Treatments Considered for COVID-19  (Updated July 31, 2020)

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

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### Antivirals

#### Favipiravir – Avigan (Fuggifilm)

**Dosage:**
- 1600 mg PO bid on day 1, then 600 mg bid on days 2-7
- Some suggest a dosage of 2400-3000 mg bid on day 1, then 1200-1800 mg bid

**Efficacy**

- **Q Cai et al. 2020**
  - **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

- **Chen et al. 2020**
  - **Population:** hospitalized patients (n=236)
  - **Design:** randomized, open-label
  - favipiravir vs arbidol (an influenza drug not available in the US); both in addition to standard therapy
  - **Results:**
    - clinical recovery rate at day 7 was similar for favipiravir and arbidol (51.67% vs 61.21%; p=0.1396)
    - in patients with moderate disease, clinical recovery rates were higher with favipiravir than arbidol (71.43% vs 55.86%; p=0.0199)
  - **Limitations:** not peer-reviewed

**Adverse Effects/Interactions**

- **Adverse Effects:**
  - Elevated LFTs, diarrhea, and elevated serum uric acid
- **Drug Interactions:**
  - May increase serum concentrations of some drugs such as acetaminophen, penicillins, tazobactam, repaglinide, pioglitazone and rosiglitazone, oseltamivir, theophylline, and progestins

**Comments**

- Not FDA-approved and not available yet in the US; approved in other countries for treatment of influenza
- Viral RNA polymerase inhibitor
- Limited data available to date; may be less effective for patients with more severe disease
- Randomized controlled trial of favipiravir alone and in combination with tocilizumab ongoing in China
- Contraindicated for use in pregnant women
- 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

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REMDESIVIR (GILEAD)
(updated 7/31/2020)

Dosage¹:
- Adults ≥40 kg: 200 mg IV on day 1, then 100 mg IV once/day for a total of 5 or 10 days²
- 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 discharge⁷

NIAID. ACTT-1. NEJM 2020³ (added 5/4/20; updated 5/25/20)
Population: 1063 hospitalized patients with advanced disease and lung involvement (88.7% had severe disease)
Design:
- randomized, double-blind, placebo-controlled trial in US, Europe and Asia
- 200 mg on day 1, then 100 mg once/day days 2-10 or until discharge or death
- median time from symptom onset to randomization was 9 days

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

Limitations:
- preliminary report

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

Drug Interactions: (updated 6/18/2020)
- No human drug trial conducted
- Substrate for CYP2C8, CYP2D6, and CYP3A4, and for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (Pgp) transporters in vitro.² Strong inducers of these enzymes/transporters may decrease serum concentrations of remdesivir⁵,⁶ and inhibitors of these enzymes/transporters could potentially increase the risk of toxicity such as hepatotoxicity¹⁴
- 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 recommended¹² (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-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO because there is uncertainty regarding benefits of remdesivir in these patients⁷ (added 7/25/2020)
- NIH guidelines state there are insufficient data to recommend for or against use in patients with mild or moderate COVID-19⁷ (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
**J Grein et al. NEJM 2020**

**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**

**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

- 31% shorter recovery time with remdesivir (11 days vs 15 days with placebo) reported in a randomized, double-blind trial *(updated 5/25/2020)*

- An editorial in NEJM suggests priority be given to a 5-day course of remdesivir for patients at early stages of severe disease *(added 5/25/2020)*

- 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 *(added 7/9/2020)*

**Pregnancy:**
- No data are available in pregnant women
**SIMPLE Trial 2020** *(added 6/1/2020)*

**Population:** hospitalized patients with moderate COVID-19 (pneumonia, but not reduced oxygen levels) (n = 584)

**Design:** randomized, open-label; remdesivir x 5 days or 10 days in addition to standard care or standard care alone

**Results:**
- significantly more patients taking remdesivir x 5 days had clinical improvement of ≥1 point on an ordinal scale than those who received standard care alone (76% vs 66%; p=0.026)
- treatment with remdesivir x 10 days did not reach statistical significance (70% vs 66%)

**Limitations:** not yet published


**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
- 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)
**REMDESIVIR (CONTINUED)**

**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

| 2. | [https://www.fda.gov/media/137566/download](https://www.fda.gov/media/137566/download) |
**Convalescent Plasma**

**CONVALESCENT PLASMA**

**Dosage:**
- Optimal dosage not established
- One or two 200-ml infusions

**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**

**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**

**Surviving Sepsis Campaign guidelines suggest against routine use of convalescent plasma in critically ill adults**

**The FDA is allowing access through expanded access and single patient emergency protocols**

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**ARDS = acute respiratory distress syndrome**

### Intravenous Immune Globulin (IVIG)

**INTRAVENTOUS 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**
- **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**
- **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)*
- Surviving Sepsis Campaign guidelines suggest against routine use of standard IVIG in critically ill adults
- 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 illness
- NIH guidelines state there are insufficient data to recommend for or against use of SARS-CoV-2 immunoglobulins *(added 7/22/2020)*
- Shortages have been an issue (even prior to COVID-19)
INTRAVENOUS IMMUNE GLOBULIN (IVIG) (CONTINUED)

Shao et al. 2020
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

Glutathione and N-acetylcysteine

**GLUTATHIONE**

**Dosage:** 2 g IV/PO used in case report

**N-ACETYLCYSTEINE (NAC; GLUTATHIONE PRECURSOR)**
6 g/day IV

*(Added 4/28/2020)*

No clinical trial results available

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

R Horowitz et al. Resp Med Case Rep 2020

**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

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<td><strong>MESENCHYMAAL STEM CELL THERAPY (updated 7/21/2020)</strong></td>
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</table>

**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-19² (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-19³ (updated 7/21/2020)**

**NIH guidelines recommend against use of mesenchymal stem cells, except in a clinical trial⁴ (updated 7/21/2020)**

**FDA has warned about safety concerns with use of unapproved or illegal stem cell therapies⁵ (updated 7/21/2020)**

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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.
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<td>Widely available corticosteroid</td>
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<td><strong>DEXAMETHASONE</strong></td>
<td></td>
<td>Anti-inflammatory effects may modulate immune-mediated lung damage</td>
</tr>
<tr>
<td><em>(updated 7/27/2020)</em></td>
<td><strong>RECOVERY Trial 2020</strong>*</td>
<td></td>
<td>Authors of RECOVERY trial state that treating 8 ventilated patients or 25 patients requiring oxygen would prevent 1 death*2</td>
</tr>
<tr>
<td></td>
<td><strong>Population:</strong> hospitalized patients in the UK <em>(n=6425)</em></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td><strong>Design:</strong></td>
<td></td>
<td>IDSA guidelines recommend use of dexamethasone for hospitalized patients with severe illness (patients with SpO2≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO)*4</td>
</tr>
<tr>
<td></td>
<td>- Randomized, controlled, open-label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone</td>
<td></td>
<td>NIH and IDSA recommend against use of dexamethasone for treatment of COVID-19 in patients who do not require supplemental oxygen*3,4</td>
</tr>
<tr>
<td></td>
<td>- Dexamethasone 6 mg PO or IV once daily <em>(n=2104)</em> x 10 days vs usual care <em>(n=4321)</em></td>
<td></td>
<td>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 <em>(added 7/20/2020)</em></td>
</tr>
<tr>
<td></td>
<td><strong>Results:</strong> 28-day mortality rates (dexamethasone vs usual care)</td>
<td></td>
<td><strong>Adverse Effects:</strong> hyperglycemia, insomnia, adrenal suppression, delirium, depression, mania</td>
</tr>
<tr>
<td></td>
<td>- <strong>Overall:</strong> 22.9% vs 25.7% <em>(p&lt;0.001)</em></td>
<td></td>
<td><strong>Drug Interactions:</strong></td>
</tr>
<tr>
<td></td>
<td>- Patients on <strong>invasive mechanical ventilation:</strong> 29.3% vs 41.4% <em>(rate ratio 0.64; 95% CI 0.51-0.81)</em></td>
<td></td>
<td>- Induces CYP3A4 and P-gp and may decrease concentrations of drugs that are substrates of CYP3A4 or P-gp</td>
</tr>
<tr>
<td></td>
<td>- <strong>Oxygen</strong> without invasive mechanical ventilation: 23.3% vs 26.2% <em>(rate ratio 0.82; 95% CI 0.72-0.94)</em></td>
<td></td>
<td>- Causes hyperglycemia; may decrease the efficacy of antihyperglycemic drugs</td>
</tr>
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<td></td>
<td>- <strong>No respiratory support at randomization:</strong> 17.8% vs 14.0% <em>(rate ratio 1.19; 95% CI 0.91-1.55)</em></td>
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</tr>
<tr>
<td></td>
<td><strong>Limitation:</strong> preliminary results; open-label study</td>
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</tbody>
</table>
### DRUG AND DOSAGE

**DEXAMETHASONE (continued)**

### EFFICACY

**Keller et al. J Hosp Med 2020**

*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 $\geq 20$ 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

### ADVERSE EFFECTS/INTERACTIONS

### COMMENTS

**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

---

## Inhaled Corticosteroids

### Efficacy

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<th>Design</th>
<th>Results</th>
<th>Limitations</th>
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<tr>
<td>Iwabuchi et al. J Infect Chemother 2020</td>
<td>hospitalized patients with poor oxygenation and CT findings in Japan (n=3)</td>
<td>case series: all given inhaled ciclesonide</td>
<td>favorable outcomes in all cases of 3 patients</td>
<td>cases series of 3 patients</td>
</tr>
<tr>
<td>Schultze et al. medRxiv 2020</td>
<td>asthma (n=817,973) and COPD (n=148,588) patients in the UK</td>
<td>cohort study using linked electronic health records (OpenSAFELY platform); compared patients using an ICS to those taking other drugs for COPD/asthma</td>
<td>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)</td>
<td>observational; not peer reviewed; possible confounding</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>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)</td>
<td></td>
</tr>
</tbody>
</table>

### Adverse Effects/Interactions

- **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

### Comments

- 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
- NIH guidelines recommend that patients with COVID-19 who are using inhaled corticosteroids for treatment of asthma or COPD should not discontinue treatment
- 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

---

### DRUG AND DOSAGE

**IL-6 Inhibitors**

#### SARILUMAB – KEVZARA®
(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**

**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*(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

**Comments:**
- 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 *(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
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>Efficacy</th>
<th>Adverse Effects/Interactions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **TOCILIZUMAB – ACTEMRA® (GENENTECH)** | Zhou et al. Lancet 2020<sup>6</sup>  
**Population:** hospitalized patients in China (n=191)  
**Design:** retrospective study  
**Results:** elevated levels of IL-6 were associated with severe illness and death | **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<sup>8</sup>  
- Infectious Diseases Society of America recommends use only in the context of a clinical trial<sup>9</sup>  
- NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-6 inhibitors<sup>3</sup> (updated 4/28/2020)  
- Randomized, controlled trials are ongoing in the US  
- 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 |
| **Dosage:** | Xu et al 2020<sup>7</sup>  
**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) |  
- not peer-reviewed | - 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<sup>8</sup>  
- Infectious Diseases Society of America recommends use only in the context of a clinical trial<sup>9</sup>  
- NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-6 inhibitors<sup>3</sup> (updated 4/28/2020)  
- Randomized, controlled trials are ongoing in the US  
- 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 |
| **Optimal dosage not established** | **Limitations:** |  
- not peer-reviewed |  
- not peer-reviewed |
| **8 mg/kg (max 400 mg) IV once**<sup>5</sup> |  
**Infuse over 1 hour** |  
- not peer-reviewed |  
- not peer-reviewed |
| **Optimal timing of administration is unclear** |

---

**TOCILIZUMAB**

**ACTEMRA® (GENENTECH)**

**Dosage:**
- Optimal dosage not established
- 8 mg/kg (max 400 mg) IV once
- Infuse over 1 hour
- Optimal timing of administration is unclear

**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**

**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<sup>1</sup>; 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

**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
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% vs 15%; p=0.42)
Limitation: observational data

1. FDA-approved for treatment of rheumatoid arthritis.
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.
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td><strong>IL-1 Receptor Antagonist</strong></td>
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<tr>
<td><strong>ANAKINRA – KINERET</strong>&lt;br&gt;(BIOVITRUM AB)&lt;br&gt;(updated 7/27/2020)</td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>Optimal dosage for COVID-19 unknown&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>Adverse Effects:</td>
<td>Clinical trials are ongoing&lt;sup&gt;1,2&lt;/sup&gt;</td>
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<td></td>
<td>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.</td>
<td>Injection-site reactions, infections, neutropenia, thrombocytopenia, hepatic transaminase elevations</td>
<td>IL-1 receptor antagonist; IL-1 mediates inflammatory and immune responses antagonist</td>
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<tr>
<td></td>
<td></td>
<td>Drug Interactions:</td>
<td>May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease</td>
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<td></td>
<td></td>
<td>Use with TNF inhibitors or other biologics may increase risk of serious infections and neutropenia and should be avoided</td>
<td>NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors&lt;sup&gt;3&lt;/sup&gt; (updated 4/28/2020)</td>
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<tr>
<td></td>
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<td></td>
<td>FDA-approved for treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease.</td>
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<td>Pregnancy:</td>
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<td></td>
<td>Not associated with adverse pregnancy outcomes in small retrospective studies in humans or in animal studies</td>
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<tr>
<td><strong>Cavalli et al. Lancet Rheum 2020&lt;sup&gt;4&lt;/sup&gt;</strong></td>
<td>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</td>
<td><strong>Adverse Effects:</strong></td>
<td></td>
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<td></td>
<td>Design: retrospective cohort study; single hospital in Italy</td>
<td><strong>Drug Interactions:</strong></td>
<td></td>
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<tr>
<td></td>
<td>Addition of anakinra vs standard treatment (HCQ + LPV/RTV)</td>
<td>Use with TNF inhibitors or other biologics may increase risk of serious infections and neutropenia and should be avoided</td>
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<tr>
<td></td>
<td>Results: at 21 days</td>
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<td>May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease</td>
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<td></td>
<td>Improved survival with high-dose (5 mg/kg IV bid) anakinra vs standard treatment (90% vs 56%; p=0.009)</td>
<td>NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors&lt;sup&gt;3&lt;/sup&gt; (updated 4/28/2020)</td>
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<tr>
<td></td>
<td>Mechanical ventilation-free survival similar between groups (72% vs 50%; p=0.15)</td>
<td></td>
<td>FDA-approved for treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease.</td>
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<td></td>
<td>Associated with reduced serum C-reactive protein and improved respiratory function</td>
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<td></td>
<td><strong>Limitations:</strong> small, retrospective study</td>
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<tr>
<td><strong>Cauchois et al. Proc Natl Acad Sci U S A 2020&lt;sup&gt;5&lt;/sup&gt; (added 7/27/2020)</strong></td>
<td>Population: hospitalized patients in France with hypoxemic pneumonia or ARDS (n=22)</td>
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<tr>
<td></td>
<td>Design: retrospective</td>
<td><strong>Adverse Effects:</strong></td>
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<td></td>
<td>anakinra plus standard care compared to standard care alone</td>
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<td></td>
<td>anakinra dosage: 300 mg IV x 5 days, then tapered to 200 mg/d x 2 days, then 100 mg x 1 day</td>
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<tr>
<td>DRUG AND DOSAGE</td>
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</table>
| 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 | | |

## Janus Kinase (JAK) Inhibitors

<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| **BARICITINIB – OLMIANT (LILLY)** | ▪ 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 | ▪ 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 effect¹ (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/mm³, the absolute neutrophil count falls below 1000 cells/mm³, or the hemoglobin level falls below 8 g/dL

**Pregnancy:**
▪ Administration to pregnant animals resulted in reduced fetal weights, embryolethality, and skeletal malformations

**Dosage:**
▪ Optimal dosage for COVID-19 not established
▪ 2 mg PO daily
**RUXOLITINIB – JAKAFI (INCYTE/NOVARTIS)**

**Dosage:**
- Optimal dosage not established
- 10 mg PO bid x 14 days
- Taper dosage when stopping: 5 mg bid x 2 days, then 5 mg once daily x 1 day

**EFFICACY**
- Manufacturer is initiating phase III clinical trials in patients with severe COVID-19 to compare ruxolitinib to standard care.

**ADVERSE EFFECTS/INTERACTIONS**

**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 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 $\geq$100 X $10^9$/L

**COMMENTS**
- NIH recommends against use of JAK inhibitors, except in the context of a clinical trial, because of their broad immunosuppressive effect (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

---

2. Dosage to be used in clinical trials for COVID-19.
## TNF Inhibitors

### Optimal dosage for treatment of COVID-19 not established

- Adalimumab (*Humira*)
- Certolizumab pegol (*Cimzia*)
- Infliximab (*Remicade*, and biosimilars)
- Etanercept (*Enbrel*)
- Golimumab (*Simponi*)

### Efficacy

**Brenner et al. Gastroenterology 2020**

**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**

**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/Interactions

**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

### Comments

- 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
- Pregnant women not treated with TNF inhibitors
- Placental transfer of anti-TNF antibodies is higher in the late second and third trimesters, especially with infliximab, adalimumab, and golimumab

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</table>
| **Anti-CD6 Monoclonal Antibody** | **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  
**Results:** at one month, no deaths occurred in patients treated with itolizumab and 3 deaths occurred in patients treated with supportive care alone  
**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 |

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<tr>
<td><strong>Antimalarials</strong></td>
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<tr>
<td><strong>CHLOROQUINE</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>Based on <em>in vitro</em> data (M Wang et al, Cell Res 2020)&lt;sup&gt;4&lt;/sup&gt;</td>
<td><em>In vitro</em> activity against SARS-CoV-2, SARS-CoV, and MERS-CoV</td>
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<tr>
<td>▪ Optimal dosage not established</td>
<td>Unpublished clinical data from China&lt;sup&gt;3&lt;/sup&gt; in approximately 100 patients suggest more rapid decline in fever, improvement on lung CT scan, shorter time to recovery vs control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Dosages used in COVID-19 clinical trials have varied</td>
<td>ChloroCovid&lt;sup&gt;19&lt;/sup&gt; <em>(updated 4/30/2020)</em></td>
<td>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&lt;sup&gt;5&lt;/sup&gt; <em>(updated 4/28/2020)</em></td>
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<tr>
<td>500 mg chloroquine phosphate (300 mg chloroquine base) bid x 7-10 days</td>
<td>Population: hospitalized patients with severe illness in Brazil <em>(n=81)</em></td>
<td>Infectious Diseases Society of America recommends use in the context of a clinical trial&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>OR</td>
<td>Design: parallel, double-blind, randomized, phase Ib</td>
<td>NIH guidelines recommend against use of chloroquine, except in a clinical trial&lt;sup&gt;19&lt;/sup&gt; <em>(updated 6/16/2020)</em></td>
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<tr>
<td>500 mg bid x 2 days, then 500 mg once/day x 12 days&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td></td>
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<td>OR</td>
<td>Results: Trial stopped early because of a higher rate of death and QT interval prolongation in the high-dose chloroquine group</td>
<td>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&lt;sup&gt;13&lt;/sup&gt; <em>(updated 6/16/2020)</em></td>
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<td>1 g on day 1, then 500 mg once daily x 4-7 days</td>
<td>Lethality was 39.0% <em>(16 of 41)</em> in the high-dose group and 15.0% <em>(6 of 40)</em> in the low-dose group at day 13</td>
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<td>QTc interval &gt;500 milliseconds occurred in 18.9% <em>(7 of 37)</em> in the high-dose group compared to 11.1% <em>(4 of 36)</em> in the low-dose group</td>
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<td>Respiratory secretion negative in 22.2% <em>(6 of 27)</em> at day 4</td>
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<td>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 <em>(in G6PD-deficient patients)</em>, neuropathy, convulsions, extrapyramidal disorders, neuropsychiatric changes, hypotension, cardiomyopathy, hypoglycemia</td>
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<td>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&lt;sup&gt;5-8&lt;/sup&gt; 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&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Cases <em>(some fatal)</em> 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&lt;sup&gt;9&lt;/sup&gt;</td>
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<tr>
<td>CHLOROQUINE¹ (CONTINUED)</td>
<td><strong>Mehra et al. 2020</strong>²² (added 5/26/20) (updated 6/4/2020) <strong>Study Retracted</strong>²⁴***</td>
<td><strong>Drug Interactions:</strong>&lt;br&gt;▪ Avoid use with QTc prolonging drugs⁶⁻⁸&lt;br▪ Substrate of CYP2C8, 2D6, and 3A4, and inhibitor of CYP2D6¹⁰,¹¹&lt;br▪ Use with antihyperglycemic drugs can increase risk of hypoglycemia&lt;br▪ Separate from antacids/kaolin by 4 hours&lt;br▪ Use with tamoxifen can increase risk of ocular toxicity and should be avoided&lt;br▪ FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended²⁶ (added 6/18/2020)</td>
<td><strong>Pregnancy:</strong>&lt;br▪ Accumulates in fetal ocular tissues and is retained there for months after elimination from remainder of body&lt;br▪ Chloroquine has been used safely in pregnant women for treatment and prophylaxis of malaria</td>
</tr>
</tbody>
</table>

| 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:**<br▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group | **Limitation:** observational |
| HYDROXYCHLOROQUINE (HCQ)¹ – GENERICS PLAQUENIL (CONCORDIA) | **P Gautret et al. Int J Antimicrob Agents 2020**¹⁴ | **Adverse Effects:**<br▪ Better tolerated than chloroquine<br▪ 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<br▪ QT interval prolongation and arrhythmias, including torsades de pointes can occur. | **In vitro activity against SARS-CoV-2**<br▪ The FDA issued a Drug Safety Communication warning against use of hydroxychloroquine outside of a clinical trial because of the risk of serious arrhythmias, including QT prolongation; it is not recommended for treatment of outpatients⁹ (updated 4/28/2020) |

| (updated 7/31/2020) | **Dosage:**<br▪ Optimal dosage not established<br▪ Dosages used in COVID-19 clinical trials have varied | **Results:**<br▪ HCQ-treated patients had more rapid viral clearance vs controls | **Population:** hospitalized patients; varying severity of illness (n=42) **Design:**<br▪ open-label, observational<br▪ HCQ + azithromycin vs HCQ vs standard care |
DRUG AND DOSAGE

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

EFFECTIVE

▪ 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

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

Population: hospitalized patients with pneumonia requiring oxygen ≥2 L (n=181)

ADVERSE EFFECTS/INTERACTIONS

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. 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.

▪ 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

▪ 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

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

COMMENTS

▪ Infectious Diseases Society of America recommends use in the context of a clinical trial

▪ NIH guidelines recommend against use of hydroxychloroquine, except in a clinical trial (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 (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 (added 7/17/2020)

▪ In one randomized controlled trial, hydroxychloroquine was not more effective than placebo for post-exposure prophylaxis; other trials are ongoing (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 (updated 6/16/2020)
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
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</thead>
</table>
| 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* ([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 coadministered6-8  
▪ 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 recommended26 (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  |
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<tr>
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</thead>
</table>
| HYDROXYCHLORQUINE (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 | | |
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**HYDROXYCHLOROQUINE (CONTINUED)**


### 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

[^22]: [Link to reference]
[^24]: [Link to reference]
<table>
<thead>
<tr>
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</table>
| HYDROXYCHLORQUINE (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** *(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 |
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<tr>
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<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
<td><strong>CP Skipper et al. Ann Intern Med 2020</strong>&lt;sup&gt;a&lt;/sup&gt; (<em>added 7/17/2020</em>)</td>
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<td><strong>Population:</strong> symptomatic outpatients with COVID-19 or probable COVID-19 within 4 days of symptom onset (n=423)</td>
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<td><strong>Design:</strong> randomized, double-blind, placebo-controlled trial</td>
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<td>▪ HCQ (800 mg once, 600 mg 6-8 hrs later, then 600 mg once/day x 4 days) vs placebo</td>
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<tr>
<td><strong>Results:</strong></td>
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<td>▪ 81% had confirmed COVID-19 or exposure to a person with confirmed infection</td>
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<td>▪ 56% enrolled within 1 day of symptom onset</td>
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<tr>
<td>▪ no significant difference in symptom severity over 14 days between HCQ and placebo groups (relative difference in symptom severity 12%; p=0.117)</td>
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<tr>
<td>▪ no significant difference in percentage of patients who had symptoms at 14 days (24% vs 30% with placebo; p=0.21)</td>
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<tr>
<td>▪ significantly more patients treated with HCQ had <strong>adverse effects</strong> (43% vs 22%; p&lt;0.001)</td>
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<td>▪ 4 hospitalizations and 1 nonhospitalized death in the HCQ group vs 10 hospitalizations and 1 hospitalized death in the placebo group (p=0.29)</td>
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<tr>
<td><strong>Limitations:</strong> only 58% of patients received COVID-19 testing</td>
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| HYDROXYCHLOROQUINE (CONTINUED) | **Rosenberg et al. JAMA 2020**<sup>30</sup> *(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**<sup>31</sup> *(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 |                                |          |
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</table>
| 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 | | |
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<tr>
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<tr>
<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
<td><strong>PROPHYLAXIS TRIALS:</strong></td>
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<td><strong>Population:</strong> adults with household or occupational exposure to an individual with confirmed COVID-19 at a distance &lt;6 feet for &gt;10 mins with no mask or eye shield (high-risk) or with a mask but no eye shield (moderate-risk) (n = 821)</td>
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<td></td>
<td><strong>Design:</strong> randomized, double-blind, placebo-controlled trial in the US and Canada</td>
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<td>Prophylaxis given within 4 days after exposure</td>
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<td></td>
<td>• HCQ (800 mg x 1, then 600 mg in 6 to 8 hrs, then 600 mg daily x 4 days) vs placebo</td>
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<tr>
<td></td>
<td><strong>Results:</strong></td>
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<tr>
<td></td>
<td>• 87.6% had a high-risk exposure</td>
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<td>• 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)</td>
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<tr>
<td></td>
<td>• Patient-reported adherence to study drug regimen was lower in HCQ group (75.4% with HCQ vs 82.6% with placebo; p=0.01)</td>
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<tr>
<td></td>
<td>• Adverse effects occurred more often with HCQ (GI effects most common)</td>
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<td></td>
<td>• No arrhythmias or deaths reported</td>
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<td><strong>Limitations:</strong> endpoint did not require laboratory-confirmed COVID-19; study population generally younger and healthier than those at most risk for COVID-19</td>
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<td><strong>COMMENTS</strong></td>
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<tr>
<td><strong>N White and W Schilling et al (COPCOV trial)</strong> (added July 1, 2020) (prophylaxis)</td>
<td><strong>Population:</strong> Healthcare workers and staff who have close contact with COVID-19 patients (anticipated enrollment is 40,000+ subjects)</td>
<td><strong>Design:</strong> ▪ Randomized, double-blind, placebo-controlled, multi-center prophylaxis trial ▪ Chloroquine/hydroxychloroquine vs placebo</td>
<td><strong>Results:</strong> trial enrolling as of July 2020</td>
</tr>
<tr>
<td><strong>Mitja et al. medRxiv 2020</strong> (added 7/31/2020)</td>
<td><strong>Population:</strong> asymptomatic contacts exposed to a PCR-positive COVID-19 case in Spain (n=2314)</td>
<td><strong>Design:</strong> open-label, cluster-randomized trial ▪ HCQ 800 mg once, then 400 mg/day x 6 days vs no therapy</td>
<td><strong>Results:</strong> 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)</td>
</tr>
</tbody>
</table>

1. FDA-approved for other indications.
2. Experimental dosage used for treatment of COVID-19 in trials, but optimal dosage not yet established.
<table>
<thead>
<tr>
<th></th>
<th>Drug and Dosage</th>
<th>Efficacy</th>
<th>Adverse Effects/Interactions</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>11</td>
<td>D Projean et al. In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoenzymes catalyzing N-desethylchloroquine formation. Drug Metab Dispos 2003; 31:748.</td>
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<td><strong>DRUG AND DOSAGE</strong></td>
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</table>
| Macrolide Antibiotic | P Gautret et al. *Int J Antimicrob Agents* 2020³ | Adverse Effects:  
- GI disturbances, headache, dizziness, hepatotoxicity, QT prolongation⁴ | *In vitro* activity against some viruses (influenza A H1N1 and Zika); no data on its activity against SARS-CoV-2 |
| **AZITHROMYCIN – GENERICS**  
**ZITHROMAX** (PFIZER)¹ |  
- 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)  
- In addition to hydroxychloroquine  
  Rosenberg et al. *JAMA* 2020¹⁰  
  *(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  
  **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 coadministered⁴⁻⁶  
  - 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 ms⁷  
  - May increase the risk of toxicity with digoxin, cyclosporine, tacrolimus  
  - Minimal data supporting efficacy in COVID-19 in humans and cardiac toxicity can occur when used with chloroquine/hydroxychloroquine  
  - Infectious Diseases Society of America recommends use only in the context of a clinical trial⁸  
  - NIH recommends against the use of hydroxychloroquine plus azithromycin, except in the context of a clinical trial, because of the potential for toxicities⁹ *(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) |
| Dosage:  
- Optimal dosage not established  
  500 mg on day 1, then 250 mg once/day on days 2-5²  
- In addition to hydroxychloroquine |
| Pregnancy:  
- No evidence of fetal harm |

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<td><strong>S Arshad et al. Int J Infect Dis 2020</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
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<td><em>(added July 7, 2020)</em></td>
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<td><strong>Population</strong>: Consecutive hospitalized patients in a hospital system in Michigan (n=2541)</td>
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<td><strong>Design</strong>: Multi-center, retrospective observational study comparing hydroxychloroquine alone or with azithromycin, azithromycin alone or neither</td>
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<td><strong>Results</strong>:</td>
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<td>▪ in-hospital mortality was 20.1% with hydroxychloroquine + azithromycin, 13.5% with hydroxychloroquine, 22.4% with azithromycin, and 26.4% with neither drug (p&lt;0.001)</td>
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<td><strong>Mehra et al. Lancet 2020</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
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<td><em>(added 5/26/20)</em></td>
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<td><em>(updated 6/4/2020)</em></td>
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<td></td>
<td><em><strong><strong>Study Retracted</strong>&lt;sup&gt;13</strong></em></td>
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<td>▪ 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</td>
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<td><strong>Population</strong>: 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)</td>
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<th>ADVERSE EFFECTS/INTERACTIONS</th>
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</tr>
</thead>
</table>
| **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** | **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 | |

*Updated 4/28/2020*
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<td>AZITHROMYCIN (continued)</td>
<td><strong>Cavalcanti et al. NEJM 2020</strong>¹⁵ (added 7/23/2020)</td>
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<td><strong>Population:</strong></td>
<td>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)</td>
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<tr>
<td><strong>Design:</strong></td>
<td>open-label, multicenter randomized controlled trial</td>
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<tr>
<td>▪</td>
<td>HCQ 400 mg bid vs HCQ 400 mg bid plus azithromycin 500 mg once/day x 7 days vs standard care alone</td>
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<tr>
<td><strong>Results:</strong></td>
<td>Treatment started a median of 7 days after symptom onset; patients who started treatment up to 14 days after symptom onset were included</td>
<td>▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone</td>
<td></td>
</tr>
<tr>
<td>▪</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limitations:</strong></td>
<td>open-label trial, some patients previously received treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. FDA-approved for other indications.
2. Experimental dosage used for treatment of COVID-19 in trials, but optimal dosage not yet established.
5. DN Juurlink. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ 2020 April 8 (epub).
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Protease Inhibitors</strong></td>
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<tr>
<td><strong>ATAZANAVIR (ATV) – REYATAZ (BMS) AND GENERICS</strong></td>
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<tr>
<td><strong>Dosage:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Optimal dosage/duration not established</td>
<td>▪ Predicted to inhibit SARS-CoV-2 replication(^3,4)</td>
<td>▪ No clinical trial data available</td>
<td>▪ No clinical trials available evaluating use of atazanavir for COVID-19</td>
</tr>
<tr>
<td>▪ 300-400 mg PO once/day(^2)</td>
<td></td>
<td></td>
<td>▪ Available in powder form or capsules can be opened for administration via enteral tube</td>
</tr>
<tr>
<td><strong>Adverse Effects:</strong></td>
<td>▪ Nausea, diarrhea, asymptomatic indirect hyperbilirubinemia, rash, nephrolithiasis, cholelithiasis, PR interval prolongation</td>
<td>▪ 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</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interactions:</strong></td>
<td>▪ Substrate of CYP3A4 and inhibitor of CYP3A4 and CYP2C8(^5)</td>
<td></td>
<td>▪ 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)</td>
</tr>
<tr>
<td><strong>Pregnancy:</strong></td>
<td>▪ Does not appear to increase the risk of major birth defects</td>
<td></td>
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<tr>
<td><strong>DARUNAVIR/Cobicistat (PREZCOBIX) (JOHNSON &amp; JOHNSON)</strong></td>
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<tr>
<td><strong>Dosage:</strong></td>
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<tr>
<td>▪ 800/150 mg PO once/day x 5 days(^7)</td>
<td></td>
<td></td>
<td>▪ An initial laboratory study had suggested darunavir (at exposures higher than those achieved in humans) may be effective against SARS-CoV-2</td>
</tr>
<tr>
<td><strong>Shanghai Public Health Clinical Center (SPHCC)(^8,9)</strong></td>
<td></td>
<td></td>
<td>▪ No evidence that darunavir is effective for treatment of COVID-19</td>
</tr>
<tr>
<td><strong>Population:</strong> hospitalized patients (n=30)</td>
<td>▪ darunavir/cobicistat 800/150 mg once/day x 5 days vs standard care</td>
<td>▪ 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)</td>
<td></td>
</tr>
<tr>
<td><strong>Design:</strong></td>
<td>▪ randomized, open label</td>
<td></td>
<td><strong>Pregnancy:</strong></td>
</tr>
<tr>
<td></td>
<td>▪ darunavir/cobicistat was not effective</td>
<td>▪ Not recommended for use in pregnant women</td>
<td></td>
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</tbody>
</table>
**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 bid²
- With or without food
- Tablets should not be crushed (decrease exposure)

**Efficacy**

**B Cao et al. NEJM 2020¹⁰**

**Population:**
- hospitalized patients w/pneumonia, SaO₂ ≤94% or PaO₂:FiO₂ ≤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


**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 (EC₅₀) 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, hepatotoxicity, pancreatitis, PR and QT interval prolongation, bradycardia¹⁴

**Drug Interactions:**
- Substrate and inhibitor of CYP3A⁵
- Avoid use with other PR or QT interval-prolonging drugs¹¹

**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 patients¹²
- Infectious Diseases Society of America recommends use only in the context of a clinical trial¹³
- NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data⁶

**Pregnancy:**
- No association with teratogenic effects; may be associated with preterm delivery
<table>
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<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
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</thead>
<tbody>
<tr>
<td>LOPINAVIR/RITONAVIR (continued)</td>
<td><strong>Limitations:</strong> small case series; only trough concentration evaluated; no \textit{in vivo} data on EC$_{50}$ dose of lopinavir for SARS-CoV-2</td>
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</table>

1. FDA-approved for other indications.
7. Dosage used for treatment of COVID-19 in trials; optimal dosage not established.
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<thead>
<tr>
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<tr>
<td><strong>Interferon Beta and Ribavirin</strong></td>
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</table>
| **INTERFERON BETA-1B – BETASERON EXTAVIA** | **Hung et al. Lancet 2020**<sup>1</sup>  
**Population:** hospitalized patients with symptom duration ≤14 days (n=127)  
**Design:** prospective, randomized, open-label, multi-center  
**Dosage used in clinical trial:** interferon beta-1b: 1 mL on alternate days x 1-3 doses depending on day of initiation | **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 | **Has antiviral properties**  
**In vitro** activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies<sup>2</sup>  
**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<sup>3</sup>** |
| **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  
**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 |  
**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  
**SG016 2020 – Inhaled Interferon**<sup>5</sup>  
*(added 7/20/2020)*  
**Population:** hospitalized patients in UK (n=101)  
**Design:** phase 2 double-blind, placebo-controlled trial  
**Dosage:** nebulized interferon beta (SNG001) vs placebo  
**Results:**  
Mean symptom duration before starting treatment (9.6 days interferon vs 9.8 days placebo) |  
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 |

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>- 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)</td>
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<tr>
<td></td>
<td>- 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)</td>
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<td></td>
<td>- Breathlessness reduced in patients receiving interferon compared to placebo (p=0.007)</td>
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<td></td>
<td>- 0 deaths with interferon; 3 deaths with placebo</td>
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<td>- In patients with more severe disease on admission (requiring supplemental oxygen), interferon nonsignificantly increased the likelihood of hospital discharge (p=0.096)</td>
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<tr>
<td></td>
<td>- Median time to discharge was 6 days with interferon and 9 days with placebo</td>
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<tr>
<td></td>
<td><strong>Limitations:</strong> phase 2 trial; data not yet published</td>
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<tr>
<td><strong>Ivermectin – Stromectol (MSD)</strong></td>
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<td><strong>Dosage:</strong></td>
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<tr>
<td>▪ Dosage for COVID-19 not established</td>
<td>▪ No data on its efficacy for treatment of COVID-19</td>
<td>▪ Generally well tolerated when used for treatment of lice; diarrhea has occurred</td>
<td>▪ FDA-approved for treatment of intestinal strongyloidiasis and onchocerciasis; used off-label for a variety of other parasitic infections including lice and scabies</td>
</tr>
<tr>
<td>200-400 mcg/kg/dose PO&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Inhibits SARS-CoV-2 in vitro; ~5000-fold reduction in viral RNA in cell culture 48 hours after a single treatment&lt;sup&gt;2&lt;/sup&gt;</td>
<td>▪ Diarrhea, nausea, dizziness, pruritis, dermatologic reactions, lymphadenitis, arthralgia, and fever have been reported when used for treatment of onchocerciasis</td>
<td>▪ Inhibited SARS-CoV-2 in vitro; may inhibit nuclear transport activity</td>
</tr>
<tr>
<td></td>
<td>▪ Adverse Effects:</td>
<td>▪ Drug Interactions:</td>
<td>▪ Clinical data on its efficacy for treatment of COVID-19 are needed</td>
</tr>
<tr>
<td></td>
<td>▪ Generally well tolerated when used for treatment of lice; diarrhea has occurred</td>
<td>▪ Azithromycin may increase serum concentrations of ivermectin</td>
<td>▪ Pregnancy:</td>
</tr>
<tr>
<td></td>
<td>▪ Diarrhea, nausea, dizziness, pruritis, dermatologic reactions, lymphadenitis, arthralgia, and fever have been reported when used for treatment of onchocerciasis</td>
<td></td>
<td>▪ Limited data available in pregnant women</td>
</tr>
</tbody>
</table>

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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.
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **Colchicine** | **GRECCO-19 trial**<sup>1</sup>  
**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:**<sup>2</sup>  
▪ 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 |

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Dipeptidyl Peptidase-4 (DPP-4) Inhibitors</strong></td>
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</table>
| **ALOGLIPTIN – NESINA**<br>**LINAGLIPTIN – TRADJENTA**<br>**SAXAGLIPTIN – ONGLYZA**<br>**SITAGLIPTIN – JANUVIA**<br>(Added 5/12/2020) | ▪ Clinical trials with linagliptin 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<sup>1,2</sup> | ▪ Adverse Effects:  
  ▪ Acute pancreatitis, fatal hepatic failure, possible worsening of heart failure, possible severe and disabling joint pain | ▪ Hypothesized that inhibition of DPP-4 may prevent infection with or progression of COVID-19 |
| **Dosage:**<br>▪ Optimal dosage in patients with COVID-19 is unclear<br>▪ Dosage adjustments are needed for reduced renal function | ▪ Drug Interactions:  
  ▪ Strong P-glycoprotein or CYP3A4 inducers<sup>5</sup> can decrease serum concentrations of linagliptin; concurrent use should be avoided if possible  
  ▪ Strong CYP3A4/5 inhibitors<sup>5</sup> 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 | ▪ 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<sup>3,4</sup> |
| Usual dosage for treatment of type 2 diabetes:<br>▪ Alglaptin: 25 mg PO once/day<br>▪ Linagliptin: 5 mg PO once/day<br>▪ Saxagliptin: 2.5-5 mg PO once/day<br>▪ Sitagliptin: 100 mg PO once/day |  |  | ▪ Pregnancy:  
  ▪ Limited data on use during pregnancy; insulin is generally preferred in pregnant women |
**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**

**DAPAGLIFLOZIN – FARXIGA (ASTRAZENECA)**  
(*Updated 4/28/2020*)

**Dosage:**
- 10 mg once/day

**Efficacy:**
- Phase III trial (DARE-19) ongoing in the US and Europe in hospitalized patients with cardiovascular (CV), metabolic, or renal risk factors

**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

**Comments:**
- 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
- 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
- Mechanism not established, but SGLT2 inhibitors may have favorable effects on mechanisms involved in respiratory failure, sepsis, and multi-organ failure/cytokine storm

**Pregnancy:**
- Not recommended during the second and third trimester; adverse renal effects have been reported in animal studies

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### DRUG AND DOSAGE

#### FAMOTIDINE – PEPCID (VALEANT)

(Updated 6/5/2020)

**Dosage:**
- Clinical trial administering high-dose IV treatment (120 mg IV q8h)

### EFFICACY

- 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**

*Population*: hospitalized, non-intubated, non-ICU  
*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**

*Population*: non-hospitalized patients  
*Design*: case series; self-administered famotidine (80 mg tid x 11 days most commonly used)

### ADVERSE EFFECTS/INTERACTIONS

#### 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

#### COMMENTS
- 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
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</thead>
<tbody>
<tr>
<td>FAMOTIDINE (continued)</td>
<td><strong>Results:</strong></td>
<td></td>
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<tr>
<td></td>
<td>▪ combined symptom score improved significantly within 24 hrs of famotidine</td>
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<td></td>
<td>▪ symptoms (cough, shortness of breath, fatigue, headache, anosmia) were scored on a 4-point ordinal scale</td>
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<tr>
<td></td>
<td>▪ no patients were hospitalized</td>
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<td></td>
<td>▪ time from onset of symptoms to start of treatment ranged from 2 to 26 days</td>
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<td><strong>Limitations:</strong> case series (small number of patients, no placebo group)</td>
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<tr>
<td><strong>ASCORBIC ACID – GENERICS</strong></td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>Trials in China and Italy of high-dose ascorbic acid in patients with severe COVID-19-associated pneumonia are ongoing</td>
<td>Adverse effects:</td>
<td>Antioxidant properties may protect host cells against infection-induced oxidative stress; may boost host defenses against infection</td>
</tr>
<tr>
<td></td>
<td>The results of these trials have not been published to date</td>
<td>▪ Large doses can acidify the urine, causing cysteine, urate, or oxalate stones; prolonged administration of high IV doses can cause oxalate nephropathy</td>
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<tr>
<td>12 g IV q12h x 7 days (infused at a rate of 12 ml/hr)</td>
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<td>▪ Nausea, vomiting, diarrhea, dizziness, and flushing can occur</td>
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<td></td>
<td></td>
<td>▪ Drug Interactions:</td>
<td></td>
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<td></td>
<td>▪ May decrease serum concentrations of amphetamines</td>
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<td>▪ May decrease the efficacy of bortezomib (<em>Velcade</em>, and generics) and cyclosporine</td>
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<td>▪ May cause deferoxamine (<em>Desferal</em>) toxicity and left ventricular dysfunction; avoid oral doses &gt;200 mg/day</td>
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<td></td>
<td>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</td>
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<td>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</td>
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<td></td>
<td>Pregnancy:</td>
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<tr>
<td></td>
<td></td>
<td>▪ No data are available in pregnant women</td>
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**DRUG AND DOSAGE**

**ZINC – ZINC SULFATE**

*(updated 7/21/2020)*

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

<table>
<thead>
<tr>
<th>EFFICACY</th>
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</table>
| **Carlucci et al. 2020** *(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 FiO₂ (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:**  
- 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 | **Impairs replication of some RNA viruses including SARS-CoV in vitro; no data on the activity of zinc against SARS-CoV-2**  
**Chloroquine/hydroxychloroquine may increase cellular uptake of zinc by SARS-CoV-2**  
**NIH guidelines state there is insufficient data to recommend for or against use of zinc; they recommend against use of doses above the recommended dietary allowance for prevention of COVID-19, except in a clinical trial *(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**  
**Pregnancy:**  
- Limited data on the safety of doses higher than the recommended daily allowance in pregnant women |

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1. Dosage regimen tried for treatment of covid-19; effective dosage has not been established in clinical trials.  
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VITAMIN D</strong></td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>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&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>▪ Excessive doses could cause toxicity (hypercalciuria, hypercalcemia, nausea, vomiting, anorexia, constipation, dehydration, fatigue, irritability, confusion, weakness)</td>
<td>▪ Vitamin D plays an important role in immune function</td>
</tr>
<tr>
<td></td>
<td>▪ Dosage in patients with COVID-19 not established</td>
<td>▪ Metabolism of vitamin D altered in patients with chronic kidney disease</td>
<td>▪ Limited data in COVID-19 and other serious illness</td>
</tr>
<tr>
<td></td>
<td>▪ 400-800 IU/day (recommended daily allowance for most people)</td>
<td></td>
<td>▪ NIH guidelines state there are insufficient data to recommend for or against use of vitamin D for prevention or treatment of COVID-19&lt;sup&gt;7&lt;/sup&gt; (added 7/22/2020)</td>
</tr>
<tr>
<td></td>
<td>▪ Serum 25(OH)D 20 to 30 ng/mL: 800-2000 IU/day</td>
<td></td>
<td>▪ NICE guidance states that there is no evidence to support use of vitamin D supplements to prevent or treat COVID-19&lt;sup&gt;5&lt;/sup&gt; (added 6/30/2020)</td>
</tr>
<tr>
<td></td>
<td>▪ Serum 25(OH)D &lt;20 ng/mL: may need 50,000 IU/week</td>
<td></td>
<td>▪ 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&lt;sup&gt;6&lt;/sup&gt; (added 6/17/2020)</td>
</tr>
<tr>
<td></td>
<td>▪ 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&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>▪ Some sources of vitamin D include exposure to sunlight, fortified cereals and dairy products, fatty fish</td>
</tr>
<tr>
<td></td>
<td>▪ 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&lt;sup&gt;4&lt;/sup&gt;</td>
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THIAMINE  
(added 7/29/2020)

Dosage:
- Dosage in patients with COVID-19 not established
- 200 mg IV q12h

<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| THIAMINE        | ▪ 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
▪ 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
▪ 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
| 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
| ▪ There are no controlled trials evaluating use of thiamine in critically ill patients with COVID-19 |

<table>
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<tr>
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<tbody>
<tr>
<td><strong>OTC Products</strong></td>
<td><strong>Nasal Saline Irrigation</strong></td>
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</table>
| **NASAL SALINE IRRIGATION – (NETI POT OR SINUS RINSE SQUEEZE BOTTLE)** | ▪ No data for treatment or prevention of COVID-19 | ▪ Adverse Effects:  
▪ Minor nasal discomfort or irritation | ▪ No evidence that regular nasal saline irrigation can prevent or treat COVID-19 infection |
| **Dosage:** Multiple times per day | ▪ 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 shedding¹ | ▪ Sterile, distilled, or boiled (and cooled) tap water should be used to prevent bacterial or protozoal infection² | ▪ 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 effects¹ | |


| **Melatonin** | | |
| **MELATONIN – GENERICS** | ▪ No data available on use of melatonin for treatment of COVID-19 | ▪ Adverse effects:  
▪ Well tolerated; dizziness, headache, nausea, and sleepiness can occur | ▪ May have anti-viral and anti-inflammatory effects; could decrease serum levels of inflammatory cytokines |
| **Dosage:** | ▪ Optimal dosage not established | ▪ Drug Interactions:  
▪ May decrease the antihypertensive effects of calcium channel blockers | ▪ Has been used in critical care patients (not COVID-19) to reduce vessel permeability, anxiety, sedation use, and improving sleeping quality² |
| 5-10 mg/day PO¹ | ▪ Based on data suggesting melatonin may be helpful in acute lung injury/acute respiratory distress syndrome caused by other pathogens² | ▪ Melatonin is a substrate of CYP1A2; inducers of CYP1A2 may decrease melatonin concentrations and inhibitors of CYP1A2 may increase melatonin concentrations³ | |

<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>BENZALKONIUM CHLORIDE</strong> (added 5/9/2020)</td>
<td>▪ The manufacturer of a nasal formulation of 0.13% benzalkonium chloride (<em>NanoBio Protect</em>) states the product has been shown to kill SARS-CoV-2 in <em>in vitro</em> studies conducted by Public Health England; published data are not yet available.(^1)</td>
<td><strong>Adverse Effects:</strong> ▪ Irritation, burning or stinging, hypersensitivity reactions</td>
<td>▪ No clinical data demonstrating efficacy of a nasal formulation of benzalkonium chloride for prevention of COVID-19 infection</td>
</tr>
<tr>
<td><strong>Dosage:</strong></td>
<td>▪ Topical use</td>
<td></td>
<td>▪ The CDC recommends alcohol-based hand sanitizers containing 80% ethanol or 75% isopropanol.(^3)</td>
</tr>
<tr>
<td></td>
<td>▪ Available OTC in hand sanitizer formulations and an intranasal formulation</td>
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## CONCOMITANT DRUGS

### 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)

**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. 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.

*P Zhang et al. Circ Res 2020*

**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*

**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

**Comments:**
- Multiple medical organizations, including the NIH, have advised against stopping or starting these drugs to prevent or treat COVID-19 infection.
- Patients who are taking an ACE inhibitor or an ARB and subsequently develop COVID-19 should continue to take the drug.
- 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.
- Prospective randomized-controlled trials evaluating these drugs in patients hospitalized for COVID-19 are in progress.
<table>
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<tr>
<th>DRUG</th>
<th>CONCERNS/MECHANISM</th>
<th>CLINICAL STUDIES</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td><strong>ACE INHIBITORS AND ARBS (CONTINUED)</strong></td>
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<td><strong>DM Bean et al. 2020</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td></td>
<td><strong>Population:</strong> hospitalized patients (n=205)</td>
<td><strong>Design:</strong> retrospective, single-center</td>
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<tr>
<td></td>
<td><strong>Results:</strong> Lower rate of death or transfer to the ICU within 7 days of symptom onset in patients on an ACE inhibitor (OR 0.29)</td>
<td><strong>Limitations:</strong> small sample size, not peer reviewed</td>
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<td><strong>Mancia et al. NEJM 2020</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td></td>
<td><strong>Population:</strong> 6272 case patients with COVID-19; 30,759 controls</td>
<td><strong>Design:</strong> population-based case-control study in Italy</td>
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<td></td>
<td><strong>Results:</strong></td>
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<tr>
<td></td>
<td>▪ 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])</td>
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<td></td>
<td>▪ 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])</td>
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<td></td>
<td><strong>Limitations:</strong> observational data</td>
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<td><strong>Mehra et al. NEJM 2020</strong>&lt;sup&gt;8&lt;/sup&gt; (updated 6/4/2020)</td>
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<td></td>
<td><strong>Study Retracted</strong>&lt;sup&gt;12&lt;/sup&gt;***</td>
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<tr>
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<td>▪ 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</td>
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<tr>
<td></td>
<td><strong>Population:</strong> 8910 hospitalized patients in Asia, Europe, and North America</td>
<td><strong>Design:</strong> observational; data collected from an international registry</td>
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<tr>
<td>DRUG</td>
<td>CONCERNS/MECHANISM</td>
<td>CLINICAL STUDIES</td>
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</table>
| 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**  
**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** (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 |
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<tr>
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<tbody>
<tr>
<td>ACE INHIBITORS AND ARBS (CONTINUED)</td>
<td></td>
<td><strong>Fosbøl et al. JAMA 2020</strong>&lt;sup&gt;14&lt;/sup&gt; (added 7/28/2020)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Population: Retrospective Cohort Study:</strong></td>
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<tr>
<td></td>
<td></td>
<td>▪ hypertensive patients with COVID-19 (n=4480)</td>
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<td><strong>Nested, Case-Control:</strong></td>
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<tr>
<td></td>
<td></td>
<td>▪ Cases (COVID-19, prior hypertension; n=571); controls (no COVID-19, prior hypertension; n=5710)</td>
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<td></td>
<td></td>
<td><strong>Design:</strong> retrospective cohort study examining outcomes in patients with COVID-19; nested, case-control design for susceptibility analysis; from Danish registry</td>
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<tr>
<td></td>
<td></td>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Retrospective Cohort Study: ACEI/ARB use vs no use</strong></td>
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<tr>
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<td>▪ 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)</td>
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<tr>
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<td></td>
<td>▪ 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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Nested Case-Control Susceptibility Analysis: ACEI/ARB use vs other hypertensive drugs</strong></td>
</tr>
<tr>
<td></td>
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<td>▪ ACEI/ARB use was not associated with a higher incidence of COVID-19, compared with use of other antihypertensives</td>
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<td></td>
<td></td>
<td><strong>Limitations:</strong> retrospective data</td>
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<tr>
<td>DRUG</td>
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</tbody>
</table>
| 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 |          |
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<thead>
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<tr>
<td>Nonsteroidal Anti-inflammatory Drugs (NSAIDs)</td>
<td>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) instead¹</td>
<td>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</td>
<td>Use of an NSAID or acetaminophen for continual fever suppression may reduce the immune response and prolong viral shedding</td>
</tr>
<tr>
<td>NSAIDS (E.G., IBUPROFEN, NAPROXEN)</td>
<td></td>
<td>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</td>
<td>NIH guidelines recommend that antipyretic strategies (e.g., with acetaminophen or NSAIDs) should not differ between patients with or without COVID-19³</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Patients who are taking NSAIDs for other indications should not stop taking them³</td>
</tr>
</tbody>
</table>

### DRUG CONCERNS/MECHANISM CLINICAL STUDIES COMMENTS

<table>
<thead>
<tr>
<th>Proton Pump Inhibitors (PPIs)</th>
<th>PPI use may increase the risk of COVID-19</th>
<th>Almario Gastroenterology 2020²</th>
<th>No randomized controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTON PUMP INHIBITORS (PPIs)</td>
<td>PPIs increase gastric pH and have been associated with an increased risk of enteric infections¹</td>
<td>Population: English-speaking adults in the US (n=53,130)</td>
<td>Twice-daily PPI use was associated with higher risk than once-daily use in an observational trial²</td>
</tr>
<tr>
<td>Dexlansoprazole (Dexilant)</td>
<td>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</td>
<td>Design: online population-based survey</td>
<td>American College of Gastroenterology (ACG) recommends use of the lowest effective dose of PPIs in patients with a clinical indication for their use¹</td>
</tr>
<tr>
<td>Esomeprazole magnesium (Nexium, Nexium 24HR, and generics)</td>
<td>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 tract¹</td>
<td>Survey included questions about PPI and/or H2-receptor antagonist use and positive test results for COVID-19</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole (Prevacid, Prevacid 24HR, and generics)</td>
<td>Results:</td>
<td></td>
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</tr>
<tr>
<td>Omeprazole (Prilosec, Prilosec OTC, and generics)</td>
<td>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</td>
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<tr>
<td>Omeprazole/sodium bicarbonate (Zegerid, Zegerid OTC, and generics)</td>
<td>Use of H2-receptor antagonists was not associated with an increased risk of COVID-19</td>
<td></td>
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</tr>
<tr>
<td>Pantoprazole (Protonix, and generics)</td>
<td>Limitations: observational data, patients taking PPIs may have more underlying risk factors than those not on PPIs</td>
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<tr>
<td>Rabeprazole (Aciphex, and generics)</td>
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### Adenovirus-Vectored Vaccines

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<tr>
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<th>EFFICACY</th>
<th>SAFETY</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| CHIMPANZEE ADENOVIRUS-VECTORED COVID-19 (ChAdOx1 nCoV-19) VACCINE (AstraZeneca) (added 7/24/2020) | **Folegatti et al. Lancet 2020**<sup>1</sup>  
**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  
- Local and systemic adverse reactions were common, but no serious adverse effects were reported |
<table>
<thead>
<tr>
<th>VACCINE</th>
<th>EFFICACY</th>
<th>SAFETY</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
**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<sup>11</sup> viral particles/mL or 5x10<sup>10</sup> 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 |

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<tr>
<td><strong>mRNA Vaccines</strong></td>
<td><strong>Jackson et al. NEJM 2020</strong></td>
<td>▪ Fatigue, chills, headache, myalgia, and pain at the injection site reported in the phase 1 trial</td>
<td>▪ Lipid nanoparticle-encapsulated, nucleoside-modified messenger RNA (mRNA)-based vaccine</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td><strong>Population</strong>: healthy adults 18-55 years old (n=45)</td>
<td>▪ Systemic adverse events more common after 2nd vaccination</td>
<td>▪ Encodes the SARS-CoV2 spike (S) glycoprotein, which is needed for host cell attachment and viral entry</td>
</tr>
<tr>
<td>(Moderna)</td>
<td><strong>Design</strong>: phase 1, dose-escalation, open-label trial</td>
<td>▪ No serious adverse events reported</td>
<td>▪ FDA granted fast track designation</td>
</tr>
<tr>
<td><em>(updated 7/30/2020)</em></td>
<td>2 vaccinations delivered 28 days apart at a 25 mcg, 100 mcg, or 250 mcg dose</td>
<td></td>
<td>▪ Phase 3 trial has begun; expected to enroll about 30,000 participants and use a dose of 100 mcg</td>
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<tr>
<td></td>
<td><strong>Results</strong>: antibody responses higher with the higher dose after 1st vaccination</td>
<td></td>
<td>▪ Reduced viral replication in the lungs and noses of primates (KS Corbett et al. NEJM 2020)*2</td>
</tr>
<tr>
<td></td>
<td>▪ serum-neutralizing activity detected after 2nd vaccination in all participants</td>
<td></td>
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<tr>
<td></td>
<td><strong>Limitations</strong>: preliminary results from a phase 1 trial</td>
<td></td>
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<tr>
<td><strong>BNT162b1 and BNT162b2</strong></td>
<td><strong>Mulligan et al. 2020</strong></td>
<td>▪ The most common adverse effects in the phase 2 trial were injection-site pain (58.3-100%), fatigue, and headache</td>
<td>▪ Both are lipid nanoparticle-formulated, nucleoside modified mRNA vaccines</td>
</tr>
<tr>
<td>(Pfizer/BioNTech)</td>
<td><strong>Population</strong>: healthy adults 18-55 years old (n=45)</td>
<td>▪ Fever, chills, muscle pain, and joint pain were also reported</td>
<td>▪ BNT162b1 encodes an optimized SARS-CoV-2 receptor-binding domain (RBD) antigen</td>
</tr>
<tr>
<td><em>(updated 7/30/2020)</em></td>
<td><strong>Design</strong>: phase 1/2 randomized, placebo-controlled, observer-blinded dose escalation study</td>
<td>▪ No serious adverse events reported</td>
<td>▪ BNT162b2 encodes an optimized SARS-CoV-2 full-length spike protein antigen</td>
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<tr>
<td></td>
<td>2 doses separated by 21 days of 10 mcg, 30 mcg, or 100 mcg of BNT162b1 or placebo</td>
<td></td>
<td>▪ FDA granted fast track designation</td>
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<tr>
<td></td>
<td><strong>Results</strong>: At day 28, all subjects in the 10- and 30-mcg groups had significantly elevated RBD-binding IgG antibodies and neutralizing antibodies</td>
<td></td>
<td>▪ Phase 3 trial has begun; expected to enroll up to 30,000 participants</td>
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<tr>
<td></td>
<td><strong>Limitations</strong>: preliminary data, not yet peer reviewed, phase 1/2</td>
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</tbody>
</table>

2. KS Corbett et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates.