COVID-19: Evidence Summary

The latest evidence on drug efficacy & recommendations.
**Remdesivir**

**Rationale**
Remdesivir is an investigational adenosine analog that binds to RNA-dependent RNA polymerase and acts as an RNA-chain terminator.\(^1\)

**Evidence**
Several in-vitro studies have demonstrated activity against SARS-CoV-2, SARS-CoV-1, and MERS-CoV.\(^1\-^4\)

Animal model studies with remdesivir have been conducted in MERS-CoV infected mice, and treatment was found to significantly reduce virus lung tiers, weight loss, lung hemorrhage, and lung injury scores. The authors found that remdesivir showed less clinical benefit with high-titer virus inoculum suggesting early initiation would be beneficial.\(^5\) Multiple clinical trials are currently underway in varying degrees of disease severity: \(^6\-^9\) NCT04302766, NCT04292899, NCT04292730 NCT04280705

**Risks**
- Elevated transaminases
- Gastrointestinal disturbance

**Dosage**
200 mg IV on day 1, then 100 mg IV q24h days 2-10

**Recommendation**
Pre-clinical data promising however data from clinical trials needed to guide use
Reasonable to consider enrolling patients in clinical trials if available

**Chloroquine**

**Rationale**
Chloroquine is known to block viral infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV1-5

**Evidence**
Several in-vitro studies have demonstrated activity against SARS-CoV and MERS-CoV\(^1\-^5\)

Clinical trials are underway, but results unavailable at this time. Gao and colleagues announced promising early results: “thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting virus-negative conversion, and shortening the disease course” in a news briefing in mid-February.\(^7\) Multiple clinical trials are currently underway in China\(^7\)

**Risks**
- Prolonged QT interval
- Hemolytic anemia (check G6PD prior to use)
- Retinal disorder
- Hypoglycemia

**Dosage**
500 mg PO BID

**Recommendation**
Clinical efficacy of chloroquine not established for treatment or prevention of COVID-19
Additional data needed to determine whether in-vitro activity corresponds to clinical efficacy
KEY: ● Not Recommended  ○ Use with Caution  ● Can Be Used Based on Available Data

● Hydroxychloroquine

RATIONAL

Hydroxychloroquine differs from chloroquine by a single hydroxyl group; it has the same mechanism of action as chloroquine against SARS-CoV, with a more favorable side effect profile.¹

EVIDENCE

An in-vitro physiologically-based pharmacokinetic model (PBPK) based study was carried out to test the potency and appropriate dosing regimen against SARS-CoV-2. Hydroxychloroquine was found to be more potent than chloroquine. Based on PBPK models, a loading dose of 400 mg PO twice daily, followed by a maintenance dose of 200 mg twice daily for 4 days reached three times the potency of chloroquine phosphate when given 500 mg PO twice daily for 5 days.²

A report from an ongoing prospective, non-randomized, open-label clinical trial analyzing SARS-CoV-2 viral load at day 6 post study inclusion included 36 patients receiving 600 mg hydroxychloroquine daily. Patients who refused treatment with hydroxychloroquine or untreated patients at another center were included as controls. The authors found that patients treated with hydroxychloroquine had a significant reduction of viral load at day 6 post study inclusion compared to controls. Interestingly they also found that patients treated with both azithromycin and hydroxychloroquine had greater reductions in viral load (see azithromycin section for more information).³

A prospective, placebo controlled study of 30 patients who received hydroxychloroquine 400 mg daily x 5 days or standard of care assessed the negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swabs on day 7 after randomization. Negative seroconversion was 86.7% in the treatment group compared to 93.3% in the control group (p>0.05). Patient baseline severity not well described in the study and patients in the standard of care arm were able to receive other agents with antiviral activity such as lopinavir-ritonavir and interferon α.⁴

An observational study of 80 patients (continuation of study reported above) with PCR documented SARS-CoV-2 infection who were treated with hydroxychloroquine and azithromycin for at least 3 days was conducted. Patients were followed for 6 days after initiation of treatment. A majority of patients (92%) fell in the low risk of clinical deterioration category and only 15% had fevers. Patients were assessed for clinical deterioration requiring transfer to ICU and for SARS-CoV-2 PCR seroconversion. A majority of patients (81.3%) were discharged from general ward and did not require ICU transfer and only 15% of patients required oxygen therapy. Three patients required transfer to ICU. PCR seroconversion was noted in 83% of patients at day 7 and in 93% at day 8. Limitations of this study include: findings not published in a peer-reviewed journal, lack of a control arm for comparison, majority of patients with mild presentation of infection and represent a population that we would not admit to the hospital for treatment, and finally the baseline viral loads of these patients were low indicating low burden of disease.⁵

A randomized control trial of hydroxychloroquine 400 mg/day x 5 days in 62 SARS-CoV-2 infected patients with mild illness (patients with pneumonia on chest CT with SaO2/SPO2 >93% or PaO2/FiO2 >300) found hydroxychloroquine shortened time to body temperature normalization (3.2 days vs 2.2 days) and remission of cough. Additionally the study found a larger proportion of patients in the treatment group had improvement in chest CT findings as compared to control (80.6% vs 54.8%, no p value reported). Study limitations include: not yet published in peer review journal, no statistical significance evaluation of endpoints, small study population size, inclusion of only mildly ill patients, and no evaluation of reduction in oxygen requirements.⁶

There are numerous clinical trials undergoing recruitment in China to assess hydroxychloroquine efficacy in SARS-CoV-2.⁷

RECOMMENDATION

Clinical efficacy of hydroxychloroquine not full established as data from available studies are conflicting for treatment or prevention of COVID-19

Additional data are needed through larger, randomized controlled trials

Hydroxychloroquine is included in some guidelines for treatment of COVID-19 and can be considered in the absence of other treatment options.

RISKS

- Prolonged QT interval
- Hypoglycemia
- Bone marrow suppression
- Cardiomyopathy

 Dosage

Several dosing strategies have been studied with no accepted consensus:

- 400 mg PO BID on day 1, then 200 mg PO BID days 2-5²
- 200 mg PO TID x 5 days³ 400 mg PO QD x 5 days⁴
### Interferon α

**Rationale**
Interferon results in induction of certain enzymes, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, augmentation of specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

**Evidence**
Data limited to in vitro study in SARS-CoV and case report in infant.1-6

**Risks**
- Requires nebulization with potential risk of viral exposure to healthcare worker
- Fatigue
- Headache
- Rigors
- Fever
- Nausea
- Rare but serious neuropsychiatric events

**Dosage**
- Adult: 5 million units per dose, nebulized BID in sterile water for injection
- Children: 200-000-400,000 IU/kg or 2-4 µg/kg in 2 ml sterile water, nebulization BID x 5-7 d.

**Recommendation**
NOT recommended at this time due to limited data, unknown equipment needed for proper nebulization and potential risk of nebulization to healthcare worker.

### IVIG

**Rationale**
Chloroquine is known to block viral infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV1-5.

**Evidence**
Case report of 3 patients.1 IVIG started ~5-10 days after initial presentation. All 3 patients received IVIG 25 g and all eventually discharged home. Report does not mention if any patient received hydroxychloroquine or chloroquine initially.

Authors recommend IVIG as a therapeutic option for deteriorating patients

**Risks**
- Fever
- Myalgia
- Arhralgia
- Chills
- Flushing
- Headache
- Anaphylaxis

**Dosage**
0.3-0.5 g/kg IV per day x 5d

**Recommendation**
NOT recommended for initial therapy.

Possible consideration for patients failing initial therapy after 5 days.

(Note: IVIG shortage has been an issue for many months)
Ribavirin

**Rationale**
Ribavirin is a synthetic guanosine nucleoside analog that interferes with synthesis of viral mRNA.

**Evidence**
Retrospective cohort studies of ribavirin + interferon in MERS-CoV reports improved survival at 14 days but not at 28 days \(^1\) and no benefit in late therapy. \(^2\)

**Risks**
- Hemolytic anemia
- Teratogenicity

**Dosage**
2000 mg po x 1, then 600 mg po q8 x 10 days

**Recommendation**
NOT recommended due lack of data in SARS-CoV2 and limited if any benefit reported in MERS-CoV studies.

Lopinavir / Ritonavir

**Rationale**
HIV-1 protease inhibitor
Potential inhibition of chymotrypsin-like protease (3CLpro) in SARS-CoV; In vitro activity against SARS-CoV and MERS-CoV; currently in vitro data lacking against SARS-CoV-2

**Evidence**

Randomized, controlled, open-label trial (n=199) that compared time to clinical improvement between lopinavir/ritonavir PLUS standard care (supplemental oxygen, noninvasive and invasive ventilation, antibiotics, vasopressor support, renal- replacement therapy, and ECMO) and standard care. This study concluded no benefit was observed (pertaining to clinical improvements or mortality as well as decrease in viral loads) when lopinavir/ritonavir was added to standard of care. Important limitations to note: patients were randomized into the study 13 days (median) after the time from onset of illness, survival endpoint was underpowered. \(^1\)

SARS-CoV \(^1\), \(^2\), \(^3\), \(^4\) Lopinavir/ritonavir in combination with ribavirin has been shown to have favorable clinical response (decrease in steroid use, intubation rates, ARDS, death) when compared to historical controls.

MERS-CoV \(^4\) Data limited to case reports for the use of lopinavir/ritonavir in the treatment of MERS. Retrospective matched cohort study (n=43) which showed lopinavir/ritonavir with ribavirin was associated with a decreased risk of infection when used as post exposure prophylaxis.

**Risks**
- Nausea, vomiting, diarrhea
- Increased LFTs, possibility of hepatotoxicity
- Pancreatitis
- PR or QT prolongation
- Hyperglycemia
- High potential for drug interactions

**Dosage**
LPV 400 mg/RTV 100 mg PO twice daily for 14 days

**Recommendation**
KEY:  ● Not Recommended  ○ Use with Caution  ▶ Can Be Used Based on Available Data

ADJUVANT AGENTS

● Azithromycin

RATIONALE
Immune modulating and anti-inflammatory effects

EVIDENCE

Very limited clinical data in treatment of COVID-19 (in combination with HCQ)

A small, open-label, non-randomized clinical trial (n = 36) assessing virological clearance of SARS-CoV-2 at day 6 post inclusion showed that HCQ treatment was significantly associated with viral load reduction in COVID-19 patients and its effect is reinforced by azithromycin.¹

Important limitations to note: small sample size, lower threshold for negative viral load compared to previous studies, less sensitive swab sample (NP samples), large number of patients on HCQ not available for primary outcome analysis, viral load higher at baseline in HCQ monotherapy group compared to HCQ + azithro group. An observational study of 80 patients (continuation of study reported above) with PCR documented SARS-CoV-2 infection who were treated with hydroxychloroquine and azithromycin for at least 3 days was conducted. Patients were followed for 6 days after initiation of treatment. A majority of patients (92%) fell in the low risk of clinical deterioration category and only 15% had fevers. Patients were assessed for clinical deterioration requiring transfer to ICU and for SARS-CoV-2 PCR seroconversion. A majority of patients (81.3%) were discharged from general ward and did not require ICU transfer and only 15% of patients required oxygen therapy. Three patients required transfer to ICU. PCR seroconversion was noted in 83% of patients at day 7 and in 93% at day 8. Limitations of this study include: findings not published in a peer-reviewed journal, lack of a control arm for comparison, majority of patients with mild presentation of infection and represent a population that we would not admit to the hospital for treatment, and finally the baseline viral loads of these patients were low indicating low burden of disease.²

MERS-CoV
Retrospective analysis of a multicenter cohort database indicated that macrolide therapy was not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance.³

RISKS
Additive effects on QTC prolongation

DOSAGE
500 mg on day 1, followed by 250 mg daily for 4 days (total duration: 5 days)

RECOMMENDATION
Efficacy for treatment of COVID-19 not definitely established.

Current data should be interpreted with caution due to significant limitations in study design, including lack of information on clinical outcomes.

Rationale

Corticosteroids can blunt the inflammatory response that leads to respiratory failure in COVID-19.\(^1\)

Evidence

Retrospective, observational study of 221 COVID-19 positive patients was conducted in China. The study included 55 patients that were categorized as severe 80% of whom were admitted to the ICU due to combined moderate or severe ARDS, requiring non-invasive or invasive mechanical ventilation therapy. Corticosteroids were administered to about half of the patients and patients categorized as severe were more likely to receive corticosteroids (73% vs. 45% \(p<0.001\)). The study compared patients that were transferred from ICU to ward to patients who died in the ICU. With regards to steroid use, results showed that patients who were transferred from ICU to ward received steroids earlier in their disease course than patients who died in the ICU.\(^2\)

Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia in China assessed the development of ARDS and death. Eighty-four (41.8%) patients developed ARDS and forty-four (52.4%) of these patients died. Among patients that developed ARDS, treatment with methylprednisolone decreased the risk of death (HR 0.38 CI, 0.20-0.72).\(^3\)

Retrospective cohort of 78 SARS patients was conducted to analyze the effectiveness of corticosteroids. Corticosteroids were received by 84.6% of patients. The corticosteroid group experienced more adverse outcomes despite younger age and less baseline co-morbidities. Corticosteroid treatment was associated with a 20.7-fold increase in risk of ICU admission or mortality. The authors did not control for differences in corticosteroid dosing regimens.\(^4\)

Several observational studies found corticosteroid therapy prolonged viral replication in SARS and MERS-CoV.\(^5,8\)

According to an expert consensus statement from China, the following principles should be followed when using corticosteroids:\(^9\):

- the benefits and harms should be carefully weighed before using corticosteroids
- corticosteroids should be used prudently in critically ill patients with 2019-nCoC pneumonia
- for patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic disease further use of corticosteroids should be cautious
- dosage should be low-to-moderate (\(\leq 0.5-1\ mg/kg\) per day
- methylprednisolone or equivalent) and the duration should be short (\(\leq 7\) days)

Risk

- Hyperglycemia
- Prolonged viral replication
- Psychosis

Dosage

Dosing often not elucidated in studies

Based on expert consensus in China: dosage should be low-to-moderate (\(\leq 0.5-1\ mg/kg\) per day
methylprednisolone or equivalent) and the duration should be short (\(\leq 7\) days)\(^9\)

Based on SCCM consensus:
Lower dosing strategies and shorter treatment courses should be considered\(^12\)

Recommendation

Recommend using steroids only in patients with underlying medical conditions in which corticosteroid therapy is considered usual care
**KEY:**
- **Not Recommended**
- **Use with Caution**
- **Can Be Used Based on Available Data**

**Baricitinib**

**Rationale**
Janus Kinase (JAK) enzyme inhibitor predicted to reduce the ability of SARS-CoV-2 to infect lung cells.

**Evidence**
No clinical data exists.

**Risks**
- Immunosuppression
- Increased risk of thrombosis, including DVT and PE, compared to placebo
- Serious infections that may lead to hospitalizations or death
- Lymphoma and other malignancies have been observed with use

**Dosage**
Dosing unknown for COVID-19 treatment at this time.

**Recommendation**
No recommendation can be made at this time due to lack of clinical data.

This agent should be avoided for treatment of COVID-19 unless a patient is being enrolled into a clinical trial (to date no clinical trials enrolling in the US).

**Tocilizumab**

**Rationale**
Humanized monoclonal antibody specific for interleukin-6 (IL-6) receptor possibly combats cytokine release syndrome (CRS) symptoms in severely ill patients.

**Evidence**

Retrospective, single center, observational cohort study (n = 21) that assessed efficacy of tocilizumab in severely ill or critical COVID-19 patients. All patients received standard of care (lopinavir, methylprednisolone, symptomatic therapy, and oxygen) for at least 7 days prior to initiation of tocilizumab. This study demonstrated improvement of clinical symptoms including fever reduction, decreased need for supplemental oxygen, and improvement on CT scans. Important limitations to note: small sample size, observational, no comparator.

Other non-randomized clinical trials are underway for the treatment of COVID-19.

**Risks**
- Immunosuppression
- Must rule out TB prior to initiation
- Hepatotoxicity
- Neutropenia
- Upper respiratory tract or infusion-related reactions

**Dosage**
Several dosing strategies have been proposed including:

- 400 mg IV x 1 dose, with a single repeat dose for patients with persistent fever within 12 hours1

- 4mg/kg – 8 mg/kg (max dose 800 mg) x 1 dose, with repeat dose every 8-12h for a total of 3 doses2

**Recommendation**
Efficacy for treatment of COVID-19 not definitely established.

Current data should be interpreted with caution due to limitations in study design and small sample size.

Additional studies needed to assess benefits of tocilizumab for the treatment of COVID-19. Clinical trials are ongoing, however none are currently available in the US.
**Ibuprofen**

**Rationale**
Symptomatic support for fever, headache, myalgia, and arthralgia.

**Evidence**
Speculative link between ibuprofen and increased ACE2 expression theoretically leading to worse outcomes in COVID-19 patients.\(^1\)

Currently, there is no compelling evidence to support an association between ibuprofen and negative outcomes in patients with COVID-19.

**Risks**
- Theoretically worsening of our coems in CoVID-19 patients
- Gastrointestinal bleed in high risk patients

**Dosage**
- Adult: 200-400 mg po every 6 hours PRN
- Pediatric (6 mo-12 yr.): 5 to 10 mg/kg po every 6 to 8 hrs. PRN (Max 4 dose/day)

**Recommendation**
FDA issued a statement on Mar 1, 2020 that it was NOT aware of scientific evidence connecting the use of NSAIDS such as ibuprofen, with worsening COVID-19 symptoms.\(^2\)

**Statins**

**Rationale**
May theoretically play a role in supporting innate immunity in viral respiratory infections, with the additional benefit of cardiovascular protection in these patients that are at risk for cardiovascular complications secondary to SARS-CoV-2 infection.

**Evidence**
A theoretical benefit of statins in immunomodulation in response to respiratory viral infections has been proposed based on data observed in SARS. SARS-CoV infection causes MYD88 gene induction, which leads to downstream activation of the NF-kb inflammatory pathway.\(^1\)

Attenuation of this pathway in SARS-CoV infected mice has been shown to improve survival.\(^2\)

A few observational studies have found a protective effect of statins in influenza.\(^3,4\)

Statins, like ACE inhibitors and ARBs, have also been found to reduce severity of acute respiratory distress syndrome in experimental models.\(^5\) This observation has not been substantiated in clinical trials to date.

**Risks**
- Myopathy
- Rhabdomyolysis
- Liver enzyme abnormalities

**Dosage**
Some institutions have recommended the following doses:\(^6\):
- Atorvastatin 40 mg daily
- Rosuvastatin 20 mg daily

**Recommendation**
Given no clinical data available for initiation of statins, recommend against routine initiation in patients with COVID-19 who do not have underlying conditions that warrant statin use.
Ascorbic Acid (Vitamin C)

**Rationale**
Vitamin C is an antioxidant and cofactor in numerous physiologic reactions; theoretically may support host defenses against infection and protect against oxidative stress.

**Evidence**
Currently no clinical data to support use in COVID-19 infection

A phase II randomized, placebo-controlled trial is currently underway in China evaluating high-dose vitamin C in ICU patients with COVID-19.

**Risks**
- Diarrhea
- Nausea
- Vomiting

**Dosage**
Dose for COVID-19 unknown

**Recommendation**
Given no data available specific to COVID-19, recommend against routine use.

Sarilumab

**Rationale**
Humanized monoclonal antibody specific for interleukin-6 (IL-6) receptor. Possibly combats cytokine release syndrome (CRS) symptoms in severely ill patients.

**Evidence**
No published clinical data to support the use of sarilumab against SARS-CoV-2.

Several clinical trials underway globally including the following in the US: NCT04315298

**Risks**
- Risk of serious infections that can lead to hospitalization or death
- Prior to initiation, test for latent TB
- Neutropenia
- Hepatotoxicity
- Infection site reactions

**Dosage**
Dose for COVID-19 unknown

**Recommendation**
No recommendation can be made at this time due to lack of clinical data. This agent should be avoided for treatment of COVID-19 unless a patient is being enrolled into a clinical trial.
ACE Inhibitors / ARBs

**Rationale**
For avoidance: Angiotensin converting enzyme 2 (ACE2) receptors have been shown to be the entry point into human cells for SARS-CoV-2. The expression of ACE2 is substantially increased in patients who are receiving treatment with either ACE inhibitors and angiotensin II blockers (ARBs).2,3 Theoretically, increased expression of ACE2 would facilitate infection with COVID-19.

For initiation: An experimental study in mice showed that both ACE inhibitors and ARBs reduce severe lung injury in certain viral pneumonias, and it has been speculated that these agents could be beneficial in COVID-19.4

**Evidence**
An experimental study in mice showed that both ACE inhibitors and ARBs reduce severe lung injury in certain viral pneumonias, and it has been speculated that these agents could be beneficial in COVID-19.4

Currently there are no clinical data demonstrating beneficial or adverse outcomes associated with ACE inhibitor or ARB use in COVID-19 patients therefore, the Heart Failure Society of America, American Heart Association, and American College of Cardiology recommend against addition or removal of ACE inhibitors or ARBs for patients with COVID-19.5

A clinical trial is underway to evaluate the effect of losartan on the sequential organ failure assessment (SOFA) respiratory score in adult patients with COVID-19.6

**Risks**
- Angioedema
- Cough
- Hyperkalemia
- Teratogenicity
- Hypotension

**Dosage**
n/a

**Recommendation**
Given no clinical data available for avoidance or initiation of ACE inhibitors or ARBS, recommend against routine discontinuation or initiation in patients with COVID-19.
**KEY:** 🔴 Not Recommended  🔴 Use with Caution  🔴 Can Be Used Based on Available Data

**REFERENCES**

**Remdesivir:**
7. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment. NCT04292730. (https://www.clinicaltrials.gov/ct2/show/NCT04292730)

**Chloroquine:**

**Hydroxychloroquine:**
KEY: ⚫ Not Recommended ⚫ Use with Caution ⚫ Can Be Used Based on Available Data


Interferon:

IVIG

Ribavirin

Lopinavir-ritonavir
Azithromycin:

Corticosteroids
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Baricitinib

Tocilizumab

Sarilumab
ACE-Inhibitor/ARB


Ibuprofen


Statins

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Ascorbic Acid