Treatments Considered for COVID-19 (Updated September 14, 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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- RECOMBINANT ADENOVIRUS TYPE-5 (Ad5)-VECTORED COVID-19 VACCINE

mRNA Vaccines

- mRNA-1273
- BNT162b1 and BNT162b2

Adjuvanted Recombinant Nanoparticle Vaccine

- NVX-CoV2373

Inactivated Vaccine

- Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain)
<table>
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<tr>
<th>DRUG AND DOSAGE</th>
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<td>FAVIPIRAVIR – AVIGAN</td>
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<tr>
<td>(FUGIFILM)</td>
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<td>(updated 8/9/2020)</td>
<td></td>
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<tr>
<td>Dosage:</td>
<td>▪ 1600 mg PO bid on day 1, then 600 mg bid on days 2-7¹</td>
<td></td>
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<tr>
<td></td>
<td>▪ Some suggest a dosage of 2400-3000 mg bid on day 1, then 1200-1800 mg bid²</td>
<td></td>
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</tr>
<tr>
<td>Population:</td>
<td>Q Cai et al. 2020¹</td>
<td>Adverse Effects: ▪ Elevated LFTs, diarrhea, nausea, vomiting, chest pain and elevated serum uric acid</td>
<td></td>
</tr>
<tr>
<td>Design:</td>
<td>Hospitalized, non-severe (n=80)</td>
<td>Drug Interactions: ▪ May increase serum concentrations of some drugs such as acetaminophen, penicillins, tazobactam, repaglinide, pioglitazone and rosiglitazone, oseltamivir, theophylline, and progestins</td>
<td></td>
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<tr>
<td>Results:</td>
<td>Open-label, non-randomized</td>
<td></td>
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<tr>
<td></td>
<td>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 caution¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al. 2020³</td>
<td>Population: Hospitalized patients (n=236)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design:</td>
<td>Randomized, open-label</td>
<td></td>
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<tr>
<td></td>
<td>Favipiravir vs arbidol (an influenza drug not available in the US); both in addition to standard therapy</td>
<td></td>
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</tr>
<tr>
<td>Results:</td>
<td>Clinical recovery rate at day 7 was similar for favipiravir and arbidol (51.67% vs 61.21%; p=0.1396)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In patients with moderate disease, clinical recovery rates were higher with favipiravir than arbidol (71.43% vs 55.86%; p=0.0199)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitations:</td>
<td>Not peer-reviewed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivashchenko et al. Clin Infect Dis 2020⁵</td>
<td>Hospitalized patients with moderate COVID-19 pneumonia in</td>
<td></td>
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<tr>
<td></td>
<td>(added 8/9/2020)</td>
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</tr>
</tbody>
</table>

¹ Q Cai et al. 2020
² Chen et al. 2020
³ Ivashchenko et al. Clin Infect Dis 2020
Russia; 25% on supplemental oxygen and 75% on ambient air (n=60)

**Design:** adaptive, multicenter, randomized, open-label trial; results from 60 patients in phase II trial presented

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

**Results:**

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

**Limitations:** interim results

---

REMDESVIR – VEKLURY (GILEAD)

(updated 8/23/2020)

Dosage:
- Adults ≥40 kg: 200 mg IV on day 1, then 100 mg IV once/day for a total of 5 or 10 days
- Infuse over 30-120 minutes
- In addition to standard care
- Not recommended if eGFR <30 ml/min or ALT >5x ULN
- NIH guidelines recommend a duration of 5 days or until hospital discharge

NIAD. ACTT-1. NEJM 2020 (added 5/4/20; updated 5/25/20)

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

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

Limitations:
- preliminary report

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

Drug Interactions: (updated 6/18/2020)
- No human drug trial conducted
- Substrate for CYP2C8, CYP2D6, and CYP3A4, and for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (Pgp) transporters in vitro. Strong inducers of these enzymes/transporters may decrease serum concentrations of remdesivir and inhibitors of these enzymes/transporters could potentially increase the risk of toxicity such as hepatotoxicity
- Inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP.
- Clinical relevance has not been established.
- FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended (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) (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 patients (added 7/25/2020)
- NIH guidelines state there are insufficient data to recommend for or against use in patients with mild or moderate COVID-19 (updated 6/16/2020)

FDA Emergency Use Authorization (EUA) expanded on August 28, 2020 to allow use of remdesivir for treatment of COVID-19 in all adult and pediatric hospitalized patients, irrespective of their severity of disease (initial EUA was
REMDESIVIR (CONTINUED)

J Grein et al. NEJM 2020
Population: 53 hospitalized patients in US, Canada, Europe and Japan with SaO₂ ≤94% on O₂ or room air (n=61)
▪ 57% on mechanical compassionate ventilation
Design: report on use
Results: median follow-up 18 days
▪ 68% had improvement in O₂ 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

- 7 -
REMDESIVIR (CONTINUED)


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

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

**Results:**
- median duration of symptoms before day 1 was 8 days in the remdesivir groups and 9 days in the standard care group
- median duration of treatment was 5 days in the 5-day group and 6 days in the 10-day group
- on day 11, the odds of a better clinical status distribution on a 7-point ordinal scale was significantly higher in those treated with remdesivir for 5 days than with standard care (OR 1.65; 95% CI 1.09-2.48; p=0.02); clinical importance unclear
- treatment with remdesivir x 10 days did not reach statistical significance

**Limitations:** open-label; median symptom duration at start of trial was 8 days; only 38% of remdesivir 10-day group received the drug for 10 days

---


**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)

**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

**NIH Adaptive COVID-19 Treatment Trial 3 (ACTT 3)** *(added 8/9/2020)*
- A randomized, double-blind trial comparing remdesivir plus interferon beta 1a to remdesivir alone has begun
- Expected to enroll >1000 adults

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### CONVALESCENT PLASMA

*updated 8/23/2020*

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

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

---

#### Li et al. *JAMA* 2020
*added 8/16/2020*

**Population:** hospitalized patients in China with severe or life-threatening COVID-19 *(n=103)*

**Design:** open-label, multicenter, randomized trial

- Convalescent plasma plus standard treatment vs standard treatment alone
- Plasma units with an S-RBD–specific IgG titer of at least 1:640 were used
- Median time from symptom onset to randomization: 30 days

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

---

#### 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
- FDA issued an Emergency Use Authorization for convalescent plasma *(added 8/19/2020)*
- NIH released statement following FDA EUA *(Sept 1, 2020)* stating insufficient data to recommend for or against use of convalescent plasma for COVID-19, serious adverse effects infrequent, but long-term risks, including whether use of convalescent plasma attenuates the immune response to SARS-Co-V-2 making patients more susceptible to reinfection, are unknown
those with life-threatening disease in 20.7% vs 24.1% (p=0.83)

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

Limitations: trial stopped early before full enrollment reached

MJ Joyner et al MedRxiv 2020
(added 8/17/2020)
Population: hospitalized patients in the US with severe or life-threatening acute COVID-19 respiratory syndrome (n=35,322)
Design: open-label exploratory analysis of patients who received convalescent plasma through an Expanded Access Program in the US
Results:
- 52.3% of patients in ICU; 27.5% on mechanical ventilation
- 7-day mortality rate 8.7% in patients transfused ≤ 3 days of diagnosis and 11.9% in patients transfused ≥ 4 days after diagnosis (p<0.001); 30-day mortality was 21.6% vs 26.7% (p<0.0001)
- 7-day mortality was 8.9% with high IgG plasma, 11.6% with medium IgG plasma, and 13.7% with low IgG plasma

Limitations: observational, not peer reviewed; authors state efficacy signals are preliminary
ARDS = acute respiratory distress syndrome

### 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 2020^1**
- **Population:** Hospitalized patients in China with severe disease and deteriorating course (n = 3)
- **Design:** Case series; patients received IVIg at the start of respiratory distress
- **Results:** all 3 patients had clinical improvement; no fever within 1-2 days, alleviation of breathing difficulties in 3-5 days
- **Limitations:** small case series, 2 patients also received antivirals, 1 received steroids

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

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

- Used for treatment of immune disorders and as an adjunct for treatment of severe pneumonia in influenza patients; modulates immune inflammation, improves passive immunity
- Existing IVIG product unlikely to contain antibodies against SARS-CoV-2
- FDA approved an investigational new drug application (IND) for a phase 3 trial with *Octagam* 10% in COVID-19 patients with severe disease progression (SpO2≤93%, requiring oxygen supplementation)^4
- Surviving Sepsis Campaign guidelines suggest against routine use of standard IVIG in critically ill adults^5
- NIH guidelines recommend against use of non-SARS-CoV-2-specific IVIG outside of the context of a clinical trial for treatment of COVID-19; they state this should not preclude use of IVIG when otherwise indicated for treatment of complications arising during the course of COVID-19 illness^6
- NIH guidelines state there are insufficient data to recommend for or against use of SARS-CoV-2 immunoglobulins^6 *(added 7/22/2020)*
- Shortages have been an issue (even prior to COVID-19)
Shao et al. 2020³

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

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
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</thead>
<tbody>
<tr>
<td><strong>LY-CoV555</strong></td>
<td><strong>NIH ACTIV-2</strong>¹</td>
</tr>
<tr>
<td>(Eli Lilly/AbCellera)</td>
<td>Phase 2 trial</td>
</tr>
<tr>
<td><em>added 8/17/2020</em></td>
<td>Expected to enroll 200 outpatients with mild to moderate COVID-19 symptoms for &lt; 10 days</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 vs placebo</td>
</tr>
<tr>
<td><strong>NIH ACTIV-3</strong>²</td>
<td>Phase 3 study; LY-CoV555 vs placebo</td>
</tr>
<tr>
<td></td>
<td>Expected to enroll 300 hospitalized patients with mild to moderate COVID-19 with &lt; 13 days of symptoms</td>
</tr>
<tr>
<td></td>
<td>Phase 3 trial of LY-CoV555 antibody for prophylaxis of COVID-19 in nursing home residents ongoing</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 is an investigational monoclonal antibody for treatment of COVID-19</td>
</tr>
<tr>
<td></td>
<td>The antibody was discovered in a blood sample from a recovered COVID-19 patient</td>
</tr>
<tr>
<td></td>
<td>Administered IV</td>
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</tbody>
</table>

### 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

---

<table>
<thead>
<tr>
<th>MESENCHYMAL STEM CELL THERAPY (updated 7/21/2020)</th>
<th>Stem Cell Therapy</th>
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<tr>
<td><strong>Remestemcel-L (Ryoncil)</strong></td>
<td><strong>Adverse Effects:</strong></td>
</tr>
<tr>
<td>▪ 10 patients with ARDS treated with remestemcel-L under the FDA compassionate use program with encouraging results</td>
<td>▪ Risks in patients with COVID-19 not established</td>
</tr>
<tr>
<td>▪ Randomized clinical trial to be conducted at Mount Sinai in NY</td>
<td>▪ Possible product contamination, infusion site reactions, thrombosis, infection, tumor growth</td>
</tr>
<tr>
<td>▪ Results: Dyspnea improved within 1 hour of administration</td>
<td>▪ Remestemcel-L well tolerated in trials reported by the manufacturer in children with GVHD</td>
</tr>
<tr>
<td><strong>Pregnancy:</strong></td>
<td><strong>Limitation:</strong> small pilot study</td>
</tr>
<tr>
<td>▪ There are inadequate data on the use of stem cell therapies in pregnant women</td>
<td><strong>Facts:</strong></td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>▪ 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</td>
</tr>
<tr>
<td>▪ Pulmonary function and symptoms improved within 2 days of transplantation</td>
<td><strong>Facts:</strong></td>
</tr>
<tr>
<td>▪ All patients in the treatment group recovered</td>
<td>▪ FDA granted an investigational new drug (IND) application for use of remestemcel-L (Ryoncil - Mesoblast), an allogenic mesenchymal stem cell therapy, to treat patients with ARDS caused by COVID-19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oleandrin</th>
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<tbody>
<tr>
<td><strong>OLEANDRIN</strong></td>
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<tr>
<td><em>(added 8/19/2020)</em></td>
</tr>
<tr>
<td>▪ No published <em>in vivo</em> data on use of oleandrin for treatment or prevention of COVID-19</td>
</tr>
<tr>
<td>▪ An <em>in vitro</em> study (not peer reviewed) suggested that oleandrin may inhibit SARS-CoV-2 replication¹</td>
</tr>
</tbody>
</table>

**Adverse Effects:**

▪ Toxicity includes nausea, vomiting, abdominal pain, diarrhea (possibly bloody stools), anorexia, arrhythmias, drowsiness, tremors, seizures, coma, death

▪ Toxicity occurs several hours after ingestion

▪ There are no available data to support use of oleandrin for COVID-19 and it can have serious, life-threatening toxicity; avoid use

▪ Toxic cardiac glycoside from the *Nerium oleander* plant

▪ All parts of the oleander plant are toxic; it is responsible for cases of accidental poisoning worldwide

---

# Repurposed Drugs

## Corticosteroids (systemic)

### Corticosteroids (Dexamethasone, Hydrocortisone)

**Updated 7/27/2020**

- 6 mg PO or IV daily x 10 days used in RECOVERY trial

<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOVERY Trial 2020¹</strong></td>
<td><strong>Population:</strong> hospitalized patients in the UK (n=6425)</td>
<td><strong>Adverse Effects:</strong> hyperglycemia, insomnia, adrenal suppression, delirium, depression, mania</td>
<td>▪ Anti-inflammatory effects may modulate immune-mediated lung damage</td>
</tr>
<tr>
<td><strong>Design:</strong></td>
<td><strong>Drug Interactions:</strong> Induces CYP3A4 and P-gp and may decrease concentrations of drugs that are substrates of CYP3A4 or P-gp</td>
<td></td>
<td>▪ Authors of RECOVERY trial state that treating 8 ventilated patients or 25 patients requiring oxygen would prevent 1 death²</td>
</tr>
<tr>
<td>Randomized, controlled, open-label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone</td>
<td>Causes hyperglycemia; may decrease the efficacy of antihyperglycemic drugs</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 oxygen³</td>
</tr>
<tr>
<td>Dexamethasone 6 mg PO or IV once daily (n=2104) x 10 days vs usual care (n=4321)</td>
<td></td>
<td>IDSA guidelines recommend use of dexamethasone (or methylprednisolone or prednisone if dexamethasone is not available) 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>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> 28-day mortality rates (dexamethasone vs usual care)</td>
<td></td>
<td>NIH and IDSA recommend against use of dexamethasone for treatment of COVID-19 in patients who do not require supplemental oxygen³,⁴</td>
<td></td>
</tr>
<tr>
<td><strong>Overall:</strong> 22.9% vs 25.7% (p&lt;0.001)</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-19³ (added 7/20/2020)</td>
<td></td>
</tr>
<tr>
<td>Patients on invasive mechanical ventilation: 29.3% vs 41.4% (rate ratio 0.64; 95% CI 0.51-0.81)</td>
<td></td>
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<tr>
<td><strong>Oxygen</strong> without invasive mechanical ventilation: 23.3% vs 26.2% (rate ratio 0.82; 95% CI 0.72-0.94)</td>
<td></td>
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</tr>
<tr>
<td><strong>No respiratory support at randomization:</strong> 17.8% vs 14.0% (rate ratio 1.19; 95% CI 0.91-1.55)</td>
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</tr>
<tr>
<td><strong>Limitation:</strong> preliminary results; open-label study</td>
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</tr>
</tbody>
</table>

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¹ 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.
² Authors of RECOVERY trial state that treating 8 ventilated patients or 25 patients requiring oxygen would prevent 1 death.
³ 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.
⁴ IDSA guidelines recommend use of dexamethasone (or methylprednisolone or prednisone if dexamethasone is not available) for hospitalized patients with severe illness (patients with SpO₂≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO).
CORTICOSTEROIDS (DEXAMETHASONE, HYDROCORTISONE) (continued)

**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 ≥ 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

**Tomazini et al. JAMA 2020**

**The CoDEX Trial**  
*(added September 3, 2020)*

**Population:** ICU patients w/ mod-severe ARDS (n=299)  
**Design:**  
- randomized, open-label trial

**WHO recommends systemic corticosteroids (dexamethasone 6 mg PO or IV daily or hydrocortisone 50 mg IV q8h x 7-10 days) to treat patients with severe and critical COVID-19** *(added September 3, 2020)*

**WHO recommends against use of systemic corticosteroids in patients with non-severe disease** *(added September 3, 2020)*

**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 *(added 7/20/2020)*

- Monitor for hypoadrenalism in newborns of mothers who received substantial doses
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE CORTICOSTEROIDS (DEXAMETHASONE, HYDROCORTISONE) (continued)</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ dexamethasone 20 mg IV daily x 5 days, then 10 mg daily x 5 days or until hospital discharge plus standard care vs standard care</td>
<td>▪ patients in dexamethasone group had significantly more ventilator-free days (days alive and free of mechanical ventilation) compared to control group (6.6 vs 4.0)</td>
<td>▪ no significant difference in all-cause mortality at 28 days, ICU-free days during first 28 days, mechanical ventilation duration at 28 days</td>
<td>▪ open-label</td>
</tr>
</tbody>
</table>

**PF Dequin et al. JAMA 2020**

*(added September 3, 2020)*

**Population:** ICU patients w/ respiratory failure

**Design:**

▪ randomized double-blind trial (n=149)
▪ low-dose hydrocortisone vs placebo

**Results:**

▪ trial ended early
▪ no significant difference in rate of treatment failure (death or respiratory support) at day 21 (42.1% w/ low-dose...*
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORTICOSTEROIDS (DEXAMETHASONE, HYDROCORTISONE) (continued)</td>
<td>hydrocortisone vs 50.7% w/placebo</td>
<td></td>
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<tr>
<td></td>
<td>Limitations:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>▪ trial stopped early so underpowered to detect significant differences</td>
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<tr>
<td>REMAP-CAP JAMA 2020*</td>
<td>(added September 3, 2020)</td>
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<tr>
<td>Population: ICU patients w/respiratory or CV support (n=384)</td>
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<tr>
<td>Design:</td>
<td></td>
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<tr>
<td>▪ open-label adaptive platform trial</td>
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<tr>
<td>▪ IV hydrocortisone 50 or 100 mg q6h x 7 days vs hydrocortisone 50 mg q6h when shock was clinically evident vs no hydrocortisone</td>
<td></td>
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<td></td>
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<tr>
<td>Results:</td>
<td></td>
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</tr>
<tr>
<td>▪ No difference in median organ-support free days in patients treated with fixed-dose or shock-dependent hydrocortisone compared to no hydrocortisone (all 0 days)</td>
<td></td>
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<tr>
<td>▪ Bayesain model found both hydrocortisone regimens probably superior to no hydrocortisone</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Limitations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ trial stopped early so underpowered to detect significant differences</td>
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<tr>
<td>DRUG AND DOSAGE</td>
<td>EFFICACY</td>
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</tbody>
</table>
| CORTICOSTEROIDS (DEXAMETHASONE, HYDROCORTISONE) (continued) | **WHO JAMA 2020**<sup>9</sup>  
*(added September 3, 2020)*  
**Population:** critically ill patients  
*(n=1703)*  
**Design:**  
- meta-analysis  
- dexamethasone, hydrocortisone or methylprednisolone vs placebo or usual care  
**Results:**  
- 28-day all-cause mortality was lower in those treated with a corticosteroid (OR 0.64 for dexamethasone; 0.69 for hydrocortisone; 0.91 for methylprednisolone) | | |

2. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19. June 16, 2020. Available at:  
**Inhaled Corticosteroids**

### Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwabuchi et al. J Infect Chemother 2020¹</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</td>
<td>cases series of 3 patients</td>
</tr>
</tbody>
</table>
| Schultze et al. medRxiv 2020² | asthma (n=817,973) and COPD (n=148,588) patients in the UK | cohort study using linked electronic health records (OpenSAFELY platform); compared patients using an ICS to those taking other drugs for COPD/asthma | COPD: risk of death higher in patients using ICSs than in those use a long-acting beta agonist and a long-acting muscarinic antagonist (adjusted HR = 1.38; 95% CI 1.08-1.75)  
Asthma: risk of death higher in patients using ICSs than in those using only a short-acting beta agonist (adjusted HR = 1.52; 95% CI 0.82-1.49) | observational; not peer reviewed; possible confounding |

### Adverse Effects/Interactions

<table>
<thead>
<tr>
<th>Adverse Effects:</th>
<th>Significance</th>
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</thead>
</table>
| ▪ local adverse effects include oral candidiasis (thrust), 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 | 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-2³
- NIH guidelines recommend that patients with COVID-19 who are using inhaled corticosteroids for treatment of asthma or COPD should not discontinue treatment⁴
- 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 pregnancy⁵

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⁵. Drugs for asthma. Med Lett Drugs Ther 2017; 59:139.
<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>IL-6 Inhibitors</strong></td>
<td><strong>SARILUMAB – KEVZARA</strong>&lt;sup&gt;1&lt;/sup&gt; (SANOFI/REGENERON) <em>(updated 8/29/2020)</em></td>
<td><strong>US-based phase 2 and 3 clinical trials ongoing</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td><strong>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</strong></td>
</tr>
<tr>
<td><strong>Dosage:</strong></td>
<td><strong>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) <em>(updated May 4, 2020)</em></strong></td>
<td><strong>Adverse Effects:</strong>&lt;br&gt;- Neutropenia, thrombocytopenia, serious infections, hypersensitivity reactions including anaphylaxis**</td>
<td><strong>NIH guidelines recommend against use of IL-6 inhibitors, except in a clinical trial</strong> <em>(updated 8/29/2020)</em></td>
</tr>
<tr>
<td>- No clinical trial data yet</td>
<td><strong>Phase 3 trials will continue to enroll critical patients only</strong>&lt;br&gt;o 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**&lt;sup&gt;11&lt;/sup&gt; <em>(updated 7/6/2020)</em></td>
<td><strong>Drug Interactions:</strong>&lt;br&gt;- May normalize CYP enzyme formation; could increase metabolism and decrease serum concentrations of drugs with narrow therapeutic indices that are metabolized by CYP isozymes**</td>
<td><strong>Parturition is associated with IL-6 increases in the cervix and myometrium; inhibition of IL-6 may lead to possible delays of parturition</strong></td>
</tr>
<tr>
<td>- Optimal dosage not established</td>
<td><strong>Hematologic toxicity may be additive with other drugs such as linezolid, clozapine, or azathioprine</strong></td>
<td><strong>Pregnancy:</strong>&lt;br&gt;- Crosses the placenta, especially in the third trimester, and may affect the immune response in an exposed infant**</td>
<td><strong>Not associated with embryotoxic or teratogenic effects when given in high doses to pregnant monkeys</strong></td>
</tr>
<tr>
<td>- High and low IV doses are expected to be studied</td>
<td></td>
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<tr>
<td>DRUG AND DOSAGE</td>
<td>EFFICACY</td>
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</tbody>
</table>
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 | ▪ 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:  
▪ Optimal dosage not established  
▪ 8 mg/kg (max 400 mg) IV once<sup>5</sup>  
▪ Infuse over 1 hour  
▪ Optimal timing of administration is unclear | **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 | ▪ Surviving Sepsis Campaign guidelines state that there is insufficient evidence to make a recommendation on use of tocilizumab<sup>8</sup> |
| | **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)  
Limitations: not peer-reviewed | ▪ Infectious Diseases Society of America recommends use only in the context of a clinical trial<sup>9</sup>  
▪ NIH guidelines recommend against use of an IL-6 inhibitor, except in a clinical trial<sup>3</sup> (updated 8/29/2020)  
▪ Randomized, controlled trials are ongoing in the US | |
| 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>19</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 | ▪ 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/embryofetal death when given to pregnant monkeys during the period of organogenesis | |

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/embryofetal death when given to pregnant monkeys during the period of organogenesis
<table>
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<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
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<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOCILIZUMAB (CONTINUED)</strong></td>
<td>Somers et al. 2020&lt;sup&gt;10&lt;/sup&gt; (<em>added 6/18/2020; updated 7/14/2020</em>)</td>
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<tr>
<td><strong>Population:</strong> hospitalized patients requiring mechanical ventilation (n=154)</td>
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<tr>
<td>▪ 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)</td>
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<tr>
<td><strong>Design:</strong> single-center cohort; patients treated with tocilizumab vs patients not treated with tocilizumab</td>
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<tr>
<td><strong>Results:</strong> median follow-up 47 days</td>
<td></td>
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<tr>
<td>▪ tocilizumab associated with a reduced risk of death (hazard ratio 0.55; 95% CI 0.33,0.90)</td>
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<tr>
<td>▪ tocilizumab associated with an increased risk of superinfections (54% vs 26%; p&lt;0.001)</td>
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<tr>
<td>▪ no significant difference in 28-day case fatality rate in patients treated with tocilizumab who had superinfections vs those who did not (22% vs15%; p=0.42)</td>
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<td></td>
</tr>
<tr>
<td><strong>Limitation:</strong> observational data</td>
<td></td>
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<tr>
<td><strong>COVACTA 2020</strong>&lt;sup&gt;12&lt;/sup&gt; (<em>added 8/16/2020</em>)</td>
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<tr>
<td><strong>Population:</strong> hospitalized patients with severe COVID-19 pneumonia (n=450)</td>
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<tr>
<td><strong>Design:</strong> randomized, double-blind, placebo-controlled</td>
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<tr>
<td>▪ IV tocilizumab plus standard of care vs placebo plus standard of care</td>
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<tr>
<td>DRUG AND DOSAGE</td>
<td>EFFICACY</td>
<td>ADVERSE EFFECTS/INTERACTIONS</td>
<td>COMMENTS</td>
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</table>
| TOCILIZUMAB (CONTINUED) | **Results:**  
▪ No significant difference between tocilizumab and placebo in the primary endpoint of clinical status on a 7-point scale at week 4  
▪ No difference between groups in percentage of patients who died by week 4 (19.7% tocilizumab vs 19.4% placebo)  
**Limitations:** not yet published | | |

1. FDA-approved for treatment of rheumatoid arthritis.  
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>
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</thead>
<tbody>
<tr>
<td><strong>IL-1 Receptor Antagonist</strong></td>
<td><strong>ANAKINRA – KINERET (BIOVITRUM AB) (updated 7/27/2020)</strong></td>
<td><strong>Cavalli et al. Lancet Rheum 2020</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td><strong>Clinical trials are ongoing</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Dosage:</strong></td>
<td><strong>Optimal dosage for COVID-19 unknown</strong>&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td></td>
<td><strong>IL-1 receptor antagonist; IL-1 mediates inflammatory and immune responses antagonist</strong></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></td>
<td><strong>May mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease</strong></td>
</tr>
<tr>
<td></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></td>
<td><strong>NIH guidelines state there are insufficient clinical data to recommend either for or against use of IL-1 inhibitors</strong>&lt;sup&gt;3&lt;/sup&gt; (updated 4/28/2020)</td>
</tr>
<tr>
<td></td>
<td>Design: retrospective cohort study; single hospital in Italy</td>
<td></td>
<td><strong>FDA-approved for treatment of rheumatoid arthritis and neonatal-onset multisystem inflammatory disease.</strong></td>
</tr>
<tr>
<td></td>
<td>Addition of anakinra vs standard treatment (HCQ + LPV/RTV)</td>
<td></td>
<td><strong>Pregnancy:</strong></td>
</tr>
<tr>
<td></td>
<td>Results: at 21 days</td>
<td></td>
<td><strong>Not associated with adverse pregnancy outcomes in small retrospective studies in humans or in animal studies</strong></td>
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<tr>
<td></td>
<td>Improved survival with high-dose (5 mg/kg IV bid) anakinra vs standard treatment (90% vs 56%; p=0.009)</td>
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<tr>
<td></td>
<td>Mechanical ventilation-free survival similar between groups (72% vs 50%; p=0.15)</td>
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<td></td>
<td>Associated with reduced serum C-reactive protein and improved respiratory function</td>
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<tr>
<td></td>
<td>Limitations: small, retrospective study</td>
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<tr>
<td></td>
<td><strong>Cauchois et al. Proc Natl Acad Sci U S A 2020</strong>&lt;sup&gt;5&lt;/sup&gt; (added 7/27/2020)</td>
<td><strong>Adverse Effects:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Population: hospitalized patients in France with hypoxemic pneumonia or ARDS (n=22)</td>
<td></td>
<td>Injection-site reactions, infections, neutropenia, thrombocytopenia, hepatic transaminase elevations</td>
</tr>
<tr>
<td></td>
<td>Design: retrospective</td>
<td></td>
<td><strong>Drug Interactions:</strong></td>
</tr>
<tr>
<td></td>
<td>anakinra plus standard care compared to standard care alone</td>
<td></td>
<td>Use with TNF inhibitors or other biologics may increase risk of serious infections and neutropenia and should be avoided</td>
</tr>
<tr>
<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>ANAKINRA (continued)</td>
<td><strong>Results:</strong> ▪ compared to standard care alone, all anakinra-treated patients had clinical improvement (p&lt;0.01), decreases in oxygen requirements (p&lt;0.05), and more days off invasive mechanical ventilation (p&lt;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 <strong>Limitations:</strong> small retrospective study</td>
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<tr>
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<tbody>
<tr>
<td>BARICITINIB – OLUMIANT (LILLY)</td>
<td>Janus Kinase (JAK) Inhibitors</td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>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</td>
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<tr>
<td>• Optimal dosage for COVID-19 not established</td>
<td>▪ Adverse Effects:</td>
<td></td>
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<tr>
<td>• 2 mg PO daily</td>
<td>▪ Nausea is common</td>
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<td></td>
<td>▪ Serious, sometimes fatal, infections, including multi-dermatomal herpes zoster and tuberculosis (TB)</td>
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<tr>
<td></td>
<td>▪ Serious, sometimes fatal, thromboembolic events</td>
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<td></td>
<td>▪ Malignancy, GI perforation, neutropenia, lymphopenia, anemia, thrombocytosis, and elevations in liver enzymes, creatine phosphokinase levels, and lipid levels have also been reported</td>
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<tr>
<td></td>
<td>▪ Drug Interactions:</td>
<td></td>
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<td></td>
<td>▪ The strong organic anion transporter 3 (OAT3) inhibitor probenecid doubled baricitinib exposure; concurrent use of with strong OAT3 inhibitors is not recommended</td>
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<tr>
<td></td>
<td>▪ FDA-approved for treatment of rheumatoid arthritis</td>
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<td></td>
<td>▪ 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</td>
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<tr>
<td></td>
<td>▪ 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)</td>
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<tr>
<td></td>
<td>▪ Should not be used in patients with severe hepatic impairment (Child-Pugh C) or moderate or severe renal impairment (eGFR &lt;60 mL/min/1.73 m²)</td>
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<td></td>
<td>▪ 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</td>
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<td></td>
<td>▪ Pregnancy:</td>
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<tr>
<td></td>
<td>▪ Administration to pregnant animals resulted in reduced fetal weights, embryolethality, and skeletal malformations</td>
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¹ Updated 4/28/2020
**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 care³,⁴

**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 inhibitor⁵ should be avoided in patients with platelet counts less than 100 X 10⁹/L; dosage reductions may be needed for patients with a platelet count ≥100 X 10⁹/L

**Comments:**
- 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)
- 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 10⁹/L

**Pregnancy:**
- No adequate studies in pregnant women
- Administration of ruxolitinib to pregnant animals resulted in an increase in late resorptions and reduced fetal weights

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

(added 7/29/2020)

- Optimal dosage for treatment of COVID-19 not established
- Adalimumab (Humira)
- Certolizumab pegol (Cimzia)
- Infliximab (Remicade, and biosimilars)
- Etanercept (Enbrel)
- Golimumab (Simponi)

### 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

**Pregnancy:**
- Generally considered safe for use during pregnancy
- Placental transfer of anti-TNF antibodies is higher in the late second and third trimesters, especially with infliximab, adalimumab, and golimumab

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<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>Anti-CD6 Monoclonal Antibody</strong></td>
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</table>
| **ITOLIZUMAB** | **Biocon Trial – 2020**<sup>1</sup>  
**Population:** hospitalized patients with moderate to severe ARDS in 4 hospitals in India (n=30)  
**Design:** Randomized, controlled, open-label trial  
**20 patients randomized to itolizumab plus best supportive care and 10 patients randomized to best supportive care**  
**Results:**  
▪ at one month, no deaths occurred in patients treated with itolizumab and 3 deaths occurred in patients treated with supportive care alone  
▪ reductions in IL-6 and TNF-α were reported in itolizumab-treated patients  
**Limitation:** trial results not yet published | **Adverse Effects:**  
▪ Infusion reactions including nausea, rash, urticaria, flushing, cough, wheezing, dyspnea, dizziness, headache; diarrhea  
▪ Increased risk of infections | **Approved in India for emergency use in COVID-19 patients; also approved in India for psoriasis**  
**Not available in the US**  
**Drug Interactions:**  
▪ Live vaccines should be avoided | **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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<tbody>
<tr>
<td><strong>Antimalarials</strong></td>
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</table>
| **CHLOROQUINE**<sup>1</sup>  
*(updated 8/29/2020)* |  |  |  |
<p>| <strong>Dosage:</strong> |  |  |  |
| ▪ Optimal dosage not established |  |  |  |
| ▪ Dosages used in COVID-19 clinical trials have varied |  |  |  |
| 500 mg chloroquine phosphate (300 mg chloroquine base) bid x 7-10 days |  |  |  |
| OR |  |  |  |
| 500 mg bid x 2 days, then 500 mg once/day x 12 days&lt;sup&gt;2,3&lt;/sup&gt; |  |  |  |
| OR |  |  |  |
| 1 g on day 1, then 500 mg once daily x 4-7 days |  |  |  |
| <strong>Based on in vitro data (M Wang et al, Cell Res 2020)&lt;sup&gt;4&lt;/sup&gt;</strong> |  |  |  |
| <strong>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</strong> |  |  |  |
| <strong>ChloroCovid-19&lt;sup&gt;5 (updated 4/30/2020)&lt;/sup&gt;</strong> <strong>Population:</strong> hospitalized patients with severe illness in Brazil (n=81) |  |  |  |
| <strong>Design:</strong> |  |  |  |
| ▪ parallel, double-blind, randomized, phase IIb |  |  |  |
| ▪ chloroquine high dose (600 mg bid x 10 days) vs low dose (450 mg bid x 1 day, then once/day x 4 days); all patients received azithromycin |  |  |  |
| <strong>Results:</strong> |  |  |  |
| ▪ Trial stopped early because of a higher rate of death and QT interval prolongation in the high-dose chloroquine group |  |  |  |
| ▪ Lethality was 39.0% (16 of 41) in the high-dosage group and 15.0% (6 of 40) in the low-dosage group at day 13 |  |  |  |
| ▪ QTc interval &gt;500 milliseconds occurred in 18.9% (7 of 37) in the high-dose group compared to 11.1% (4 of 36) in the low-dosage group |  |  |  |
| ▪ Respiratory secretion negative in 22.2% (6 of 27) at day 4 |  |  |  |
| ▪ In vitro activity against SARS-CoV-2, SARS-CoV, and MERS-CoV |  |  |  |
| ▪ FDA issued a Drug Safety Communication warning against use of chloroquine outside of a clinical trial because of the risk of serious cardiac arrhythmias, including QT prolongation; it is not recommended for treatment of outpatients&lt;sup&gt;9&lt;/sup&gt; (updated 4/28/2020) |  |  |  |
| ▪ Infectious Diseases Society of America recommends against use with or without azithromycin in the hospital setting&lt;sup&gt;12&lt;/sup&gt; (updated 8/23/2020) |  |  |  |
| ▪ NIH guidelines recommend against use of chloroquine (with or without azithromycin) in hospitalized patients; in outpatients, they recommend against use, except in a clinical trial&lt;sup&gt;19&lt;/sup&gt; (updated 8/29/2020) |  |  |  |
| ▪ Clinical trials evaluating the efficacy and safety of chloroquine for pre-exposure and post-exposure prophylaxis and treatment of mild, moderate, or severe COVID-19 are underway in the US |  |  |  |
| ▪ FDA revoked Emergency Use Authorization that allowed use in some hospitalized patients for whom a clinical trial was not feasible; ongoing analysis indicated that chloroquine and hydroxychloroquine are unlikely to be effective for treatment of COVID-19 and are associated with serious cardiac |  |  |  |</p>
<table>
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<tr>
<th>DRUG AND DOSAGE</th>
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</table>
| CHLOROQUINE² (CONTINUED) | Mehra et al. 2020²² (added 5/26/20) (updated 6/4/2020) ***Study Retracted²⁴*** | Drug Interactions:  
- Avoid use with QTc prolonging drugs⁶⁻⁸  
- Substrate of CYP2C8, 2D6, and 3A4, and inhibitor of CYP2D6¹⁰,¹¹  
- Use with antihyperglycemic drugs can increase risk of hypoglycemia  
- Separate from antacids/kaolin by 4 hours  
- Use with tamoxifen can increase risk of ocular toxicity and should be avoided  
- FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended²⁶ (added 6/18/2020) | adverse events; FDA concluded benefit no longer outweighs risk¹³ (updated 6/16/2020) |
| 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 | Adverse Effects:  
- Better tolerated than chloroquine  
- Retinopathy and other ocular disorders (sometimes irreversible, but generally associated with longer use), serious cardiomyopathy, worsening of psoriasis and porphyria, proximal myopathy, neuropathy, suicidality, hypoglycemia  
- QT interval prolongation and arrhythmias, including torsades de pointes can occur.  
- In vitro activity against SARS-CoV-2 | Pregnancy:  
- Accumulates in fetal ocular tissues and is retained there for months after elimination from remainder of body  
- Chloroquine has been used safely in pregnant women for treatment and prophylaxis of malaria |

HYDROXYCHLOROQUINE (HCQ)¹ – GENERICS  
PLAQUENIL (CONCORDIA)  
(updated 9/11/2020)

Dosage:  
- Optimal dosage not established  
- Dosages used in COVID-19 clinical trials have varied

P Gautret et al. Int J Antimicrob Agents 2020¹⁴  
Population: hospitalized patients; varying severity of illness (n=42)  
Design: open-label, observational  
HCQ + azithromycin vs HCQ vs standard care  
Results: HCQ-treated patients had more rapid viral clearance vs controls

Adverse Effects:  
- Better tolerated than chloroquine  
- Retinopathy and other ocular disorders (sometimes irreversible, but generally associated with longer use), serious cardiomyopathy, worsening of psoriasis and porphyria, proximal myopathy, neuropathy, suicidality, hypoglycemia  
- QT interval prolongation and arrhythmias, including torsades de pointes can occur.  
- In vitro activity against SARS-CoV-2  
- The FDA issued a Drug Safety Communication warning against use of hydroxychloroquine outside of a clinical trial because of the risk of serious arrhythmias, including QT prolongation; it is not recommended for treatment of outpatients⁹ (updated 4/28/2020)
### 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.

### EFFICACY

- 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.
  - 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 against use with or without azithromycin in the hospital setting (updated 8/23/2020)
- NIH guidelines recommend against use of hydroxychloroquine (with or without azithromycin) in hospitalized patients; in outpatients, they recommend against use, except in a clinical trial (updated 8/29/2020)
- Some clinicians claim the combination of HCQ plus azithromycin is effective for early outpatient treatment of COVID-19, but randomized, controlled trials are lacking (added 9/10/2020)
- 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)
- Some clinicians claim the combination of HCQ plus azithromycin is effective for early outpatient treatment of COVID-19, but randomized, controlled trials are lacking (added 9/10/2020)
- In one randomized controlled trial, hydroxychloroquine was not more effective than placebo for post-exposure prophylaxis; other trials are ongoing (added 7/17/2020)
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### Pregnancy:
- No evidence of increased rate of birth defects in pregnant women
<table>
<thead>
<tr>
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<th><strong>COMMENTS</strong></th>
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<tbody>
<tr>
<td><strong>HYDROXYCHLOROQUINE (CONTINUED)</strong></td>
<td><strong>Design:</strong> ▪ Retrospective; HQC 600 mg/day within 48 hrs of admission vs no HCQ <strong>Results:</strong> ▪ Transferred to ICU or died w/in 7 days: 20.2% HCQ vs 22.1% w/o HCQ (no significant difference) <strong>Limitations:</strong> not randomized or peer reviewed</td>
<td>avoidance of other QT prolonging agents is recommended if coadministered(^6)(^8) ▪ May inhibit CYP2D6 and may be metabolized by CYP2C8, 2D6, and 3A4 to some extent; less likely to cause CYP-related interactions than chloroquine ▪ Separate from antacids/kaolin by 4 hours ▪ May increase digoxin levels ▪ May impair activity of antiepileptic drugs</td>
<td>▪ Embryonic deaths and ocular malformations have occurred in pregnant rats</td>
</tr>
<tr>
<td><strong>J Magagnoli et al 2020(^7) [updated 4/28/2020]</strong></td>
<td><strong>Population:</strong> hospitalized male patients in VA medical centers across the US (n=368) <strong>Design:</strong> ▪ Retrospective; HCQ vs HCQ plus azithromycin vs no HCQ <strong>Results:</strong> ▪ 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) <strong>Limitations:</strong> retrospective, not peer reviewed</td>
<td>FDA warns that coadministration of remdesivir and chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; concurrent use is not recommended(^2)(^6) (added 6/18/2020)</td>
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<tr>
<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
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<tr>
<td><strong>J Geleris et al. NEJM 2020</strong>&lt;sup&gt;20&lt;/sup&gt; <em>(added 5/9/2020)</em></td>
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<tr>
<td><strong>Population</strong>: consecutive hospitalized patients (n=1376 patients in analysis)</td>
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<tr>
<td><strong>Design</strong>: observational; single medical center in New York City; median follow-up 22.5 days</td>
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<tr>
<td><strong>Results</strong>:</td>
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<tr>
<td>▪ 811 (58.9%) patients treated with HCQ</td>
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<tr>
<td>▪ HCQ-treated patients had more severe illness than those who were not treated with the drug</td>
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<td>▪ No significant association between HCQ use and intubation or death (HR 1.04; 95% CI 0.82-1.32)</td>
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<tr>
<td><strong>Limitations</strong>: observational data</td>
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<tr>
<td><strong>W Tang et al. BMJ 2020</strong>&lt;sup&gt;21&lt;/sup&gt; <em>(added 5/18/20)</em></td>
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<tr>
<td><strong>Population</strong>: hospitalized patients, mostly mild to moderate disease (n=150)</td>
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<tr>
<td><strong>Design</strong>: open-label HCQ 1200mg x 3 days, then 800 mg/day x2-3 weeks vs standard care</td>
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<tr>
<td><strong>Results</strong>:</td>
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<tr>
<td>▪ No significant difference in probability of negative conversion</td>
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<tr>
<td>▪ Adverse effects more common with HCQ (mainly diarrhea)</td>
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<tr>
<td><strong>Limitations</strong>: open label, tx initiated late, confounding tx allowed</td>
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<tr>
<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
<td>Mehra et al. Lancet 2020(^{22}) (added 5/26/20) (updated 6/4/2020)</td>
<td>*<strong>Study Retracted(^{24})</strong></td>
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<tr>
<td></td>
<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>
<td>-</td>
<td><strong>Study Retracted</strong></td>
</tr>
<tr>
<td></td>
<td>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)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Design: observational analysis of multinational registry</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Results: treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Limitation: observational</td>
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<td>-</td>
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<td>WHO Solidarity Trial 2020(^{23}) (updated 6/20/2020)</td>
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<td>HCQ arm stopped based on data from the Solidarity trial, the RECOVERY trial, and a Cochrane review of other HCQ evidence</td>
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<td></td>
<td>Data showed no reduction of mortality with HCQ</td>
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</tbody>
</table>
### Hydroxychloroquine (Continued)

#### Recovery Trial 2020 (Added 6/20/2020)
- **Population:** Hospitalized adults in the UK (n=4674)
- **Design:** Randomized controlled trial; HCQ vs usual care
- **Results:**
  - 28-day mortality was not significantly different between patients treated with HCQ and those who received usual care (25.7% vs 23.5%)
  - Enrollment in the HCQ arm of the trial has been stopped
- **Limitations:** Data not yet published

- **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

**Population:** Symptomatic outpatients with COVID-19 or probable COVID-19 within 4 days of symptom onset (n=423)

**Design:** Randomized, double-blind, placebo-controlled trial

- HCQ (800 mg once, 600 mg 6-8 hrs later, then 600 mg once/day x 4 days) vs placebo

**Results:**
- 81% had confirmed COVID-19 or exposure to a person with confirmed infection
- 56% enrolled within 1 day of symptom onset
- No significant difference in symptom severity over 14 days between HCQ and placebo groups (relative difference in symptom severity 12%; p=0.117)
- No significant difference in percentage of patients who had symptoms at 14 days (24% vs 30% with placebo; p=0.21)
- Significantly more patients treated with HCQ had adverse effects (43% vs 22%; p<0.001)
- 4 hospitalizations and 1 nonhospitalized death in the HCQ group vs 10 hospitalizations and 1 hospitalized death in the placebo group (p=0.29)

**Limitations:** Only 58% of patients received COVID-19 testing
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
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</thead>
</table>
| 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 | | |
<table>
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</thead>
</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 | | |

*Mitja et al. Clin Infect Dis 2020*  
(added 9/9/2020)

**Population:** non-hospitalized adults in Spain with COVID-19 and <5 days of symptoms (n=293)  
**Design:** open-label, randomized trial  
- HCQ 800 mg x 1 day, then 400 mg once/day x 6 days vs no antiviral treatment (not placebo controlled)  
**Results:**  
- Median time from symptom onset to randomization: 3 days  
- No significant difference in mean reduction of viral load at day 3 or at day 7
### DRUG AND DOSAGE

#### HYDROXYCHLOROQUINE (CONTINUED)

### EFFICACY
- Risk of hospitalization was not significantly different between the groups (5.9% HCQ vs 7.1% control)
- Time to resolution of symptoms was similar (10 days HCQ vs 12 days control; p=0.38) (study not powered for this endpoint)
- No cardiovascular events reported

**Limitations:** open-label trial, did not evaluate HCQ with azithromycin; 7-day evaluations not included in original protocol

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**Million et al. Travel Med Infect Dis 2020**

**Population:** patients with mild (95% of patients) to severe COVID-19 in France (n=1061)

**Design:** retrospective analysis of outcomes of patients who were given early treatment with HCQ + azithromycin for ≥3 days

**Results:**
- Mean time from onset of symptoms to treatment was 6.4 days
- Good clinical outcome and virologic cure occurred in 973 patients (91.7%) within 10 days
- Poor clinical outcome (death, transfer to ICU, or hospitalization for >10 days) occurred in 46 patients (4.3%) and 10 patients (0.9%) died
- Poor clinical outcomes were associated with older age, illness severity, and low HCQ serum concentrations
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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<th>ADVERSE EFFECTS/INTERACTIONS</th>
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<tbody>
<tr>
<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
<td>- 9 patients had QTc prolongation ≥ 60 ms from baseline; none were &gt; 500 ms</td>
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<td><strong>Limitations:</strong> retrospective data, no control group; data incomplete for some patients</td>
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<td><strong>Scholz, Derwand, Zelenko. 2020</strong> <em>(added 9/10/2020)</em></td>
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<td><strong>Population:</strong> outpatients with COVID-19 (n=141)</td>
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<td><strong>Design:</strong> retrospective case series</td>
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<td><strong>Cases</strong> received treatment with HCQ + azithromycin + zinc x 5 days after risk stratification criteria were met</td>
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<td><strong>Untreated controls:</strong> independent public reference data from 337 patients with COVID-19 from the same community</td>
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<tr>
<td><strong>Results:</strong></td>
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<tr>
<td>Treatment started after 4 days of symptom onset</td>
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<td>4 of 141 (2.8%) treated patients were hospitalized; 58 of 377 (15.4%) controls were hospitalized (p&lt;0.001)</td>
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<td>1 of 141 (0.7%) treated patients died vs 13 of 377 (3.5%) controls (p=0.16)</td>
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<tr>
<td><strong>Limitations:</strong> not peer reviewed; retrospective case series; risk criteria unclear; control group characteristics unclear</td>
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</table>
### Hydroxychloroquine (Continued)

**Barbosa Esper et al. 2020**<sup>36</sup> (added 9/11/2020)

**Population:** Symptomatic outpatients with suspected COVID-19 evaluated by telemedicine in Brazil (n=636)

**Design:** Prospective, observational
- Patients given hydroxychloroquine plus azithromycin (n=412) were compared to those who refused medication (n=224)

**Results:**
- Mean time from symptom onset to treatment was 5 days
- 1.9% of treatment group required hospitalization compared to 5.4% of control group (p<0.001)
- 1.17% of patients treated before day 7 of symptoms needed hospitalization compared to 3.2% of patients treated after day 7

**Limitations:** Not peer reviewed, observational data

### Prophylaxis Trials:

**DR Boulware et al NEJM 2020**<sup>25</sup> (prophylaxis) (added 6/4/2020)

**Population:** Adults with household or occupational exposure to an individual with confirmed COVID-19 at a distance <6 feet for >10 mins with no mask or eye shield (high-risk) or with a mask but no eye shield (moderate-risk) (n = 821)
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
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</table>
| HYDROXYCHLOROQUINE (CONTINUED) | **Design:** randomized, double-blind, placebo-controlled trial in the US and Canada  
Prophylaxis given within 4 days after exposure  
- HCQ (800 mg x 1, then 600 mg in 6 to 8 hrs, then 600 mg daily x 4 days) vs placebo  
**Results:**  
- 87.6% had a high-risk exposure  
- New illness compatible with COVID-19 within 14 days was similar between the 2 groups (11.8% HCQ vs 14.3% placebo; p=0.35)  
- Patient-reported adherence to study drug regimen was lower in HCQ group (75.4% with HCQ vs 82.6% with placebo; p=0.01)  
- Adverse effects occurred more often with HCQ (GI effects most common)  
- No arrhythmias or deaths reported  
**Limitations:** endpoint did not require laboratory-confirmed COVID-19; study population generally younger and healthier than those at most risk for COVID-19 | | |

*N White and W Schilling et al (COPCOV trial)*\(^2\) (added July 1, 2020)  
(prophylaxis)  
**Population:** Healthcare workers and staff who have close contact with COVID-19 patients (anticipated enrollment is 40,000+ subjects)  
**Design:**
<table>
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<th>DRUG AND DOSAGE</th>
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<th>ADVERSE EFFECTS/INTERACTIONS</th>
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<tbody>
<tr>
<td>HYDROXYCHLOROQUINE (CONTINUED)</td>
<td>• Randomized, double-blind, placebo-controlled, multi-center prophylaxis trial</td>
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<td>• Chloroquine/hydroxychloroquine vs placebo</td>
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<td><strong>Results</strong>: trial enrolling as of July 2020</td>
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<td><strong>Mitja et al. medRxiv 2020</strong>&lt;sup&gt;32&lt;/sup&gt; (added 7/31/2020)</td>
<td><strong>Population</strong>: asymptomatic contacts exposed to a PCR-positive COVID-19 case in Spain (n=2314)</td>
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<td><strong>Design</strong>: open-label, cluster-randomized trial</td>
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<td></td>
<td>▪ HCQ 800 mg once, then 400 mg/day x 6 days vs no therapy</td>
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<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>
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<td></td>
<td><strong>Limitations</strong>: not peer reviewed</td>
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<td>DRUG AND DOSAGE</td>
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<td><strong>AZITHROMYCIN – GENERICS</strong>&lt;br&gt;<strong>ZITHROMAX (PFIZER)</strong>&lt;br&gt;(updated 9/11/2020)</td>
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<td><strong>Dosage:</strong>&lt;br&gt;▪ Optimal dosage not established&lt;br&gt;500 mg on day 1, then 250 mg once/day on days 2-5&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;▪ In addition to hydroxychloroquine</td>
<td>P Gautret et al. Int J Antimicrob Agents 2020&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;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)</td>
<td>Adverse Effects:&lt;br&gt;▪ GI disturbances, headache, dizziness, hepatotoxicity, QT prolongation&lt;sup&gt;4&lt;/sup&gt;</td>
<td>▪ <em>In vitro</em> activity against some viruses (influenza A H1N1 and Zika); no data on its activity against SARS-CoV-2</td>
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<td>Rosenberg et al. JAMA 2020&lt;sup&gt;10&lt;/sup&gt;&lt;br&gt;(added 7/22/2020)</td>
<td>Population: hospitalized patients&lt;br&gt;Design: retrospective multicenter cohort study&lt;br▪ HCQ plus azithromycin, HCQ alone, azithromycin alone, or neither</td>
<td>Drug Interactions:&lt;br&gt;▪ Use with other drugs that prolong the QT interval (such as chloroquine and hydroxychloroquine) can result in additive effects; avoid coadministration in patients at high risk of QT interval prolongation; ECG monitoring, correction of electrolyte abnormalities, and avoidance of other QT prolonging agents is recommended if coadministered&lt;sup&gt;4-6&lt;/sup&gt;</td>
<td>▪ Minimal data supporting efficacy in COVID-19 in humans and cardiac toxicity can occur when used with chloroquine/hydroxychloroquine</td>
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<td>Results:&lt;br▪ Patients in the treatment groups had more severe disease at baseline than those not treated&lt;br▪ 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&lt;br▪ Patients who received HCQ plus azithromycin had a higher risk of cardiac arrest compared to those who received neither drug</td>
<td>▪ 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 &gt;500 ms&lt;sup&gt;7&lt;/sup&gt;</td>
<td>▪ Infectious Diseases Society of America recommends against use with chloroquine or hydroxychloroquine in the hospital setting&lt;sup&gt;8&lt;/sup&gt;</td>
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<td></td>
<td>Limitations: observational data</td>
<td>▪ May increase the risk of toxicity with digoxin, cyclosporine, tacrolimus</td>
<td>▪ NIH guidelines recommend against use of hydroxychloroquine or chloroquine with or without azithromycin in hospitalized patients; in outpatients, they recommend against use, except in a clinical trial&lt;sup&gt;9&lt;/sup&gt; (updated 8/29/2020)</td>
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<td>▪ Some evidence of immunomodulatory and anti-inflammatory activity; it has been used as adjunctive treatment for other respiratory conditions (such as COPD)</td>
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<td>Pregnancy:&lt;br▪ No evidence of fetal harm</td>
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<tr>
<td>DRUG AND DOSAGE</td>
<td>EFFICACY</td>
<td>ADVERSE EFFECTS/INTERACTIONS</td>
<td>COMMENTS</td>
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| AZITHROMYCIN (continued) | **S Arshad et al. Int J Infect Dis 2020**<sup>11</sup>  
(added July 7, 2020)  
**Population:** Consecutive hospitalized patients in a hospital system in Michigan (n=2541)  
**Design:** Multi-center, retrospective observational study comparing hydroxychloroquine alone or with azithromycin, azithromycin alone or neither  
**Results:**  
* in-hospital mortality was 20.1% with hydroxychloroquine + azithromycin, 13.5% with hydroxychloroquine, 22.4% with azithromycin, and 26.4% with neither drug (p<0.001)  
* 82% of patients received hydroxychloroquine within 24 hours of admission  
**Limitations:** retrospective, observational data | | |
| Mehra et al. Lancet 2020<sup>12</sup>  
(added 5/26/20)  
(updated 6/4/20)  
***Study Retracted***<sup>13</sup>***  
* 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) | | |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>AZITHROMYCIN (continued)</strong></td>
<td>Design: observational analysis of multinational registry</td>
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<td></td>
<td><strong>Results:</strong></td>
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<td>▪ treatment was associated with an increased risk of in-hospital mortality and ventricular arrhythmia compared to control group</td>
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<td><strong>Limitation:</strong> observational</td>
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<td></td>
<td><a href="#">J Magagnoli et al 2020</a></td>
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<tr>
<td></td>
<td><strong>Design:</strong></td>
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<td></td>
<td>▪ Retrospective; HCQ vs HCQ plus azithromycin vs no HCQ</td>
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<tr>
<td></td>
<td><strong>Results:</strong></td>
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<td></td>
<td>▪ No significant difference in the rate of mechanical ventilation between groups (13.3% HCQ, 6.9% HCQ + azithromycin, and 14.1% no HCQ)</td>
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<td>▪ 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)</td>
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<tr>
<td></td>
<td><strong>Limitations:</strong> retrospective, not peer reviewed</td>
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**AZITHROMYCIN (continued)**

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<td><strong>Cavalcanti et al. NEJM 2020</strong>&lt;sup&gt;15&lt;/sup&gt; (added 7/23/2020)</td>
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<td><strong>Population:</strong></td>
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<td>open-label, multicenter randomized controlled trial</td>
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<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>
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<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>
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<td>▪ QT interval prolongation and liver enzyme elevations occurred more frequently with HCQ with or without azithromycin than with standard care alone</td>
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<tr>
<td><strong>Limitations:</strong></td>
<td>open-label trial, some patients previously received treatment</td>
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</table>
AZITHROMYCIN (continued)

**Population:** symptomatic outpatients with suspected COVID-19 evaluated by telemedicine in Brazil (n=636)

**Design:** Prospective, observational
- patients given hydroxychloroquine plus azithromycin (n=412) were compared to those who refused medication (n=224)

**Results:**
- mean time from symptom onset to treatment was 5 days
- 1.9% of treatment group required hospitalization compared to 5.4% of control group (p<0.001)
- 1.17% of patients treated before day 7 of symptoms needed hospitalization compared to 3.2% of patients treated after day 7

**Limitations:**
- not peer reviewed, observational data

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>
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<tr>
<td><strong>HIV Protease Inhibitors</strong></td>
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</table>
| **ATAZANAVIR** (ATV) – REYATAZ (BMS) AND GENERICS** | ▪ Predicted to inhibit SARS-CoV-2 replication⁴  
▪ No clinical trial data available | **Adverse Effects:**  
▪ Nausea, diarrhea, asymptomatic indirect hyperbilirubinemia, rash, nephrolithiasis, cholelithiasis, PR interval prolongation  
**Drug Interactions:**  
▪ Substrate of CYP3A4 and inhibitor of CYP3A4 and CYP2C8⁵  
▪ Use of drugs that increase gastric pH, such as PPIs, H2-antihistamines, and antacids may decrease absorption of atazanavir; administer atazanavir 2 hours before or 10 hours after an H2-antihistimine; consider avoiding use of PPIs | ▪ No clinical trials available evaluating use of atazanavir for COVID-19  
▪ Available in powder form or capsules can be opened for administration via enteral tube  
▪ NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data⁶  
▪ Pregnancy:  
▪ Does not appear to increase the risk of major birth defects |
| **DARUNAVIR/Cobicistat** (JOHNSON & JOHNSON) | **Shanghai Public Health Clinical Center (SPHCC)**⁸,⁹  
**Population:** hospitalized patients (n=30)  
**Design:**  
▪ randomized, open label  
▪ darunavir/cobicistat 800/150 mg once/day x 5 days vs standard care  
**Results:**  
▪ darunavir/cobicistat was not effective | **Adverse Effects:**  
▪ Nausea, diarrhea, increased transaminases, headache, rash, severe skin reactions (including Stevens-Johnson syndrome)  
**Drug Interactions:**  
▪ Substrate and inhibitor of CYP3A4 and CYP2D6⁵  
**Pregnancy:**  
▪ Not recommended for use in pregnant women | ▪ An initial laboratory study had suggested darunavir (at exposures higher than those achieved in humans) may be effective against SARS-CoV-2  
▪ No evidence that darunavir is effective for treatment of COVID-19  
▪ NIH recommends against use of HIV protease inhibitors, except in the context of a clinical trial, because of unfavorable pharmacodynamics and negative clinical trial data⁶  
▪ Pregnancy:  
▪ Not recommended for use in pregnant women |
**DRUG AND DOSAGE**

**LOPINAVIR/RITONAVIR**

**(LPV/RTV) – KALETRA (ABBVIE)**

**Dosage:**
- Optimal dosage/duration not established
- Dosages/duration/concomitant drugs used in COVID-19 clinical trials have varied
- 400/100 mg PO bid
- With or without food
- Tablets should not be crushed (decrease exposure)

**EFFICACY**

* B Cao et al. NEJM 2020

**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, bradycardia

**Drug Interactions:**
- Substrate and inhibitor of CYP3A
- Avoid use with other PR or QT interval-prolonging drugs

**COMMENTS**

- In vitro activity against SARS-CoV, and MERS-CoV; data in SARS-CoV-2 limited
- Society of Critical Care Medicine recommends against use of LPV/RTV in critically ill patients
- Infectious Diseases Society of America recommends use only in the context of a clinical trial
- 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
- Pregnancy:
  - No association with teratogenic effects; may be associated with preterm delivery
<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
<th>EFFICACY</th>
<th>ADVERSE EFFECTS/INTERACTIONS</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td>LOPINAVIR/РИТОНАВИР (continued)</td>
<td>Limitations: small case series; only trough concentration evaluated; no in vivo data on EC50 dose of lopinavir for SARS-CoV-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. FDA-approved for other indications.
7. Dosage used for treatment of COVID-19 in trials; optimal dosage not established.
## DRUG AND DOSAGE

### EFFICACY

<table>
<thead>
<tr>
<th>Drug Interferon Beta and Ribavirin</th>
<th>Efficacy</th>
<th>Adverse Effects/Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERFERON BETA-1B –</strong>&lt;br&gt;<strong>BETASERON</strong>&lt;br&gt;<strong>EXTAVIA</strong>&lt;br&gt;<strong>RIBAVIRIN –</strong>&lt;br&gt;<strong>REBETOL, AND GENERICS</strong>&lt;br&gt;(added 5/14/2020)</td>
<td><strong>Population:</strong> hospitalized patients with symptom duration ≤14 days (n=127)&lt;br&gt;<strong>Design:</strong> prospective, randomized, open-label, multi-center&lt;br&gt;<strong>Dosage:</strong> optimal dosage unknown&lt;br&gt;<strong>Limitations:</strong> patients presenting ≥7 days from symptom onset did not receive interferon due to concerns about proinflammatory effects; no critically ill patients included</td>
<td><strong>Interferon:</strong> injection- depression site reactions, flu-like symptoms, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia&lt;br&gt;<strong>Ribavirin:</strong> hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, rash, conjunctival irritation, neuropsychologic symptoms</td>
<td><strong>Has antiviral properties</strong>&lt;br&gt;<strong>In vitro</strong> activity against SARS-CoV and MERS-CoV, but did not appear to improve disease outcomes in human studies&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;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&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;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 (&lt;7 days from symptom onset) mild and moderate illness&lt;br&gt;<strong>Pregnancy:</strong> interferon: may cause fetal harm, based on data from animal studies&lt;br&gt;Ribavirin: contraindicated in pregnant women and in men whose partners are pregnant&lt;br&gt;Pregnancy should be avoided for 6 months after treatment in women who received the drug and in women whose partners received the drug&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Interferon beta-1b:</strong> 1 mL on alternate days x 1-3 doses depending on day of initiation</td>
<td><strong>Results:</strong>&lt;br&gt;Time to negative nasopharyngeal swab shorter with triple combination vs LPV/RTV (7 vs 12 days; p=0.0010)&lt;br&gt;Time to alleviation of symptoms: 4 days with combination vs 8 days with LPV/RTV (p&lt;0.0001)&lt;br&gt;<strong>Limitations:</strong> patients presenting ≥7 days from symptom onset did not receive interferon due to concerns about proinflammatory effects; no critically ill patients included</td>
<td><strong>Drug Interactions:</strong>&lt;br&gt;<strong>Ribavirin:</strong> 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&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Ribavirin:</strong> 400 mg q12h x 14 days</td>
<td><strong>Adverse Effects:</strong>&lt;br&gt;Hung et al trial found no difference in adverse events between 2 groups&lt;br&gt;<strong>Interferon:</strong> injection- depression site reactions, flu-like symptoms, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia&lt;br&gt;<strong>Ribavirin:</strong> hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, rash, conjunctival irritation, neuropsychologic symptoms</td>
<td><strong>SG016 2020 – Inhaled Interferon</strong>&lt;br&gt;(added 7/20/2020)&lt;br&gt;<strong>Population:</strong> hospitalized patients in UK (n=101)&lt;br&gt;<strong>Design:</strong> phase 2 double-blind, placebo-controlled trial&lt;br&gt;<strong>Dosage:</strong> nebulized interferon beta (SNG001) vs placebo&lt;br&gt;<strong>Results:</strong>&lt;br&gt;Mean symptom duration before starting treatment (9.6 days interferon vs 9.8 days placebo)&lt;br&gt;<strong>Limitations:</strong> patients presenting ≥7 days from symptom onset did not receive interferon due to concerns about proinflammatory effects; no critically ill patients included</td>
<td><strong>Adverse Effects:</strong>&lt;br&gt;Hung et al trial found no difference in adverse events between 2 groups&lt;br&gt;<strong>Interferon:</strong> injection- depression site reactions, flu-like symptoms, transaminase elevations, possible cardiac toxicity, autoimmune disorders, allergic reactions, hepatotoxicity, seizures, suicidal ideation, lymphopenia&lt;br&gt;<strong>Ribavirin:</strong> hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, rash, conjunctival irritation, neuropsychologic symptoms</td>
</tr>
</tbody>
</table>

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<sup>1</sup> Hung et al. Lancet 2020

<sup>2</sup> Has antiviral properties

<sup>3</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>4</sup> 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

<sup>5</sup> SG016 2020 – Inhaled Interferon
### DRUG AND DOSAGE

**INTERFERON BETA-1B – BETASERON (continued)**

### EFFICACY
- Development of severe disease (requiring ventilation or death) was less likely with interferon than with placebo (OR 0.21; 95% CI 0.04-0.97; p=0.046)
- Recovery (no limitation of activities or no evidence of infection) was more likely with interferon (HR 2.19; 95% CI 1.03-4.69; p=0.043)
- Breathlessness reduced in patients receiving interferon compared to placebo (p=0.007)
- 0 deaths with interferon; 3 deaths with placebo
- In patients with more severe disease on admission (requiring supplemental oxygen), interferon nonsignificantly increased the likelihood of hospital discharge (p=0.096)
- Median time to discharge was 6 days with interferon and 9 days with placebo

**Limitations:** phase 2 trial; data not yet published

### ADVERSE EFFECTS/INTERACTIONS

### COMMENTS

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<tr>
<th>DRUG AND DOSAGE</th>
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</thead>
<tbody>
<tr>
<td><strong>Antiparasitic</strong></td>
<td>▪ Inhibits SARS-CoV-2 in vitro; ~5000-fold reduction in viral RNA in cell culture 48 hours after a single treatment[^2]</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>
<td>▪ Inhibited SARS-CoV-2 in vitro; may inhibit nuclear transport activity</td>
</tr>
<tr>
<td>▪ Dosage for COVID-19 not established</td>
<td></td>
<td>▪ FDA warns against human use of ivermectin intended for use in animals[^4]</td>
<td></td>
</tr>
<tr>
<td>200-400 mcg/kg/dose PO[^1]</td>
<td></td>
<td>Pregnant: ▪ Limited data available in pregnant women</td>
<td></td>
</tr>
</tbody>
</table>

**Dosage:**
- Dosage for COVID-19 not established
- 200-400 mcg/kg/dose PO

**Population:** hospitalized patients (n=280)

**Design:** retrospective cohort; ivermectin compared to usual care
- 200 mcg/kg x 1 dose, 2nd dose given after 7 days if still hospitalized

**Results:**
- All-cause mortality was 15.0% with ivermectin and 25.2% with usual care group (p=0.03); difference remained significant after adjustment (OR 0.27; p=0.03)
- In 75 patients with severe pulmonary disease, mortality was lower with ivermectin (38.8% vs 80.7%, p=0.001)
- No significant difference in extubation rates (36.1% vs 15.4%, p=0.07)

**Limitations:** retrospective data; not peer reviewed; unclear what other treatments patients received; intervention timing not standardized

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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>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Bradykinin Inhibitor</strong></td>
<td><strong>van de Veerdonk et al. JAMA Netw Open 2020</strong>¹</td>
<td><strong>Adverse Effects:</strong></td>
<td><strong>FDA-approved for treatment of acute attacks of hereditary angioedema (HAE)</strong></td>
</tr>
<tr>
<td><strong>ICATIBANT – FIRAZYR, and generics</strong></td>
<td><strong>Population:</strong> hospitalized patients with confirmed COVID-19 in the Netherlands (n=27; 9 cases/18 controls)</td>
<td>▪ Injection site reactions, pyrexia, transaminase increases, dizziness, rash</td>
<td><strong>SARS-CoV-2 enters cells via ACE2, which breaks down bradykinin; loss of ACE2 may result in stimulation of the bradykinin 2 receptor, which could be a contributing factor in pulmonary edema in patients with COVID-19</strong></td>
</tr>
<tr>
<td><strong>Dosage:</strong></td>
<td>▪ 30 mg SC x 3 doses given 6 hours apart¹</td>
<td>▪ ostein saturation &lt;90% without supplemental oxygen, requiring ≥3 L/min supplemental oxygen, and with computed tomography severity score ≥7</td>
<td><strong>Icatibant is a competitive antagonist selective for the bradykinin B2 receptor</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Design:</strong> case-control study</td>
<td><strong>Drug Interactions:</strong></td>
<td><strong>Pregnancy:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Results:</strong> icatibant-treated patients required less oxygen supplementation vs controls</td>
<td>▪ May attenuate antihypertensive effect of ACE inhibitors</td>
<td>▪ Icatibant use has not been associated with a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes based on available data from published literature and the pharmacovigilance database</td>
</tr>
<tr>
<td></td>
<td>▪ 4 of 9 patients given icatibant were no longer oxygen dependent within 10-35 hours</td>
<td></td>
<td>▪ Adverse maternal and fetal outcomes have been reported in animal studies</td>
</tr>
<tr>
<td></td>
<td>▪ 8 of 9 had a reduction of oxygen requirements ≥3 L/min after 24 hrs with icatibant vs 3 of 18 controls</td>
<td></td>
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<tr>
<td></td>
<td>▪ 3 patients had a resurgence in need for oxygen supplementation; possibly due to short half-life of icatibant</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Limitations:</strong> retrospective data; 9 cases</td>
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<tr>
<th>DRUG AND DOSAGE</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Colchicine</strong></td>
<td><strong>GRECCO-19 trial</strong>¹</td>
<td>**Adverse Effects:**²</td>
<td></td>
</tr>
<tr>
<td><strong>COLCHICINE</strong></td>
<td><strong>Population:</strong> Hospitalized patients (n=105)</td>
<td>▪ Diarrhea, nausea, and vomiting are common with use of colchicine.</td>
<td></td>
</tr>
<tr>
<td><strong>(Added 7/1/2020)</strong></td>
<td><strong>Design:</strong> ▪ Randomized, open-label trial in Greece</td>
<td>▪ Blood dyscrasias have been reported.</td>
<td></td>
</tr>
<tr>
<td><strong>Dosage:</strong> ▪ Optimal dosage in patients with COVID-19 is unclear</td>
<td>▪ Colchicine plus standard of care vs standard of care alone x 3 weeks</td>
<td>▪ Neuromyopathy is rare; it typically occurs in elderly patients or in those with hepatic or renal impairment.</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> ▪ Differences in inflammatory biomarkers (high sensitivity cardiac troponin, C-reactive protein) were not statistically significant between groups</td>
<td>▪ Overdosage of colchicine can be fatal.</td>
<td>▪ More trials are ongoing to evaluate the efficacy of colchicine for treatment of COVID-19</td>
<td></td>
</tr>
<tr>
<td>▪ 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)</td>
<td><strong>Drug Interactions:</strong> ▪ 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</td>
<td>▪ Pregnancy: ▪ No adequate studies in pregnant women</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations:</strong> ▪ Small, open-label trial</td>
<td>▪ Dosage should be reduced when colchicine is taken concurrently with or within 2 weeks after a CYP3A4 or P-gp inhibitor</td>
<td>▪ Embryofetal toxicity and teratogenicity and altered postnatal development reported in animal studies</td>
<td></td>
</tr>
<tr>
<td>▪ Almost all patients also received treatment with hydroxychloroquine and azithromycin or lopinavir/ritonavir</td>
<td>▪ Myopathy and rhabdomyolysis have occurred in patients taking colchicine with a statin or a fibrate</td>
<td></td>
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</tbody>
</table>

### Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Adverse Effects/Interactions</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Alogliptin</td>
<td>Clinical trials with linagliptin in patients with type 2 diabetes and</td>
<td>Adverse Effects: Acute pancreatitis, fatal hepatic failure, possible worsening of heart failure,</td>
<td>Hypothesized that inhibition of DPP-4 may prevent infection with or progression of</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>mild or moderate COVID-19 are expected to begin to determine if use of</td>
<td>possible severe and disabling joint pain</td>
<td>COVID-19</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>the drug can improve glucose control and reduce the severity of COVID-19</td>
<td>Drug Interactions: Strong P-glycoprotein or CYP3A4 inducers can decrease serum concentrations</td>
<td>Mechanism not established, but it has been suggested that DPP-4 may be involved in SARS-CoV-2</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>of linagliptin; concurrent use should be avoided if possible</td>
<td>saxagliptin concentrations; the dose of saxagliptin should not exceed 2.5 mg when used</td>
<td>-2 cell adhesion and DPP-4 inhibitors may have effects on inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in combination with a CYP3A4/5 inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin may increase digoxin concentrations; monitor patients taking digoxin</td>
<td></td>
</tr>
</tbody>
</table>

#### Dosage:
- Optimal dosage in patients with COVID-19 is unclear
- Dosage adjustments are needed for reduced renal function

#### Usual dosage for treatment of type 2 diabetes:
- Alogliptin: 25 mg PO once/day
- Linagliptin: 5 mg PO once/day
- Saxagliptin: 2.5-5 mg PO once/day
- Sitagliptin: 100 mg PO once/day

---

## 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 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

---

### DRUG AND DOSAGE

**H2-Receptor Antagonists (H2RAs)**

**FAMOTIDINE – PEPCID (VALEANT)**

*(Updated 8/19/2020)*

**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** *(updated 6/5/2020)*

**Population:** hospitalized, non-intubated, non-ICU (n=1620)

**Design:** Retrospective cohort, famotidine vs no famotidine

**Results:**
- Reduced risk for death or intubation (adjusted HR 0.42)
- PPI use not associated with lower risk
- 5.1% of patients were given famotidine within 24 hours of admission

**Limitations:** observational, retrospective, single center, not peer reviewed

**T Janowitz et al.**
**Gut 2020** *(added 6/5/2020)*

**Population:** non-hospitalized patients (n=10)

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

---

**ADVERSE EFFECTS/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

**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)**

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**Pregnancy:**
- No adequate data in pregnant women; no evidence of risk in animal studies

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</table>
| FAMOTIDINE (continued) | Results:  
- combined symptom score improved significantly within 24 hrs of famotidine  
- symptoms (cough, shortness of breath, fatigue, headache, anosmia) were scored on a 4-point ordinal scale  
- no patients were hospitalized  
- time from onset of symptoms to start of treatment ranged from 2 to 26 days  
Limitations: case series (small number of patients, no placebo group) | | |
| | **Mather et al. Am J Gastroenterol 2020** (added 8/19/2020) | | |
| | **Population:** hospitalized patients with COVID-19 at a single center in Connecticut (n=878; 83 received famotidine)  
**Design:** retrospective, propensity-matched observational study  
- compared patients receiving famotidine (PO or IV at any dose within 7 days of COVID screening or hospital admission) to those not receiving the drug  
**Results:**  
- patients treated with famotidine were younger than those who were not  
- famotidine use associated with decreased risk of in-hospital mortality (OR 0.37; 95% CI 0.16-0.86; p=0.021) | | |
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>FAMOTIDINE</strong> (continued)</td>
<td>• famotidine also associated with decreased risk of combined death or intubation and lower levels of serum markers for severe disease (CRP, procalcitonin, ferritin)</td>
<td><strong>Limitations:</strong> observational data</td>
<td></td>
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</thead>
<tbody>
<tr>
<td>ASCORBIC ACID — GENERICS</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>Dosage:</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>
<td>Infection may reduce vitamin C concentrations</td>
</tr>
<tr>
<td>12 g IV q12h x 7 days (infused at a rate of 12 ml/hr)</td>
<td></td>
<td>▪ Nausea, vomiting, diarrhea, dizziness, and flushing can occur</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>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug Interactions:</td>
<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 (added 7/21/2020)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ May decrease serum concentrations of amphetamines</td>
<td></td>
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<td></td>
<td></td>
<td>▪ May decrease the efficacy of bortezomib (Velcade, and generics) and cyclosporine</td>
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<td>▪ May cause deferoxamine (Desferal) toxicity and left ventricular dysfunction; avoid oral doses &gt;200 mg/day</td>
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<td></td>
<td>Pregnancy:</td>
<td>No data are available in pregnant women</td>
</tr>
</tbody>
</table>
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

**Efficacy**

Carlucci et al. 2020\(^2\) (added 7/21/2020)

**Population:** patients (n=932)

**Design:** retrospective observational study hospitalized
- Zinc plus hydroxychloroquine and azithromycin compared to hydroxychloroquine and azithromycin alone

**Results:**
- No difference in duration of hospitalization or mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO\(_2\) (in univariate analysis)
- Zinc associated with increased frequency of discharge and reduced mortality or transfer to hospice (in bivariate logistic regression analysis)
- Association with decreased mortality no longer significant when non-ICU patients were excluded

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

**Adverse Effects/Interactions**

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

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

**Pregnancy:**
- Limited data on the safety of doses higher than the recommended daily allowance in pregnant women

---

1. Dosage regimen tried for treatment of covid-19; effective dosage has not been established in clinical trials.
<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>
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<tr>
<td>▪ Dosage in patients with COVID-19 not established</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>▪ Vitamin D plays an important role in immune function</td>
<td></td>
</tr>
<tr>
<td>▪ 400-800 IU/day (recommended daily allowance for most people)</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>▪ Limited data in COVID-19 and other serious illness</td>
<td></td>
</tr>
<tr>
<td>▪ Serum 25(OH)D 20 to 30 ng/mL: 800-2000 IU/day</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>
<td>▪ NIH guidelines state 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>
<td></td>
</tr>
<tr>
<td>▪ Serum 25(OH)D &lt;20 ng/mL: may need 50,000 IU/week</td>
<td>▪ Excessive doses could cause toxicity (hypercalciuria, hypercalcemia, nausea, vomiting, anorexia, constipation, dehydration, fatigue, irritability, confusion, weakness)</td>
<td>▪ NICE guidance states that there is no evidence to support use of vitamin D supplements 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>
<td></td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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<tbody>
<tr>
<td>THIAMINE</td>
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<td><em>(added 7/29/2020)</em></td>
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<tr>
<td><strong>Dosage:</strong></td>
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<tr>
<td>▪ Dosage in patients with COVID-19 not established</td>
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<tr>
<td>▪ 200 mg IV q12h¹</td>
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<tr>
<td><strong>Dosage:</strong></td>
<td>▪ There are no published trials evaluating use of thiamine for treatment or prevention of COVID-19</td>
<td>▪ Adverse Effects:</td>
<td>▪ 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 conflicting²³</td>
</tr>
<tr>
<td><strong>Efficacy:</strong></td>
<td>▪ 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-19¹</td>
<td>▪ Thiamine is water-soluble and toxic levels are not expected</td>
<td>▪ There are no controlled trials evaluating use of thiamine in critically ill patients with COVID-19</td>
</tr>
<tr>
<td><strong>Efficacy:</strong></td>
<td>▪ 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 controls²</td>
<td></td>
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</tr>
<tr>
<td><strong>Efficacy:</strong></td>
<td>▪ 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 alone³</td>
<td></td>
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</tr>
</tbody>
</table>

### OTC Products

#### Nasal Saline Irrigation

**Nasal Saline Irrigation** – *(NETI POT OR SINUS RINSE SQUEEZE BOTTLE)*

**Dosage:**
- Multiple times per day

**Efficacy:**
- No data for treatment or prevention of COVID-19
- Open-label, randomized trial in 61 patients with viral upper respiratory tract infections (including rhinovirus and coronavirus), hypertonic nasal saline irrigation shortened the duration of illness, lowered transmission to household contacts, and reduced viral shedding

**Adverse Effects:**
- Minor nasal discomfort or irritation
- Sterile, distilled, or boiled (and cooled) tap water should be used to prevent bacterial or protozoal infection

**Comments:**
- No evidence that regular nasal saline irrigation can prevent or treat COVID-19 infection
- Some limited evidence that nasal irrigation with hypertonic saline can shorten the duration of the common cold
- Hypothesized mechanism is cellular use of chloride ions to produce hypochlorous acid (HOCL), which has antiviral effects


#### Melatonin

**Melatonin** – **GENERICS**

**Dosage:**
- Optimal dosage not established
- 5-10 mg/day PO

**Efficacy:**
- No data available on use of melatonin for treatment of COVID-19
- Based on data suggesting melatonin may be helpful in acute lung injury/acute respiratory distress syndrome caused by other pathogens

**Adverse effects:**
- Well tolerated; dizziness, headache, nausea, and sleepiness can occur

**Drug Interactions:**
- May decrease the antihypertensive effects of calcium channel blockers
- Melatonin is a substrate of CYP1A2; inducers of CYP1A2 may decrease melatonin concentrations and inhibitors of CYP1A2 may increase melatonin concentrations

**Comments:**
- May have anti-viral and anti-inflammatory effects; could decrease serum levels of inflammatory cytokines
- Has been used in critical care patients (not COVID-19) to reduce vessel permeability, anxiety, sedation use, and improving sleeping quality
- Limited data on the safety of melatonin use during pregnancy

<table>
<thead>
<tr>
<th>DRUG AND DOSAGE</th>
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</tr>
</thead>
</table>
| Benzalkonium Chloride                 | ▪ The manufacturer of a nasal formulation of 0.13% benzalkonium chloride (NanoBio Protect) states the product has been shown to kill SARS-CoV-2 in *in vitro* studies conducted by Public Health England; published data are not yet available. Previous studies have reported that 0.05-0.2% benzalkonium chloride formulations were less effective than alcohol-based disinfectants against other coronaviruses. | ▪ Irritation, burning or stinging, hypersensitivity reactions. No clinical data demonstrating efficacy of a nasal formulation of benzalkonium chloride for prevention of COVID-19 infection. The CDC recommends alcohol-based hand sanitizers containing 80% ethanol or 75% isopropanol. |}

### Renin-Angiotensin System (RAS) Inhibitors

- **Benazepril (Lotensin, and generics)**
- **Captopril (generic)**
- **Enalapril (Vasotec, and others)**
- **Fosinopril (generic)**
- **Lisinopril (Zestril, Prinivil, and others)**
- **Moexipril (generic)**
- **Perindopril (generic)**
- **Quinapril (Accupril, and generics)**
- **Ramipril (Altace, and generics)**
- **Trandolapril (generic)**

#### ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

(Updated 7/28/2020)

- Increased risk of severe COVID-19 in patients with cardiovascular disease
- ACE inhibitors and ARBs increase expression of ACE2 by epithelial cells in the lung, and pathogenic coronaviruses such as SARS-CoV-2 enter these cells via ACE2 receptors[^1]
- Some researchers have suggested that this increase in risk may be due to use of ACE inhibitors or ARBs in patients with diabetes, hypertension, or heart failure
- Others have suggested, however, that ACE2 may protect against lung injury in coronavirus infection and that taking an ACE inhibitor or an ARB might be beneficial[^2,3]

#### ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

- **Azilsartan (Edarbi)**
- **Candesartan (Atacand, and generics)**
- **Eprosartan (Teveten and generics)**
- **Irbesartan (Avapro, and generics)**
- **Losartan (Cozaar, and generics)**
- **Olmesartan (Benicar, and generics)**
- **Telmisartan (Micardis, and generics)**

---

**P Zhang et al. Circ Res 2020[^4]**

**Population:** hospitalized patients w/ hypertension (n=1128)
- 188 taking an ACE inhibitor or ARB

**Design:** retrospective, multi-center

**Results:**
- All-cause mortality was lower in patients taking an ACE inhibitor or ARB compared to those not taking an ACE inhibitor or ARB (3.7% vs 9.8%)
- Adjusted HR 0.37 (95% CI, 0.15-0.89; P = 0.03) in a propensity score-matched analysis

**Limitations:** retrospective

---

**J Li et al. JAMA Cardiol 2020[^5]**

**Population:** hospitalized patients (n = 1178); 362 patients with hypertension, 115 taking an ACE inhibitor or ARB

**Design:** retrospective, single-center

**Results:** percentage of patients taking an ACE inhibitor or ARB was similar between patients with (32.9%) and without (30.7%) severe infection and between survivors (33.0%) and non-survivors (27.3%)

**Limitations:** no adjustment for confounding factors

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**Comments:**

- Multiple medical organizations, including the NIH, have advised against stopping or starting these drugs to prevent or treat COVID-19 infection[^3,10,11]
- Patients who are taking an ACE inhibitor or an ARB and subsequently develop COVID-19 should continue to take the drug[^3,10]
- Some evidence from retrospective trials suggesting that use of an ACE inhibitor or an ARB in patients with hypertension who were hospitalized for COVID-19 was associated with similar or lower mortality rates compared to patients who were not taking a drug from either class prior to infection.[^4,5,6]
- Prospective randomized-controlled trials evaluating these drugs in patients hospitalized for COVID-19 are in progress[^16]
<table>
<thead>
<tr>
<th>DRUG</th>
<th>CONCERNS/MECHANISM</th>
<th>CLINICAL STUDIES</th>
<th>COMMENTS</th>
</tr>
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<tbody>
<tr>
<td>▪  Valsartan (<em>Diovan</em>, and generics)</td>
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</table>

DM Bean *et al.* 2020<sup>6</sup>  
**Population:** hospitalized patients (n=205)  
**Design:** retrospective, single-center  
**Results:** Lower rate of death or transfer to the ICU within 7 days of symptom onset in patients on an ACE inhibitor (OR 0.29)  
**Limitations:** small sample size, not peer reviewed

Mancia *et al.* NEJM 2020<sup>7</sup>  
**Population:** 6272 case patients with COVID-19; 30,759 controls  
**Design:** population-based case-control study in Italy  
**Results:**  
▪ use of ACE inhibitors or ARBs was not associated with COVID-19 among case patients (adjusted OR for ACE inhibitors 0.96 [CI 0.87-1.07] and for ARBs 0.95 [CI 0.86-1.05])  
▪ no association between use of ACE inhibitors or ARBs and severe or fatal disease (adjusted OR for ACE inhibitors 0.91 [CI 0.69-1.21] and for ARBs 0.83 [CI 0.63-1.10])  
**Limitations:** observational data

Mehra *et al.* NEJM 2020<sup>8</sup>  
(updated 6/4/2020)  
***Study Retracted***<sup>12</sup>  
**Retracted because of concerns about the accuracy of the data and analysis; an independent audit was not possible because the full dataset was not made available**  
**Population:** 8910 hospitalized patients in Asia, Europe, and North America  
**Design:** observational; data collected from an international registry  

▪ A review of multiple trials of ACEI or ARB use in patients with COVID-19 concluded there is high-certainty evidence that use of these drugs is not associated with more severe disease<sup>17</sup>  
(added 7/28/2020)
### ACE INHIBITORS AND ARBS (CONTINUED)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CONCERNS/MECHANISM</th>
<th>CLINICAL STUDIES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results:</strong></td>
<td>Use of ACE inhibitors or ARBs was not found to be associated with an increased risk of in-hospital death</td>
<td></td>
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</tr>
<tr>
<td><strong>Limitations:</strong></td>
<td>observational data</td>
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</tbody>
</table>

**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
**ACE INHIBITORS AND ARBS (CONTINUED)**

**CONCERNS/MECHANISM**

**CLINICAL STUDIES**

**COMMENTS**

Fosbøl et al. JAMA 2020

*Added 7/28/2020*

**Population: Retrospective Cohort Study:**

- Hypertensive patients with COVID-19 (n=4480)

**Nested, Case-Control:**

- Cases (COVID-19, prior hypertension; n=571); controls (no COVID-19, prior hypertension; n=5710)

**Design:** retrospective cohort study examining outcomes in patients with COVID-19; nested, case-control design for susceptibility analysis; from Danish registry

**Results:**

**Retrospective Cohort Study: ACEI/ARB use vs no use**

- Mortality within 30 days was 18.1% in the ACEI/ARB group compared to 7.3% in the nonuser group (significant difference in unadjusted analysis; not statistically significant after adjustment for age, sex, and medical history)
- Death or severe COVID-19 occurred in 31.9% of ACEI/ARB users and 14.2% of nonusers by 30 days (significant difference in unadjusted analysis; not statistically significant after adjustment)

**Nested Case-Control Susceptibility Analysis: ACEI/ARB use vs other hypertensive drugs**

- ACEI/ARB use was not associated with a higher incidence of COVID-19, compared with use of other antihypertensives

**Limitations:** retrospective data
<table>
<thead>
<tr>
<th>DRUG</th>
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</thead>
<tbody>
<tr>
<td>ACE INHIBITORS AND ARBS (CONTINUED)</td>
<td></td>
<td>Felice et al. Am J Hypertens 2020&lt;sup&gt;15&lt;/sup&gt; (added 7/28/2020)</td>
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<tr>
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<td>Population: consecutive hypertensive patients presenting to ER in Italy with acute respiratory symptoms and/or fever or diagnosis of COVID-19 (n=133)</td>
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<td></td>
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<td>Design: single center, retrospective study</td>
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<tr>
<td></td>
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<td>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</td>
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<tr>
<td></td>
<td></td>
<td>Limitations: small retrospective study</td>
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<tr>
<td></td>
<td></td>
<td>Population: consecutive hypertensive patients hospitalized for COVID-19 in Turkey (n=113)</td>
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<tr>
<td></td>
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<td>Design: retrospective study</td>
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<tr>
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<td>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</td>
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<tr>
<td></td>
<td></td>
<td>Limitations: small retrospective study; patients on ACEIs/ARBS more likely to have coronary artery disease and were older</td>
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<td>Lopes et al. BRACE CORONA Trial (Presented at ESC Sept 1, 2020)</td>
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<td>Population: hospitalized for mild-moderate COVID-19 who were taking an ACEI or ARB on admission (n=659)</td>
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<tr>
<td></td>
<td></td>
<td>Design: randomized trial</td>
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<tr>
<td>DRUG</td>
<td>CONCERNS/MECHANISM</td>
<td>CLINICAL STUDIES</td>
<td>COMMENTS</td>
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<tr>
<td></td>
<td></td>
<td><strong>Results:</strong> No significant difference between those who stopped taking the ACEI or ARB and those who continued taking it. Number of days alive and out of hospital 21.9 in those who stopped vs 22.9 in those who continued</td>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Nonsteroidal Anti-inflammatory Drugs (NSAIDs)</strong></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>
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<tr>
<td></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>
<td></td>
<td>▪ Patients who are taking NSAIDs for other indications should not stop taking them³</td>
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</tbody>
</table>

¹ M Day. COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020; 368:m1086.  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Proton Pump Inhibitors (PPIs)</td>
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<tr>
<td>PROTON PUMP INHIBITORS (PPIs)</td>
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<tr>
<td>▪ Dexlansoprazole (<em>Dexilant</em>)</td>
<td>▪ PPI use may increase the risk of COVID-19</td>
<td></td>
<td>▪ No randomized controlled trials</td>
</tr>
<tr>
<td>▪ Esomeprazole magnesium (<em>Nexium</em>, <em>Nexium 24HR</em>, and generics)</td>
<td>▪ PPIs increase gastric pH and have been associated with an increased risk of enteric infections&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>▪ Twice-daily PPI use was associated with higher risk than once-daily use in an observational trial&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Lansoprazole (<em>Prevacid, Prevacid 24HR</em>, and generics)</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></td>
<td>▪ American College of Gastroenterology (ACG) recommends use of the lowest effective dose of PPIs in patients with a clinical indication for their use&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Omeprazole (<em>Prilosec, Prilosec OTC</em>, 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 tract&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>▪ Omeprazole/sodium bicarbonate (<em>Zegerid, Zegerid OTC</em>, and generics)</td>
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<tr>
<td>▪ Pantoprazole (<em>Protonix</em>, and generics)</td>
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<tr>
<td>▪ Rabeprazole (<em>Aciphex</em>, and generics)</td>
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</tbody>
</table>

<sup>1</sup> American College of Gastroenterology. Information sheet and FAQs about proton pump inhibitors (PPIs) and risk of COVID-19. Available at: [https://webfiles.gi.org/links/media/ACG_Almario_et_al_Info_Sheet_and_FAQs_About_PPIs_COVID19_07072020_FINAL.pdf](https://webfiles.gi.org/links/media/ACG_Almario_et_al_Info_Sheet_and_FAQs_About_PPIs_COVID19_07072020_FINAL.pdf). Accessed July 30, 2020.

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

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# VACCINES

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>EFFICACY</th>
<th>SAFETY</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td><strong>Adenovirus-Vectored Vaccines</strong></td>
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<tr>
<td>CHIMPANZEE ADENOVIRUS-VECTORED COVID-19 (ChAdOx1 nCoV-19) VACCINE</td>
<td>Folegatti et al. Lancet 2020</td>
<td>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%)</td>
<td>Chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein</td>
</tr>
<tr>
<td>(AstraZeneca)</td>
<td>(updated 8/20/2020)</td>
<td>Use of acetaminophen reduced adverse effects</td>
<td>Demonstrated immunogenicity in a phase 1/2 trial</td>
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<td>Transient neutropenia was reported in 46%</td>
<td>Phase 2/3 trials ongoing in several countries including the US</td>
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<td></td>
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<td>No serious adverse events were reported</td>
<td>Manufacturer may be able to deliver emergency doses of the vaccine by fall 2020</td>
</tr>
</tbody>
</table>

**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
<table>
<thead>
<tr>
<th>VACCINE</th>
<th>EFFICACY</th>
<th>SAFETY</th>
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| **RECOMBINANT ADENOVIRUS TYPE-5 (Ad5)-VECTORED COVID-19 VACCINE**  
(CanSino Biologics)  
*(added 7/24/2020)* | **Zhu et al. Lancet 2020²**  
**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 1x10¹¹ viral particles/mL or 5x10¹⁰ 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 |


| ADENOVIRUS SEROTYPE 26 (Ad26) VECTOR-BASED COVID-19 VACCINE (Ad26.COV2.S)  
(Johnson & Johnson)  
*(added 8/20/2020)* | **A single dose induced neutralizing antibody responses in primates** (Mercado et al. Nature 2020¹)  
**Phase 1/2a human trials started in July** | **Awaiting outcomes of phase 1/2a human trials** | **Adenovirus serotype 26 (Ad26) vector-based vaccine expressing the SARS-CoV-2 spike (S) protein**  
**Ad26 technology used in the manufacturer’s Ebola vaccine recently approved by the European Commission**  
**Phase 3 trial enrolling up to 60,000 patients expected to begin in September²** |

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</table>
| **mRNA-1273** (Moderna) *(updated 7/30/2020)* | **Jackson et al. NEJM 2020**<sup>1</sup>  
Population: healthy adults 18-55 years old (n=45)  
Design: phase 1, dose-escalation, open-label trial  
- 2 vaccinations delivered 28 days apart at a 25 mcg, 100 mcg, or 250 mcg dose  
Results:  
- antibody responses higher with the higher dose after 1<sup>st</sup> vaccination  
- serum-neutralizing activity detected after 2<sup>nd</sup> vaccination in all participants  
Limitations: preliminary results from a phase 1 trial | ▪ Fatigue, chills, headache, myalgia, and pain at the injection site reported in the phase 1 trial  
- Systemic adverse events more common after 2<sup>nd</sup> vaccination  
- No serious adverse events reported | ▪ Lipid nanoparticle-encapsulated, nucleoside-modified messenger RNA (mRNA)-based vaccine  
- Encodes the SARS-CoV2 spike (S) glycoprotein, which is needed for host cell attachment and viral entry  
- FDA granted fast track designation  
- Phase 3 trial has begun; expected to enroll about 30,000 participants and use a dose of 100 mcg  
- Reduced viral replication in the lungs and noses of primates (KS Corbett et al. NEJM 2020)<sup>2</sup> |
| **BNT162b1 and BNT162b2** (Pfizer/BioNTech) *(updated 8/23/2020)* | **Mulligan et al. 2020**<sup>3</sup>  
Population: healthy adults 18-55 years old (n=45)  
Design: phase 1/2 randomized, placebo-controlled, observer-blinded dose escalation study  
- 2 doses separated by 21 days of 10 mcg, 30 mcg, or 100 mcg of BNT162b1 or placebo  
Results:  
- At day 28, all subjects in the 10- and 30-mcg groups had significantly elevated RBD-binding IgG antibodies and neutralizing antibodies  
Limitations: phase 1/2 results | ▪ The most common adverse effects in the phase 2 trial were injection-site pain (58.3-100%), fatigue, and headache  
- Fever, chills, muscle pain, and joint pain were also reported  
- No serious adverse events reported | ▪ Both are lipid nanoparticle-formulated, nucleoside modified mRNA vaccines  
- BNT162b1 encodes an optimized SARS-CoV-2 receptor-binding domain (RBD) antigen  
- BNT162b2 encodes an optimized SARS-CoV-2 full-length spike protein antigen  
- FDA granted fast track designation  
- The manufacturer advanced BNT162b2 to phase 2/3 clinical trials based on data from phase 1 trials indicating it caused fewer adverse events than BNT1621b1<sup>2</sup> *(added 8/23/2020)*  
- Phase 3 trial has begun; expected to enroll up to 30,000 participants |
<table>
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<tbody>
<tr>
<td>BNT162b1 and BNT162b2</td>
<td><strong>Walsh et al. MedRxiv 2020</strong> <em>(added 8/23/2020)</em></td>
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<tr>
<td><strong>Population:</strong></td>
<td>healthy adults 18-55 and 65-85 years old (n=131)</td>
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<tr>
<td><strong>Design:</strong></td>
<td>phase 1, randomized, observer-blinded, placebo-controlled trial</td>
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<td></td>
<td>▪ 2 vaccinations delivered 21 days apart of 1 of 3 doses of BNT162b1 or BNT162b2 or placebo</td>
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<td><strong>Results:</strong></td>
<td>▪ In 65-85-year old subjects, SARS-CoV-2-neutralizing geometric mean titers (GMTs) were 1.1-1.6 times the convalescent serum panel GMTs 7 days after the second dose</td>
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<td>▪ In 18-55-year old subjects, neutralizing GMTs were 2.8-3.8 times the convalescent serum panel GMTs</td>
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<tr>
<td></td>
<td>▪ Antibody responses were similar between BNT162b1 and BNT162b2</td>
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<td></td>
<td>▪ Systemic adverse events were milder with BNT162b2 than with BNT162b1</td>
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<tr>
<td><strong>Limitations:</strong></td>
<td>preliminary results from a phase 1 trial; not peer reviewed</td>
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2. KS Corbett et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates.
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<tr>
<td>NVX-CoV2373</td>
<td><strong>Keech et al. MedRxiv 2020</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Tenderness and pain at the injection site</td>
<td>▪ Recombinant nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Novavax)</td>
<td><strong>Population:</strong> healthy adults 18-59 years old (n=131)</td>
<td>▪ Headache, fatigue, myalgia</td>
<td>▪ Contains saponin-based Matrix-M adjuvant</td>
</tr>
<tr>
<td></td>
<td><strong>Design:</strong> phase 1, randomized, observer-blinded, placebo-controlled trial</td>
<td>▪ No serious adverse events reported</td>
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<td></td>
<td>▪ 2 vaccinations delivered 21 days apart with or without Matrix-M1 adjuvant or placebo</td>
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<td><strong>Results:</strong></td>
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<tr>
<td></td>
<td>▪ The adjuvanted vaccine induced neutralizing antibody responses and antigen-specific T cells</td>
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<td><strong>Limitations:</strong> preliminary results from a phase 1 trial</td>
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<td>Inactivated Vaccine</td>
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<tr>
<td>Whole-Virus Inactivated SARS-CoV-2 Vaccine (WIV04 strain)</td>
<td><strong>Xia et al. JAMA 2020</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Pain at the injection site, fever</td>
<td>Whole-virus inactivated vaccine</td>
</tr>
<tr>
<td>(Sinopharm)</td>
<td><em>Population:</em> healthy adults 18-59 years old in China (phase 1 trial n=96; phase 2 trial n=224)</td>
<td>No serious adverse events reported</td>
<td>Phase 3 trial enrolling 15,000 volunteers started in Abu Dhabi in July</td>
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<tr>
<td>(added 8/21/2020)</td>
<td><em>Design:</em> randomized, double-blind, placebo-controlled phase 1 and 2 trials</td>
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<td><em>Phase 1:</em> 3 injections at day 0, 28, and 56 of a 2.5, 5, or 10 mcg vaccine or aluminum hydroxide adjuvant only</td>
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<td><em>Phase 2:</em> 5 mcg vaccine at days 0 and 14, 5 mcg vaccine at days 0 and 21, or aluminum hydroxide adjuvant only</td>
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<tr>
<td></td>
<td><strong>Results:</strong></td>
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<tr>
<td></td>
<td>Neutralizing antibodies reported in all dose groups 14 days after completion of 3 injections in phase 1 and 2 injections in phase 2</td>
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<td>100% seroconversion in patients in the phase 1 trial and in those who received injections on days 0 and 21 in phase 2</td>
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<td></td>
<td>Antibody titers increased after second and third injections</td>
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<td><strong>Limitations:</strong> phase 1/2 interim data; did not use comparator group of convalescent serum samples</td>
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