at: https://www.globenewswire.com/news-release/2020/07/13/2060993/0/en/Clinical-Trial-Shows-Itolizumab-Reduces-Mortality-in-Patients-Hospitalized-with-COVID-19.html. Accessed July 16, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
Antimalarials			
CHLOROQUINE[1] *(updated 8/23/2020)* **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 against use with or without azithromycin in the hospital setting[12] *(updated 8/23/2020)* ▪ 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

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)*	longer outweighs risk[13] *(updated 6/16/2020)* **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) *(updated 7/31/2020)* **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 ▪ 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 **Z Chen et al. 2020[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 **M Mahevas et al. 2020[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 against use with or without azithromycin in the hospital setting[12] *(updated 8/23/2020)* ▪ 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)* ▪ In a randomized controlled trial in outpatients with early, mild COVID-19, hydroxychloroquine was not more effective than placebo in decreasing symptom severity[29] *(added 7/17/2020)* ▪ In one randomized controlled trial, hydroxychloroquine was not more effective than placebo for post-exposure prophylaxis; other trials are ongoing[25] *(added 7/17/2020)* ▪ 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 **WHO Solidarity Trial 2020[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		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**RECOVERY Trial 2020** *(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 **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		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**CP Skipper et al. Ann Intern Med 2020[29]** *(added 7/17/2020)* **Population:** symptomatic outpatients with COVID-19 or probable COVID-19 within 4 days of symptom onset (n=423) **Design:** randomized, double-blind, placebo-controlled trial ▪ HCQ (800 mg once, 600 mg 6-8 hrs later, then 600 mg once/day x 4 days) vs placebo **Results:** ▪ 81% had confirmed COVID-19 or exposure to a person with confirmed infection ▪ 56% enrolled within 1 day of symptom onset ▪ no significant difference in **symptom severity** over 14 days between HCQ and placebo groups (relative difference in symptom severity 12%; p=0.117) ▪ no significant difference in percentage of patients who had symptoms at 14 days (24% vs 30% with placebo; p=0.21) ▪ significantly more patients treated with HCQ had **adverse effects** (43% vs 22%; p<0.001) ▪ 4 hospitalizations and 1 nonhospitalized death in the HCQ group vs 10 hospitalizations and 1 hospitalized death in the placebo group (p=0.29) **Limitations:** only 58% of patients received COVID-19 testing		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**Rosenberg et al. JAMA 2020**[30] *(added 7/22/2020)* **Population:** hospitalized patients **Design:** retrospective multicenter cohort study ▪ HCQ plus azithromycin, HCQ alone, azithromycin alone, or neither **Results:** ▪ Patients in the treatment groups had more severe disease at baseline than those not treated ▪ Compared with patients receiving neither drug, there was no difference in the in-hospital mortality rate in patients who received any of the 3 treatments ▪ Patients who received HCQ plus azithromycin had a higher risk of cardiac arrest compared to those who received neither drug **Limitations:** observational data **Cavalcanti et al. NEJM 2020**[31] *(added 7/23/2020)* **Population:** hospitalized patients with suspected or confirmed COVID-19 receiving no supplemental oxygen or a max of 4 L/min (n=667 randomized; n=504 with confirmed COVID-19 in the modified intention-to-treat) **Design:** open-label, multicenter randomized controlled trial ▪ HCQ 400 mg bid vs HCQ 400 mg bid plus azithromycin 500 mg once/day x 7 days vs standard care alone		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**Results:** ▪ Treatment started a median of 7 days after symptom onset; patients who started treatment up to 14 days after symptom onset were included ▪ HCQ alone or with azithromycin did not improve clinical status at 15 days on an ordinal scale compared to standard care alone (primary endpoint in the modified intention-to-treat population, which included only those with confirmed COVID-19) ▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone **Limitations:** open-label trial, some patients previously received treatment		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
HYDROXYCHLOROQUINE (CONTINUED)	**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 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		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	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 **Mitja et al. medRxiv 2020**[32] *(added 7/31/2020)* **Population:** asymptomatic contacts exposed to a PCR-positive COVID-19 case in Spain (n=2314) **Design:** open-label, cluster-randomized trial ▪ HCQ 800 mg once, then 400 mg/day x 6 days vs no therapy **Results:** PCR-confirmed symptomatic COVID-19 within 14 days was not statistically significant between the two groups (5.7% with HCQ vs 6.2% with usual care) **Limitations:** not peer reviewed		

1. FDA-approved for other indications.
2. Experimental dosage used for treatment of COVID-19 in trials, but optimal dosage not yet established.
3. A Cortegiani et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020 March 10 (epub).
4. M Wang et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30:269.
5. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857
6. DN Juurlink. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ 2020 April 8 (epub).
7. DM Roden et al. Drug interactions on QTc in exploratory COVID-19 treatment. Circulation 2020 April 8 (epub).
8. RL Woosley and KA Romero. QT drugs list. Available at: www.crediblemeds.Org. Accessed March 31, 2020.

9. FDA Drug Safety Communication. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed April 27, 2020.
10. 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.
11. D Projean et al. In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation. Drug Metab Dispos 2003; 31:748.
12. 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 August 23, 2020.
13. FDA. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. Accessed June 16, 2020.
14. 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).
15. Z Chen et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Medrxiv 2020 (epub). Available At: https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2. Accessed April 13, 2020.
16. M Mahevas et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020; May 14 (epub).
17. J Magagnoli et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Medrxiv 2020 (epub) Available At: https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf+html. Accessed April 28, 2020.
18. E Chorin et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020 April 24 (epub).
19. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 22, 2020.
20. J Geleris et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020 May 7 (epub).
21. Tang et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ 2020; May 14 (epub).
22. MR Mehra et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020 May 22 (epub).
23. WHO "Solidarity" clinical trial for COVID-19 treatments. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed May 28, 2020.
24. MR Mehra et al. Retraction – hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020 June 4 (epub).
25. DR Boulware et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020 June 3 (epub).
26. FDA. Remdesivir by Gilead 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.
27. N White and W Schilling et al. MORU Tropical Health Network. COPCOV trial. Available at: https://www.tropmedres.ac/covid-19/copcov/copcov-key-messages. Accessed July 1, 2020.
28. S Arshad et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020 July 1 (pre-proof).
29. CP Skipper et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med 2020 July 16 (epub).
30. ES Rosenberg et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323:2493.
31. AB Cavalcanti et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 2020 July 23 (epub).
32. O Mitja et al. A cluster-randomized trial of hydroxychloroquine as prevention of COVID-19 transmission and disease. MedRxiv 2020 July 20. Available at: https://www.medrxiv.org/content/10.1101/2020.07.20.20157651v1. Accessed July 31, 2020.

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) **Rosenberg et al. JAMA 2020[10]** *(added 7/22/2020)* **Population:** hospitalized patients **Design:** retrospective multicenter cohort study ▪ HCQ plus azithromycin, HCQ alone, azithromycin alone, or neither **Results:** ▪ Patients in the treatment groups had more severe disease at baseline than those not treated ▪ Compared with patients receiving neither drug, there was no difference in the in-hospital mortality rate in patients who received any of the 3 treatments ▪ Patients who received HCQ plus azithromycin had a higher risk of cardiac arrest compared to those who received neither drug **Limitations:** observational data	**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 against use with chloroquine or hydroxychloroquine in the hospital setting [8] ▪ NIH recommends against the use of hydroxychloroquine plus azithromycin, except in the context of a clinical trial, because of the potential for toxicities[9] *(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

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZITHROMYCIN (continued)	**S Arshad et al. Int J Infect Dis 2020[11]** *(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 **Mehra et al. Lancet 2020[12]** *(added 5/26/20)* *(updated 6/4/2020)* *****Study Retracted[13]***** ▪ *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)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZITHROMYCIN (continued)	**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 **J Magagnoli et al 2020[14]** *(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		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
AZITHROMYCIN (continued)	**Cavalcanti et al. NEJM 2020[15]** *(added 7/23/2020)* **Population:** hospitalized patients with suspected or confirmed COVID-19 receiving no supplemental oxygen or a max of 4 L/min (n=667 randomized; n=504 with confirmed COVID-19 in the modified intention-to-treat) **Design:** open-label, multicenter randomized controlled trial ▪ HCQ 400 mg bid vs HCQ 400 mg bid plus azithromycin 500 mg once/day x 7 days vs standard care alone **Results:** ▪ Treatment started a median of 7 days after symptom onset; patients who started treatment up to 14 days after symptom onset were included ▪ HCQ alone or with azithromycin did not improve clinical status at 15 days on an ordinal scale compared to standard care alone (primary endpoint in the modified intention-to-treat population, which included only those with confirmed COVID-19) ▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone **Limitations:** open-label trial, some patients previously received treatment		

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 August 23, 2020.
9. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 22, 2020.
10. ES Rosenberg et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323:2493.
11. S Arshad et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020 July 1 (pre-proof).
12. MR Mehra et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020 May 22 (epub).
13. MR Mehra et al. Retraction – hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020 June 4 (epub).
14. J Magagnoli et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Medrxiv 2020 (epub) Available At: https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.full.pdf+html. Accessed April 28, 2020.
15. AB Cavalcanti et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 2020 July 23 (epub).

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

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)

EFFICACY

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

Schoergenhofer et al. Ann Intern Med 2020[15] *(added 7/22/2020)*

Population: hospitalized patients admitted to "normal care" ward (n=8)

Design: case series; pharmacokinetic analysis

Results:

- median trough lopinavir concentrations 13.6 mcg/mL
- to achieve half-maximal effective concentration (EC_{50}) for SARS-CoV-2, lopinavir trough concentrations would need to be 60- to 120-fold higher

ADVERSE EFFECTS/INTERACTIONS

Adverse Effects:

- Diarrhea, nausea, vomiting, headache, asthenia, hepatoxicity, pancreatitis, PR and QT interval prolongation, bradycardia[14]

Drug Interactions:

- Substrate and inhibitor of CYP3A4[5]
- Avoid use with other PR or QT interval-prolonging drugs[11]

COMMENTS

- *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

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
LOPINAVIR/RITONAVIR (continued)	**Limitations:** small case series; only trough concentration evaluated; no *in vivo* data on EC_{50} dose of lopinavir for SARS-CoV-2		

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.
14. C Beyls et al. Lopinavir-ritonavir treatment for COVID-19 infection in intensive care unit: risk of bradycardia. Circ Arrhythm Electrophysiol 2020 July 9 (epub).
15. C Schoergenhofer et al. Pharmacokinetics of lopinavir and ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). Ann Intern Med 2020 May 12 (epub).

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 **SG016 2020 – Inhaled Interferon[5]** *(added 7/20/2020)* **Population:** hospitalized patients in UK (n=101) **Design:** phase 2 double-blind, placebo-controlled trial ▪ Nebulized interferon beta (SNG001) vs placebo **Results:** ▪ Mean symptom duration before starting treatment (9.6 days interferon vs 9.8 days placebo)	**Adverse Effects:** ▪ Hung et al trial found no difference in adverse events between 2 groups ▪ **Interferon:** injection- depression site reactions, flu-like symptoms, 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	▪ Has antiviral properties ▪ *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 in patients with severe or critical illness, except in a clinical trial; they state there are insufficient data to recommend for or against use in patients with early (<7 days from symptom onset) mild and moderate illness ▪ If administered, should be given early in course of disease ▪ Nebulized interferon not available in the US *(added 7/20/2020)* **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

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
	▪ Development of severe disease (requiring ventilation or death) was less likely with interferon than with placebo (OR 0.21; 95% CI 0.04-0.97; p=0.046) ▪ Recovery (no limitation of activities or no evidence of infection) was more likely with interferon (HR 2.19; 95% CI 1.03-4.69; p=0.043) ▪ Breathlessness reduced in patients receiving interferon compared to placebo (p=0.007) ▪ 0 deaths with interferon; 3 deaths with placebo ▪ In patients with more severe disease on admission (requiring supplemental oxygen), interferon nonsignificantly increased the likelihood of hospital discharge (p=0.096) ▪ Median time to discharge was 6 days with interferon and 9 days with placebo **Limitations:** phase 2 trial; data not yet published		

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 July 20, 2020.
5. Press Release. Synairgen. COVID-19 – SG016 clinical trial data readout. Available at: https://www.synairgen.com/covid-19/. Accessed July 20, 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
Bradykinin Inhibitor			
ICATIBANT – *FIRAZYR,* and generics **Dosage:** ▪ Dosage for COVID-19 not established ▪ 30 mg SC x 3 doses given 6 hours apart[1]	**van de Veerdonk et al. JAMA Netw Open 2020[1]** **Population:** hospitalized patients with confirmed COVID-19 in the Netherlands (n=27; 9 cases/18 controls) ▪ oxygen saturation <90% without supplemental oxygen, requiring ≥3 L/min supplemental oxygen, and with computed tomography severity score ≥7 **Design:** case-control study **Results:** ▪ icatibant-treated patients required less oxygen supplementation vs controls ▪ 4 of 9 patients given icatibant were no longer oxygen dependent within 10-35 hours ▪ 8 of 9 had a reduction of oxygen requirements ≥3 L/min after 24 hrs with icatibant vs 3 of 18 controls ▪ 3 patients had a resurgence in need for oxygen supplementation; possibly due to short half-life of icatibant **Limitations:** retrospective data; 9 cases	**Adverse Effects:** ▪ Injection site reactions, pyrexia, transaminase increases, dizziness, rash **Drug Interactions:** ▪ May attenuate antihypertensive effect of ACE inhibitors	▪ FDA-approved for treatment of acute attacks of hereditary angioedema (HAE) ▪ SARS-CoV-2 enters cells via ACE2, which breaks down bradykinin; loss of ACE2 may result in stimulation of the bradykinin 2 receptor, which could be a contributing factor in pulmonary edema in patients with COVID-19 ▪ Icatibant is a competitive antagonist selective for the bradykinin B2 receptor **Pregnancy:** ▪ Icatibant use has not been associated with a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes based on available data from published literature and the pharmacovigilance database ▪ Adverse maternal and fetal outcomes have been reported in animal studies

1. FL van de Veerdonk et al. Outcomes associated with use of a kinin B2 receptor antagonist among patients with COVID-19. JAMA Netw Open 2020; 3:e2017708.

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 8/19/2020)* **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) **Mather et al. Am J Gastroenterol 2020**[3] *(added 8/19/2020)* **Population:** hospitalized patients with COVID-19 at a single center in Connecticut (n=878; 83 received famotidine) **Design:** retrospective, propensity-matched observational study ▪ compared patients receiving famotidine (PO or IV at any dose within 7 days of COVID screening or hospital admission) to those not receiving the drug **Results:** ▪ patients treated with famotidine were younger than those who were not ▪ famotidine use associated with decreased risk of in-hospital mortality (OR 0.37; 95% CI 0.16-0.86; p=0.021)		

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
FAMOTIDINE (continued)	▪ famotidine also associated with decreased risk of combined death or intubation and lower levels of serum markers for severe disease (CRP, procalcitonin, ferritin) **Limitations:** observational data		

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).
3. JF Mather et al. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. Am J Gastroenterol 2020 (preprint). Available at: https://journals.lww.com/ajg/Documents/AJG-20-2074_R1.pdf. Accessed August 19, 2020.

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] ▪ NIH guidelines state there are insufficient data to recommend for or against use of vitamin C in non-critically ill patients or in critically ill patients[3] *(added 7/21/2020)* **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.
3. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 21, 2020.

DRUG AND DOSAGE

ZINC –
ZINC SULFATE

(updated 7/21/2020)

Dosage:
- Optimal dosage not established
- 220 mg daily x 5 days[1]
- Recommended dietary allowance: 11 mg/day for men and 8 mg/day for nonpregnant women

EFFICACY

Carlucci et al. 2020[2] *(added 7/21/2020)*
Population: patients (n=932)
Design: retrospective observational study hospitalized
- Zinc plus hydroxychloroquine and azithromycin compared to hydroxychloroquine and azithromycin alone

Results:
- no difference in duration of hospitalization or mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO_2 (in univariate analysis)
- zinc associated with increased frequency of discharge and reduced mortality or transfer to hospice (in bivariate logistic regression analysis)
- association with decreased mortality no longer significant when non-ICU patients were excluded

Limitations: observational data, only in combination with hydroxychloroquine and azithromycin, not peer-reviewed or published

ADVERSE EFFECTS/INTERACTIONS

Adverse Effects:
- Bad taste and nausea
- Irreversible anosmia when administered intranasally
- GI symptoms have occurred with high doses
- Long-term use: copper deficiency leading to reversible hematologic (anemia, leukopenia) and neurologic adverse effects (myelopathy, paresthesia, ataxia, spasticity)

Drug Interactions:
- Zinc can interfere with absorption of many drugs including fluoroquinolones

COMMENTS

- Impairs replication of some RNA viruses including SARS-CoV *in vitro*[4]; no data on the activity of zinc against SARS-CoV-2
- Chloroquine/hydroxychloroquine may increase cellular uptake of zinc by SARS-CoV-2[5]
- NIH guidelines state there is insufficient data to recommend for or against use or zinc; they recommend against use of doses above the recommended dietary allowance for prevention of COVID-19, except in a clinical trial[6] *(added 7/21/2020)*
- Several trials are ongoing assessing the efficacy of zinc, some in combination with other vitamins, such as ascorbic acid, and/or drugs, such as hydroxychloroquine[3]

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. PM Carlucci et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv May 8, 2020.
3. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=Covid19&term=zinc&cntry=&state=&city=&dist=. Accessed July 22, 2020.
4. 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.
5. X xue j et al. Chloroquine is a zinc ionophore. Plos one 2014; 9:e109180.
6. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 21, 2020.

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]	**Adverse Effects:** ▪ 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 ▪ NIH guidelines state there are insufficient data to recommend for or against use of vitamin D for prevention or treatment of COVID-19[7] *(added 7/22/2020)* ▪ 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).
7. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at: https://covid19treatmentguidelines.nih.gov/. Accessed July 22, 2020.

DRUG AND DOSAGE	EFFICACY	ADVERSE EFFECTS/INTERACTIONS	COMMENTS
THIAMINE *(added 7/29/2020)* **Dosage:** ▪ Dosage in patients with COVID-19 not established ▪ 200 mg IV q12h[1]	▪ There are no published trials evaluating use of thiamine for treatment or prevention of COVID-19 ▪ One protocol that has not yet been evaluated in randomized controlled trials includes thiamine in addition to methylprednisolone, ascorbic acid, and heparin for treatment of hospitalized patients with COVID-19[1] ▪ In a retrospective study in (non-COVID) patients with septic shock, thiamine was associated with improved lactate clearance and reduced 28-day mortality compared to controls[2] ▪ In a randomized clinical trial of ICU patients (non-COVID), administration of an intervention consisting of IV vitamin C, hydrocortisone, and thiamine did not increase time alive or vasopressor free compared to hydrocortisone alone[3]	**Adverse Effects:** ▪ Thiamine is water-soluble and toxic levels are not expected	▪ Thiamine deficiency has been reported to occur commonly in critically ill patients; evidence on whether thiamine use can improve mortality in critically ill (non-COVID) patients has been conflicting[2,3] ▪ There are no controlled trials evaluating use of thiamine in critically ill patients with COVID-19

1. Dosage used in MATH+ protocol. Available at https://covid19criticalcare.com/treatment-protocol/. Accessed July 29, 2020.
2. JA Woolum et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Crit Care Med 2018; 46:1747.
3. T Fujii et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA 2020 323:423.

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	**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 (updated 7/28/2020) ▪ 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)	▪ 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[16]

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
▪ Valsartan (*Diovan*, and generics)		**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	▪ A review of multiple trials of ACEI or ARB use in patients with COVID-19 concluded there is high-certainty evidence that use of these drugs is not associated with more severe disease[17] *(added 7/28/2020)*

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 **Flacco et al. Heart 2020**[13] *(added 7/15/2020)* **Population:** 9890 hypertensive patients treated with ACE inhibitors, ARBs, or both vs untreated patients **Design:** meta-analysis of observational data from 10 cohort or case-control studies comparing risk of severe/fatal COVID-19 in patients treated with ACE inhibitors/ARBs vs untreated patients **Results:** The risk of severe/fatal COVID-19 was similar between patients treated with ACE inhibitors/ARBs and untreated patients (OR 0.90, 95% CI 0.65 to 1.26 for ACE inhibitors; OR 0.92, 95% CI 0.75 to 1.12 for ARBs) **Limitations:** meta-analysis of observational data; intermediate-to-high level of heterogeneity	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Fosbøl et al. JAMA 2020[14]** *(added 7/28/2020)* **Population: Retrospective Cohort Study:** ▪ hypertensive patients with COVID-19 (n=4480) **Nested, Case-Control:** ▪ Cases (COVID-19, prior hypertension; n=571); controls (no COVID-19, prior hypertension; n=5710) **Design:** retrospective cohort study examining outcomes in patients with COVID-19; nested, case-control design for susceptibility analysis; from Danish registry **Results:** **Retrospective Cohort Study: ACEI/ARB use vs no use** ▪ Mortality within 30 days was 18.1% in the ACEI/ARB group compared to 7.3% in the nonuser group (significant difference in unadjusted analysis; not statistically significant after adjustment for age, sex, and medical history) ▪ Death or severe COVID-19 occurred in 31.9% of ACEI/ARB users and 14.2% of nonusers by 30 days (significant difference in unadjusted analysis; not statistically significant after adjustment) **Nested Case-Control Susceptibility Analysis: ACEI/ARB use vs other hypertensive drugs** ▪ ACEI/ARB use was not associated with a higher incidence of COVID-19, compared with use of other antihypertensives **Limitations:** retrospective data	

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
ACE INHIBITORS AND ARBS (CONTINUED)		**Felice et al. Am J Hypertens 2020[15]** *(added 7/28/2020)* **Population:** consecutive hypertensive patients presenting to ER in Italy with acute respiratory symptoms and/or fever or diagnosis of COVID-19 (n=133) **Design:** single center, retrospective study **Results:** rate of admission to semi-intensive/intensive care units was lower patients treated with ACEIs or ARBs, compared to patients not treated with ACEIs or ARBs **Limitations:** small retrospective study **Selçuk et al. Clin Exp Hypertens 2020[18]** *(added 7/28/2020)* **Population:** consecutive hypertensive patients hospitalized for COVID-19 in Turkey (n=113) **Design:** retrospective study **Results:** ▪ Patients in the ACEI/ARB group were older and were more likely to have coronary artery disease than those taking other antihypertensives ▪ Use of an ACEI or ARB was associated with a higher frequency of admission to the ICU, endotracheal intubation, and death compared with other antihypertensives **Limitations:** small retrospective study; patients on ACEIs/ARBs more likely to have coronary artery disease and were older	

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).
13. ME Flacco et al. Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart 2020 July 1 (epub).
14. EL Fosbøl et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 2020; 324:168.
15. C Felice et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. Am J Hypertens 2020 June 8 (epub).
16. DHF Gommans et al. Rationale and design of the PRAETORIAN-COVID trial: a double-blind, placebo-controlled randomized clinical trial with valsartan for prevention of acute respiratory distress syndrome in patients with SARS-COV-2 infection disease. Am Heart J 2020; 226:60.
17. K Mackey et al. Update Alert 2: Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults. Ann Intern Med 2020 July 23 (epub).
18. M Selçuk et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens 2020; 42:738.

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.

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Proton Pump Inhibitors (PPIs)			
PROTON PUMP INHIBITORS (PPIs) ▪ Dexlansoprazole *(Dexilant)* ▪ Esomeprazole magnesium (*Nexium*, *Nexium 24HR*, and generics) ▪ Lansoprazole (*Prevacid*, *Prevacid 24HR*, and generics) ▪ Omeprazole (*Prilosec*, *Prilosec OTC*, and generics) ▪ Omeprazole/sodium bicarbonate (*Zegerid*, *Zegerid OTC*, and generics) ▪ Pantoprazole (*Protonix*, and generics) ▪ Rabeprazole (*Aciphex*, and generics)	▪ PPI use may increase the risk of COVID-19 ▪ PPIs increase gastric pH and have been associated with an increased risk of enteric infections[1] ▪ SARS-CoV-1 is impaired at a pH of 3 or below; it is possible that pH has a similar effect on SARS-CoV-2 ▪ Theoretically, higher gastric pH may allow viral replication in the gut; SARS-CoV-2 enters cells via ACE-2 receptors, which are widely expressed in the GI tract[1]	**Almario Gastroenterology 2020[2]** **Population:** English-speaking adults in the US (n=53,130) **Design:** online population-based survey ▪ Survey included questions about PPI and/or H2-receptor antagonist use and positive test results for COVID-19 **Results:** ▪ Twice-daily PPI use was associated with a 3.7-fold increased odds of COVID-19 and once-daily PPI use was associated with a 2.2-fold increase, compared to no PPI use ▪ Use of H2-receptor antagonists was not associated with an increased risk of COVID-19 **Limitations:** observational data, patients taking PPIs may have more underlying risk factors than those not on PPIs	▪ No randomized controlled trials ▪ Twice-daily PPI use was associated with higher risk than once-daily use in an observational trial[2] ▪ American College of Gastroenterology (ACG) recommends use of the lowest effective dose of PPIs in patients with a clinical indication for their use[1]

1. American College of Gastroenterology. Information sheet and FAQs about proton pump inhibitors (PPIs) and risk of COVID-19. Available at: https://webfiles.gi.org/links/media/ACG_Almario_et_al_Info_Sheet_and_FAQs_About_PPIs_COVID19_07072020_FINAL.pdf. Accessed July 30, 2020.
2. CV Almario et al. Increased risk of COVID-19 among users of proton pump inhibitors. Am J Gastroenerol 2020 July 7 (epub). Available at: https://journals.lww.com/ajg/Documents/AJG-20-1811_R1(PUBLISH%20AS%20WEBPART).pdf. Accessed July 30, 2020.

DRUG	CONCERNS/MECHANISM	CLINICAL STUDIES	COMMENTS
Biguanide			
METFORMIN *(added 8/19/2020)* ▪ *Glucophage*, *Glucophage XR,* and generics ▪ *Riomet, Riomet ER* ▪ *Glumetza* ▪ Also available in multiple combinations with other antihyperglycemic agents	▪ Metformin associated with reduced risk of death from COVID-19 in patients with type 2 diabetes in observational studies[1] ▪ Mechanism not established, but may be associated with effects of metformin on glucose control, body weight, and insulin resistance, anti-inflammatory effects of metformin, and decreased viral entry due to effects of metformin on ACE2[1]	**Crouse et al MedRxiv 2020[2]** **Population:** hospitalized patients tested for COVID-19 at a single hospital in the Southern US (n=25,326) **Design:** retrospective review of electronic health records **Results:** in patients with diabetes and COVID-19, metformin was associated with a significant reduction in mortality (OR 0.33; 95% CI 0.13-0.84; p=0.0210) **Limitations:** not peer reviewed, observational data, possible confounders	▪ No randomized controlled trials ▪ Diabetes is a risk factor severe COVID-19 illness and death
	▪ Potential risk of lactic acidosis in hospitalized COVID-19 patients with multiple organ failure	**Bramante et al. MedRxiv 2020[3]** **Population:** hospitalized patients with COVID-19 (n-6,256) **Design:** retrospective review of records from a large health insurance organization **Results:** metformin was associated with a decreased risk of mortality in women (OR 0.792; 95% CI 0.640-0.979) **Limitations:** not peer reviewed, observational data, possible confounders	

1. AJ Scheen. Metformin and COVID-19: from cellular mechanisms to reduced mortality. Diabetes Metab 2020 August 1 (epub). Available at:
2. A Crouse et al. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. MedRxiv 2020 July 29. Available at: https://www.medrxiv.org/content/10.1101/2020.07.29.20164020v1. Accessed August 19, 2020.
3. C Bramante et al. Observtional study of metformin and risk of mortality in patients hospitalized with COVID-19. MedRxiv 2020 June 18. Available at: https://www.medrxiv.org/content/10.1101/2020.06.19.20135095v2. Accessed August 19, 2020.

VACCINE	EFFICACY	SAFETY	COMMENTS
Adenovirus-Vectored Vaccines			
CHIMPANZEE ADENOVIRUS-VECTORED COVID-19 (ChAdOx1 nCoV-19) VACCINE (AstraZeneca) *(updated 8/20/2020)*	**Folegatti et al. Lancet 2020[1]** **Population:** healthy adults 18-55 years old in the UK (n=1077) **Design:** phase 1/2, single-blind, multicenter, randomized controlled trial ▪ participants randomized to 1 dose of ChAdOx1 nCoV-19 vaccine or a comparator meningococcal conjugate vaccine (MenACWY) **Results:** ▪ >90% of participants developed neutralizing antibodies; in 10 patients who received a booster dose, 100% had neutralizing antibodies ▪ Increases in SARS-CoV-2 spike-specific effector T-cell responses occurred by day 7, peaked at day 14, and were maintained up to day 56 ▪ Local and systemic adverse effects were common **Limitations:** preliminary results of phase 1/2 trial	▪ Common adverse effects in the phase 1/2 trial included injection-site pain (67%) and tenderness (83%), fatigue (70%), headache (68%), muscle ache (60%), malaise (61%), chills (56%), feeling feverish (51%), fever (18%) ▪ Use of acetaminophen reduced adverse effects ▪ Transient neutropenia was reported in 46% ▪ No serious adverse events were reported	▪ Chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein ▪ Demonstrated immunogenicity in a phase 1/2 trial ▪ Phase 2/3 trials ongoing in several countries including the US ▪ Manufacturer may be able to deliver emergency doses of the vaccine by fall 2020

VACCINE	EFFICACY	SAFETY	COMMENTS
RECOMBINANT ADENOVIRUS TYPE-5 (Ad5)-VECTORED COVID-19 VACCINE (CanSino Biologics) *(added 7/24/2020)*	**Zhu et al. Lancet 2020**[2] **Population:** healthy adults >18 years old (n=508) **Design:** phase 2, randomized, double-blind, placebo-controlled trial ▪ Participants randomized to 1 dose of vaccine with $1x10^{11}$ viral particles/mL or $5x10^{10}$ viral particles/mL or to placebo **Results:** ▪ Seroconversion rates were >96% ▪ >90% had T-cell responses ▪ antibody responses were lower in participants >55 years old and in those with previous vector immunity ▪ local and systemic adverse reactions were common **Limitations:** phase 2 data; possible lack of power to show a difference between dose groups	▪ The most common adverse effects in the phase 2 trial were injection-site pain (56-57%), fatigue (34-42%), fever (16-32%), and headache (28-29%) ▪ No serious adverse events were reported	▪ Non-replicating adenovirus type-5 (Ad5)-vectored COVID-19 vaccine ▪ Contained replication-defective Ad5 vectors expressing the full-length spike gene based on Wuhan-Hu-1 ▪ Possibly lower responses in people with previous immunity to the vector and in those >55 years old ▪ Approved for military use in China

1. PM Folegatti et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020 July 20 (epub).
2. FC Zhu et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2020 July 20 (epub)

ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S) (Johnson & Johnson) *(added 8/20/2020)*	▪ A single dose induced neutralizing antibody responses in primates (Mercado et al. Nature 2020)[1] ▪ Phase 1/2a human trials started in July	▪ Awaiting outcomes of phase 1/2a human trials	▪ Adenovirus serotype 26 (Ad26) vector-based vaccine expressing the SARS-CoV-2 spike (S) protein ▪ Ad26 technology used in the manufacturer's Ebola vaccine recently approved by the European Commission ▪ Phase 3 trial enrolling up to 60,000 patients expected to begin in September[2]

1. NB Mercado et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020 July 30 (epub).
2. A study of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adult participants (ENSEMBLE). Available at: https://clinicaltrials.gov/ct2/show/NCT04505722. Accessed August 20, 2020.

VACCINE	EFFICACY	SAFETY	COMMENTS
mRNA Vaccines			
mRNA-1273 (Moderna) *(updated 7/30/2020)*	**Jackson et al. NEJM 2020[1]** **Population:** healthy adults 18-55 years old (n=45) **Design:** phase 1, dose-escalation, open-label trial ▪ 2 vaccinations delivered 28 days apart at a 25 mcg, 100 mcg, or 250 mcg dose **Results:** ▪ antibody responses higher with the higher dose after 1st vaccination ▪ serum-neutralizing activity detected after 2nd vaccination in all participants **Limitations:** preliminary results from a phase 1 trial	▪ Fatigue, chills, headache, myalgia, and pain at the injection site reported in the phase 1 trial ▪ Systemic adverse events more common after 2nd vaccination ▪ No serious adverse events reported	▪ Lipid nanoparticle-encapsulated, nucleoside-modified messenger RNA (mRNA)-based vaccine ▪ Encodes the SARS-CoV2 spike (S) glycoprotein, which is needed for host cell attachment and viral entry ▪ FDA granted fast track designation ▪ Phase 3 trial has begun; expected to enroll about 30,000 participants and use a dose of 100 mcg ▪ Reduced viral replication in the lungs and noses of primates (KS Corbett et al. NEJM 2020)[2]
BNT162b1 and BNT162b2 (Pfizer/BioNTech) *(updated 8/23/2020)*	**Mulligan et al. 2020[3]** **Population:** healthy adults 18-55 years old (n=45) **Design:** phase 1/2 randomized, placebo-controlled, observer-blinded dose escalation study ▪ 2 doses separated by 21 days of 10 mcg, 30 mcg, or 100 mcg of BNT162b1 or placebo **Results:** ▪ At day 28, all subjects in the 10- and 30-mcg groups had significantly elevated RBD-binding IgG antibodies and neutralizing antibodies **Limitations:** phase 1/2 results	▪ The most common adverse effects in the phase 2 trial were injection-site pain (58.3-100%), fatigue, and headache ▪ Fever, chills, muscle pain, and joint pain were also reported ▪ No serious adverse events reported	▪ Both are lipid nanoparticle-formulated, nucleoside modified mRNA vaccines ▪ BNT162b1 encodes an optimized SARS-CoV-2 receptor-binding domain (RBD) antigen ▪ BNT162b2 encodes an optimized SARS-CoV-2 full-length spike protein antigen ▪ FDA granted fast track designation ▪ The manufacturer advanced BNT162b2 to phase 2/3 clinical trials based on data from phase 1 trials indicating it caused fewer adverse events than BNT1621b1[2] *(added 8/23/2020)* ▪ Phase 3 trial has begun; expected to enroll up to 30,000 participants

VACCINE	EFFICACY	SAFETY	COMMENTS
BNT162b1 and BNT162b2	**Walsh et al. MedRxiv 2020[2]** *(added 8/23/2020)* **Population:** healthy adults 18-55 and 65-85 years old (n=131) **Design:** phase 1, randomized, observer-blinded, placebo-controlled trial ▪ 2 vaccinations delivered 21 days apart of 1 of 3 doses of BNT162b1 or BNT162b2 or placebo **Results:** ▪ In 65-85-year old subjects, SARS-CoV-2-neutralizing geometric mean titers (GMTs) were 1.1-1.6 times the convalescent serum panel GMTs 7 days after the second dose ▪ In 18-55-year old subjects, neutralizing GMTs were 2.8-3.8 times the convalescent serum panel GMTs ▪ Antibody responses were similar between BNT162b1 and BNT162b2 ▪ Systemic adverse events were milder with BNT162b2 than with BNT162b1 **Limitations:** preliminary results from a phase 1 trial; not peer reviewed		

1. LA Jackson et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. N Engl J Med 2020 July 14 (epub).
2. KS Corrbett et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates.
3. MJ Mulligan et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020 August 12 (epub).

VACCINE	EFFICACY	SAFETY	COMMENTS
Adjuvanted Recombinant Nanoparticle Vaccine			
NVX-CoV2373 (Novavax) *(added 8/21/2020)*	**Keech et al. MedRxiv 2020**[1] **Population:** healthy adults 18-59 years old (n=131) **Design:** phase 1, randomized, observer-blinded, placebo-controlled trial ▪ 2 vaccinations delivered 21 days apart with or without *Matrix-M1* adjuvant or placebo **Results:** ▪ The adjuvanted vaccine induced neutralizing antibody responses and antigen-specific T cells **Limitations:** preliminary results from a phase 1 trial	▪ Tenderness and pain at the injection site ▪ Headache, fatigue, myalgia ▪ No serious adverse events reported	▪ Recombinant nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins[2] ▪ Contains saponin-based *Matrix-M* adjuvant

1. C Keech et al. First-in-human trial of a SARS CoV 2 recombinant spike protein nanoparticle vaccine. MedRxiv 2020 August 5. Available at: https://www.medrxiv.org/content/10.1101/2020.08.05.20168435v1. Accessed August 21, 2020.
2. Press Release. Novavax announces positive phase 1 data for its COVID-19 vaccines candidate. 2020 August 4. Available at: https://ir.novavax.com/news-releases/news-release-details/novavax-announces-positive-phase-1-data-its-covid-19-vaccine. Accessed August 21, 2020.

VACCINE	EFFICACY	SAFETY	COMMENTS
Inactivated Vaccine			
Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain) (Sinopharm) (added 8/21/2020)	**Xia et al. JAMA 2020**[1] **Population:** healthy adults 18-59 years old in China (phase 1 trial n=96; phase 2 trial n=224) **Design:** randomized, double-blind, placebo-controlled phase 1 and 2 trials ▪ Phase 1: 3 injections at day 0, 28, and 56 of a 2.5, 5, or 10 mcg vaccine or aluminum hydroxide adjuvant only ▪ Phase 2: 5 mcg vaccine at days 0 and 14, 5 mcg vaccine at days 0 and 21, or aluminum hydroxide adjuvant only **Results:** ▪ Neutralizing antibodies reported in all dose groups 14 days after completion of 3 injections in phase 1 and 2 injections in phase 2 ▪ 100% seroconversion in patients in the phase 1 trial and in those who received injections on days 0 and 21 in phase 2 ▪ Antibody titers increased after second and third injections **Limitations:** phase 1/2 interim data; did not use comparator group of convalescent serum samples	▪ Pain at the injection site, fever ▪ No serious adverse events reported	▪ Whole-virus inactivated vaccine ▪ Phase 3 trial enrolling 15,000 volunteers started in Abu Dhabi in July

1. S Xia et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes. Interim analysis of 2 randomized clinical trials. JAMA 2020 August 13 (epub).

Subscription Services

Address:
The Medical Letter, Inc.
145 Huguenot St. Ste. 312
New Rochelle, NY 10801-7537
www.medicalletter.org

Customer Service:
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
E-mail: custserv@medicalletter.org

Permissions:
To reproduce any portion of this issue, please e-mail your request to:
permissions@medicalletter.org

Subscriptions (US):
1 year - $159; 2 years - $298;
3 years - $398. $65 per year
for students, interns, residents,
and fellows in the US and Canada.
Reprints - $45 per issue or article

Site License Inquiries:
E-mail: SubQuote@medicalletter.org
Call: 800-211-2769
Special rates available for bulk subscriptions.

Get Connected:

 ISSN 0025-732X