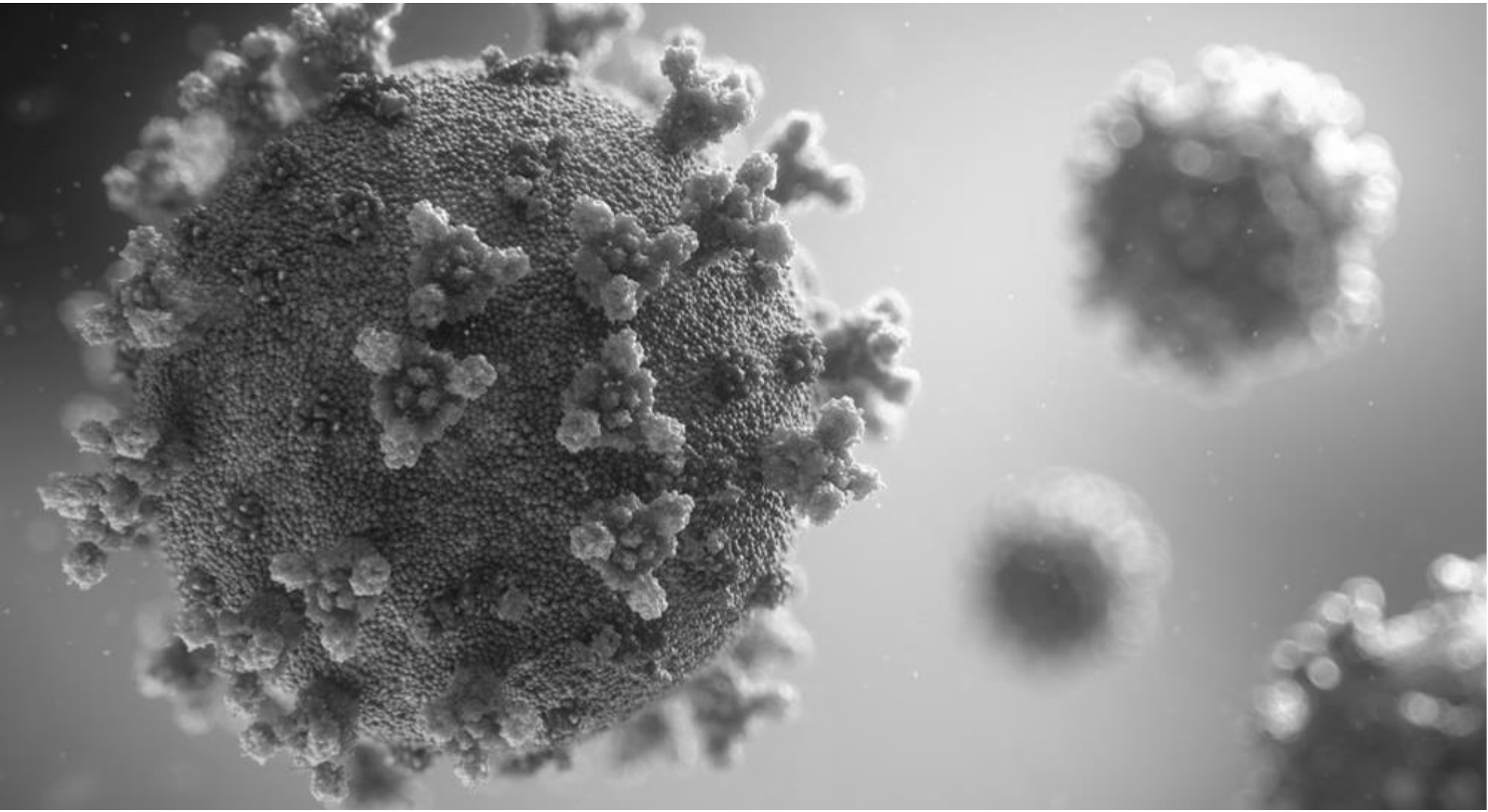
EVIDENCE SUMMARY

COVID-19: Evidence Summary

The latest evidence on drug efficacy & recommendations.



UPDATED APRIL 3, 2020

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

ANTIVIRAL AGENTS

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.[6] 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

RATIONALE

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]

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 2-5[2]

200 mg PO TID x 5 days[3] 400 mg PO QD x 5 days[4]

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.

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

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 health care 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)

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

Ribavarin

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

Limited data in treatment of COVID-19.

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[3] 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

Efficacy for treatment of COVID-19 not definitely established.

Additional studies needed to evaluate possible clinical benefits of LPV/RTV earlier in treatment of COVID-19.

Additional studies needed to evaluate the benefits of LPV/RTV in combination with other antivirals for treatment of COVID-19.

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

ADJUCTIVE 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.

Additional studies needed to assess benefits of azithromycin with HCQ for the treatment of COVID-19.

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

Corticosteroids

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 to have received 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 (≤0.5-1 mg/kg per day
- methylprednisolone or equivalent) and the duration should be short (≤7 days)

World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend against use of steroids for COVID-19 management unless patient has other indications that warrant use i.e. COPD exacerbation or refractory septic shock[10,11]

The Society of Critical Care Medicine (SCCM) recommends against routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 except in cases of ARDS.[12]

RISKS

- Hyperglycemia
- Prolonged viral replication
- Psychosis

DOSAGE

Dosing often not elucidated in studies

Based on expert consensus in China: dosage should be low-to-moderate (≤0.5-1 mg/kg per day methylprednisolone or equivalent) and the duration should be short (≤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[1]

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

Limited clinical data in treatment of COVID- 19.

Retrospective, single center, observational cohort study (n = 21) that assessed efficacy of tocilizumab in severely ill or critical COVID- 19 patients.1 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. .

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

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

- Thoeretically worsening of ourcoems 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.

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

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 COVID19[1]

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.1 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.

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

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 angiotension 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:

1. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269-271. (PubMed 32020029) (DOI 10.1038/s41422-020-0282-0)
2. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. The Journal of biological chemistry. 2020.
3. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature communications. 2020;11(1):222.
4. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science translational medicine. 2017;9(396).
5. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature communications. 2020;11(1):222.
6. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with severe coronavirus disease (COVID-19). NCT04292899. (https://www.clinicaltrials.gov/ct2/show/ NCT04292899)
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)
8. Expanded access remdesivir (RDV; GS-5734). (https://www.clinicaltrials.gov/ct2/show/NCT04302766)
9. National Institute of Allergy and Infectious Diseases. NIH clinical trial of remdesivir to treat COVID-19. (https://www.niaid.nih.gov/news-events/nih-clinical-trial- remdesivir-treat-covid-19-begins)
10. Midgley CM ea. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Available at: https://www.medrxiv.org/content/10.1101/2020.03.09.20032896v1.full.pdf. Accessed 14 Mar 2020

Chloroquine:

1. Colson P, Rolain J, Lagier J et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Intern J of Antimicrob Agents. March 17 2020 [In press]
2. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research February 2020
3. Keyaerts E, Vijgen L, Maes P et al. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004; 323:264-8. (PubMed 15351731) (DOI 10.1016/j. bbrc.2004.08.085)
4. Vincent MJ, Bergeron E, Benjannet S et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2:69. (PubMed 16115318) (DOI 10.1186/1743-422X-2-69)
5. Devaux CA, Rolain JM, Colson P et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. Int J Antimicrob Agents. 2020; :105938. (PubMed 32171740) (DOI 10.1016/j. ijantimicag.2020.105938)
6. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020.
7. Cortegiani A, Ingoglia G, Ippolito M et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J of Crit Care. 2020
8. Chloroquine [Package insert]. Philadelphia, PA: Global Pharmaceuticals; 2012.

Hydroxychloroquine:

1. Colson P, Rolain J, Lagier J et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Intern J of Antimicrob Agents. March 17 2020 [In press]
2. Xueting Y, Fei Y, Miao Z et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2. Clin Infect Dis. March 9 2020. [Epub ahead of print]
3. Gautret P, Lagier J, Parola P et al. Hydroxychloroquine and azithromycin as treatment of COVID-19: results of an open-label non-randomized clinical trial. Pre-print published online March 19 2020. Available at: https://www.mediterranee-infection.com/wp-content/uploads/2020/03/Hydroxychloroquine_final_DOI_IJAA.pdf

4. Jun C et al. Hydroxychlorowuine sulfate Normal treatment 2019 Coronavirus Disease (COVID-19) Patient. J of Zhejiang University. March 2020. DOI: 10.3785 / j.issn.1008-9292.2020.03.03
5. Gautret et al. Clinical and microbiological effect of a combination of hydrocloroquine and azithromycin in 80 COVID-19 patients with at least six-day follow up: an observational study. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf. accessed March 30, 2020.
6. Chen Z, Hu J, Zhang Z et al. Efficacy of hydroxychloroquine in patients with COVID19: results of randomized clinical trial. doi: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/covid-19_domID_statin.pdf
7. Study to evaluate efficacy and safety of hydroxychloroquine for treatment of pneumonia caused by 2019-nCoV (HC-nCoV). NCT04261517. https://www.clinicaltrials.gov/ct2/show/NCT04261517.
8. Cortegiani A, Ingoglia G, Ippolito M et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J of Crit Care. 2020
9. Hydroxychloroquine [package insert]. St. Michael, Barbados: Concordia Pharmaceuticals Inc; 2015.

Interferon:

1. Stroher, U. Dicaro A., Li Y, et al. Severe acute respiratory syndrome – related coronavirus is inhibited by Interferon-α. J Infect Dis 2004; 189-1164-7.
2. Hensley L, Fritz E, Jahrling P, et al. Interferon-β 1a and SARS coronavirus replication. Emerg Infect Dis. 2004; 10(2):317-319.
3. Falzarano D, de Wit E, Martellaro C, et al. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 2013; 3: 1686: 1-6.
4. Cui Y, Tian M, Huang D, et al. A 55 day old female infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. J Infect Dis 2020, https://doi.org/10.1093/infdis/jiaa113
5. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020; 7(1):4 https://doi.org/10.1186/s40779-020-0233-6
6. Shen K, Yang Y, Wang T, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020, https://doi.org/10.1007/s12519-020-00343-7

IVIG

1. Cao W, Liu X, Bai T, et al. High dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis 2020, https://doi.org/10.1093/ofid/ofaa102

Ribavirin

1. Omrani AS, Saad MM, Baig K et al. Ribavirin and interferon alfa-2a for servere Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis. 2014 14(11): 1090-1095.
2. Al-Tawfiq J, Momattin H, Dib J. Et al. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis 2014 (20): 42-46.

Lopinavir-ritonavir

1. Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020; (PubMed 32187464) (DOI 10.1056/NEJMoa2001282)
2. Chu CM, Cheng VC, Hung IF et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59:252-6. doi: 10.1136/thorax.2003.012658
3. Yao TT, Qian JD, Zhu WY et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treat-ment option. J Med Virol. 2020. doi: 10.1002/jmv.25729
4. Chan KS, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicenter retrospective matched cohort study. Hong Kong Med J. 2003;9(6):399-406

KEY: 🔴 Not Recommended 🟡 Use with Caution 🟢 Can Be Used Based on Available Data

Azithromycin:

1. Gautret et al. Hydroxychloroquine and azithromycin as a treatment for COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In press 17 March 2020. doi: 10.1016/j.ijantimicag.2020.105949
2. Gautret et al. Clinical and microbiological effect of a combination of hydrocloroquine and azithromycin in 80 COVID-19 patients with at least six-day follow up: an observational study. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf. accessed March 30, 2020.
3. Arabi et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. International Journal of Infectious Diseases 81 (2019) 184-190. doi: 10.1016/j.ijid.2019.01.041

Corticosteroids

1. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020 Feb 6; S0140-6736(20)30305-6
2. Guqin Z et al. Clinical features and outcomes of 221 paitents with COVID-19 in Wuhan, China. doi: https://doi.org/10.1101/2020.03.02.20030452
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13. doi: 10.1001/jamainternmed.2020.0994. PMID: 32167524.
4. Auyeung TW et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51:98-102.
5. Centers for Disease Control. Healthcare professionals: Frequently asked questions and answers. From CDC website. Accessed 2020 Mar 18. https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html.
6. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed 2020 Mar 19. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus- (ncov)-infection-is-suspected.
7. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015 Sep 5;386(9997):995-1007. doi: 10.1016/S0140-6736(15)60454-8. Epub 2015 Jun 3. Review
8. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, et al; Saudi Critical Care Trial Group. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018 Mar 15;197(6):757-767.
9. Zhao JP, Hu Y, Du RH, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia (in Chinese). Zhonghua Jie He He Hu Xi Za Zhi 2020; 43: E007.
10. Centers for Disease Control. Healthcare professionals: Frequently asked questions and answers. From CDC website. Accessed 2020 Mar 18. https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html.
11. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed 2020 Mar 19. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus- (ncov)-infection-is-suspected.
12. Alhazzani W, Moller M, Arabi Y et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). SCC Journal. March 2020.

Baricitnib

1. Richardson et al. Baricitinib as a potential treatment for 2019-nCoV acute respiratory disease. Lancet 395 (2020) e30. doi: 10.1016/S0140-6736(20)30304-4.

Tocilizumab

1. Xu et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available on chinaXiv website. Accessed 2020 Mar 20.
2. Italian COVID19 Treatment Guidelines. https://drive.google.com/file/d/1eXE6espkYp6_k2XCyTf_6kgT6tFbnQjg/view. Accessed March 30,2020.

Sarilumab

1. Sarilumab [package insert]. Bridgewater, NJ. Sanofi Company US. 2018

KEY: 🔴 Not Recommended 🟡 Use with Caution 🟢 Can Be Used Based on Available Data

ACE-Inhibitor/ARB

1. Wan Y, Shang J, Graham R et al. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virology 2020;published online Jan 29.
2. Zheng, Y., Ma, Y., Zhang, J. et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020.
3. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020
4. 7.Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. (July 2005). "Angiotensin-converting enzyme 2 protects from severe acute lung failure". Nature. 436 (7047): 112–6
5. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in covid-19. From American College of Cardiology website. Accessed Mar 34 2020. Available from https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19
6. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Mar 19. Available from https://clinicaltrials.gov/ct2/show/study/NCT04312009. NLM identifier: NCT04312009
7. Cozaar [package insert]. Whitehouse Station, NJ. 2015.

Ibuprofen

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020. PMID: 32171062 DOI: 10.1016/S2213-2600(20)30116-8
2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19

Statins

1. Yuan S. Statins May Decrease the Fatality Rate of Middle East Respiratory Syndrome Infection. mBio. 2015;6(4):e01120-15.
2. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeño JM, Fernandez-Delgado R, Fett C, et al. Inhibition of NF-κB-Mediated Inflammation in Severe Acute Respiratory Syndrome Coronavirus-Infected Mice Increases Survival. Journal of Virology. 2014;88(2):913.
3. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007;131(4):1006-12.
4. Vandermeer ML, Thomas AR, Kamimoto L, Reingold A, Gershman K, Meek J, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis. 2012;205(1):13-9.
5. Wösten-van Asperen RM, Bos AP et al. Imbalance between pulmonary angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome. Pediatri Crit Care Med. 2013;14:e438-e441. https://doi.org/10.1097/PCC.0b013e3182a55735.
6. Massachusetts General Hospital. Rationale for Consideration of Statins for COVID-19.https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/covid- 19_domID_statin.pdf
7. Crestor [Package Insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. 2010

Ascorbic Acid

1. Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia. NCT04264533. (https://clinicaltrials.gov/ct2/show/NCT04264533).