# Critical Care COVID-19 Management Protocol

***(updated 7-09-2020)***

## Prophylaxis

While there is very limited data (and none specific for COVID-19), the following "cocktail" may have a role in the prevention/mitigation of COVID-19 disease.

- Vitamin C 500 mg BID and Quercetin 250-500 mg BID
- Zinc 75-100 mg/day
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night
- Vitamin D3 1000-4000 u/day
- *Optional:* Famotidine 20-40mg/day

## Mildly Symptomatic patients (at home):

- Vitamin C 500mg BID and Quercetin 250-500 mg BID
- Zinc 75-100 mg/day
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 2000-4000 u/day
- *Optional: Ivermectin 150-200ug/kg (single dose)*
- *Optional: ASA 81/325mg/day*
- *Optional: Famotidine 20-40mg/day*

In symptomatic patients, monitoring with home pulse oximetry is recommended. Ambulatory desaturation below 94% should prompt hospital admission

## Mildly Symptomatic patients (on floor):

- Vitamin C 500 mg PO q 6 hourly and Quercetin 250-500 mg BID (if available)
- Zinc 75-100 mg/day
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 2000-4000 u/day
- Enoxaparin 60 mg daily
- Famotidine 40mg daily (20mg in renal impairment)
- Methylprednisolone 40 mg q 12 hourly; increase to 80 mg q 12 if poor response
- *Optional:* Remdesivir 200mg D1 then 100mg daily for 9 days.

## General schema for respiratory support in patients with COVID-19

**TRY TO AVOID INTUBATION IF POSSIBLE**

Deterioration

**Low-Flow Nasal Cannula**
- Typically set at 1-6 Liters/Min

**High Flow Nasal Cannula**
- Accept permissive hypoxemia ($O_2$ Saturation > 86%)
- Titrate $FiO_2$ based on patient's saturation
- Accept flow rates of 60 to 80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative proning)

**Invasive Mechanical Ventilation**
- Target tidal volumes of ~6 cc/kg
- Lowest driving pressure and PEEP
- Sedation to avoid self-extubation
- Trial of inhaled Flolan

**Prone Positioning**
- Exact indication for prone ventilation is unclear
- Consider in patients with $PaO_2/FiO_2$ ratio < 150

**SALVAGE THERAPIES**
- High dose corticosteroids; 120 -250 mg methylprednisolone q 6-8 hourly
- Plasma exchange
- "Half-dose" rTPA
- Siltuximab and Tocilizumab (IL-6 inhibitors)
- ?? ECMO < 60 yrs. and no severe comorbidities/organ failure

Recovery

- *Optional:* Ivermectin 150-200 ug/kg (single dose)
- N/C 2L /min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- T/f EARLY to the ICU for increasing respiratory signs/symptoms and arterial desaturations.

*continued on next page*

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*(updated 6-17-2020)*

## Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU):

### Essential Treatment (dampening the STORM)

1. Methylprednisolone 80 mg loading dose then 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with poor response, increase to 80 mg q 12 hourly.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly for at least 7 days and/or until transferred out of ICU. Note caution with POC glucose testing.
3. Full anticoagulation: Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min). Heparin is suggested with CrCl < 15 ml/min.

   *Note: Early termination of ascorbic acid and corticosteroids will likely result in a rebound effect.*

### Additional Treatment Components (the Full Monty)

4. Melatonin 6-12 mg at night (the optimal dose is unknown).
5. Famotidine 40mg daily (20mg in renal impairment)
6. Vitamin D 2000-4000 u/day
7. Thiamine 200mg IV q 12 hourly
8. Simvastatin 80 mg/day (caution drug-drug interactions) or Atorvastatin 80mg/day
9. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc).
10. Optional: Azithromycin 500 mg day 1 then 250 mg for 4 days
11. Optional: Remdesivir, 200 mg IV loading dose D1, followed by 100mg day IV for 9 days
12. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy).
13. Maintain EUVOLEMIA
14. Early norepinephrine for hypotension.
15. Escalation of respiratory support; See General Schema for Respiratory Support in Patients with COVID-19.

### Salvage Treatments

- Plasma exchange. Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy. Patients may require up to 5 exchanges.
- High dose corticosteroids; 120 mg methylprednisolone q 6-8 hourly
- Siltuximab and Tocilizumab (IL-6 inhibitors)
- Convalescent serum; the role and timing of convalescent serum are uncertain.

### Treatment of Macrophage Activation Syndrome (MAS)

- A sub-group of patients will develop MAS. A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and increasing CRP.
- Methylprednisolone 120 mg q 6-8 hourly for at least 3 days, then wean according to Ferritin, CRP, AST/ALT. Ferritin should decrease by at least 15% before weaning corticosteroids.

### Monitoring:

- On admission: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg.
- Daily: CRP, Ferritin, D-Dimer and PCT. CRP and Ferritin track disease severity closely (although ferritin tends to lag behind CRP).
- Thromboelastogram (TEG) in patients with high D-dimer and repeated as indicated.
- In patients receiving IV vitamin C, the Accu-Chek™ POC glucose monitor will result in spuriously high blood glucose values. Therefore, a laboratory glucose is recommended to confirm the blood glucose levels

### Post ICU management

a. Enoxaparin 40-60 mg s/c daily
b. Methylprednisone 40 mg day, then wean slowly
c. Vitamin C 500 mg PO BID
d. Melatonin 3-6 mg at night



*Developed and updated by Paul Marik, MD, Chief of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA*

MEDPAGE TODAY®

# Quercetin: New Hype for COVID-19?

## — Parallels drawn with early data on hydroxychloroquine

by Elizabeth Hlavinka, Staff Writer, MedPage Today
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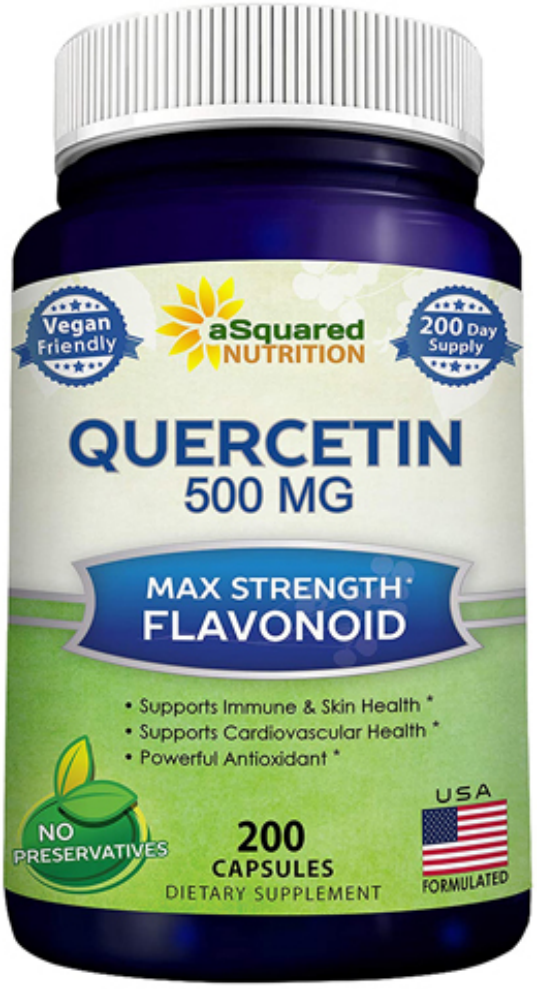


A plant flavonoid found in capers and green tea is being eyed by some as a potential adjunct therapy for patients with COVID-19, but whether quercetin will stand the test of rigorous trials remains unclear.

Proponents of the supplement say it could be one part of a treatment regimen along with interventions like remdesivir or convalescent plasma, and that its over-the-counter availability and relatively good safety profile serve as advantages.

Skeptics see it as yet another small molecule in which researchers have overinvested hope. Long-time drug discoverer Derek Lowe, PhD, said small molecule drugs like quercetin are known as "frequent hitters," because the molecular targets quercetin has been shown to interact with are so varied, numerous, and impotent that it makes it difficult to find meaningful associations.

With the disappointment of much-hyped hydroxychloroquine still fresh, clinicians may be hearing more about quercetin -- so *MedPage Today* took a deep dive into the science behind the supplement.

**Antiviral, Antioxidant Mechanisms**

Quercetin has long been evaluated for its potential protective effects against cancers, heart disease, and cells that release histamines.

The agent promotes SIRT2, which then inhibits the NLRP3 inflammasome assembly involved with COVID-19 infection, said Samuel F. Yanuck, DC, of the Program on Integrative Medicine at the University of North Carolina Chapel Hill School of Medicine, who co-authored a review of emerging research on the subject. It also plays a role in facilitating zinc transportation across lipid membranes, Yanuck said.

"It's not a bizarre or experimental substance and given it has these potential important biological roles, I think it's worth being considered as part of an overall strategy," Yanuck told *MedPage Today*, adding that quercetin would need to be one part of a multifactorial treatment regimen.

In cell cultures, quercetin has been shown to prevent viral entry and reduce the cytopathic effects of many viruses, including rhinovirus and poliovirus. In a 2016 animal study, rodents administered quercetin before being exposed to a lethal load of Ebola virus survived.

COVID-19 has been associated with high levels of interleukin-6, depleted levels of interferons, and a cytokine storm that damages the body and is related to respiratory failure, said Ruben Colunga Biancatelli, MD, of Old Dominion University in Norfolk, Virginia, and first author of a paper on quercetin and vitamin C as a potential therapy for treating SARS-CoV-2 in *Frontiers in Immunology.*

Using this rationale, researchers are postulating that vitamin C should be administered with quercetin because it can recycle oxidized quercetin, producing a synergistic effect and enhancing quercetin's antiviral capability, Biancatelli added.

After the 2003 SARS-CoV-1 coronavirus outbreak, researchers in China found quercetin and other small molecules bound to the spike protein of the virus, interfering with its ability to infect host cells.

**Human Studies**

The signal from the SARS-CoV-1 study led researcher Hasan Önal, MD, and co-authors to conduct an open-label randomized control trial in Turkey examining quercetin's role in COVID-19. In the trial, 95 patients with COVID-19 are receiving a 1,000-mg active treatment dose and 113 healthcare workers are receiving a 500-mg dose as prophylaxis. In both treatment arms, quercetin is administered with vitamin C and bromelain, a supplement extracted from pineapples that is used for burns or inflammation.

As of March, no COVID-19 cases were recorded among healthcare workers taking prophylactic quercetin and no deaths were observed among patients with COVID-19 on quercetin treatment, Önal told *MedPage Today* in an email. However, there is no active comparator or placebo group in the trial and patients on quercetin self-selected the treatment, Önal added.

Önal's team also drew on a lone hospital practice guidance from Eastern Virginia Medical School in Norfolk, Virginia, written by Paul E. Marik, MD, chief of pulmonary and critical care medicine there. Marik included quercetin in the institution's COVID-19 management protocol for prophylaxis and mild to moderate cases. He co-authored the *Frontiers in Immunology* paper on quercetin and vitamin C as a potential COVID-19 therapy.

"It's based on good, basic science and there are some really interesting papers postulating it's benefit, but unfortunately we don't have any [clinical] data," Marik told *MedPage Today*. "If you have something that is potentially beneficial, safe, and cheap, what do you have to lose?"

Given the antiviral activity that has been demonstrated in preclinical data, it would be reasonable to prescribe quercetin in the context of a properly designed clinical trial for treating COVID-19, commented David M. Aronoff, MD, of Vanderbilt University in Nashville,

Tennessee.

However, Aronoff told *MedPage Today* in an email that "it should be subjected to rigorous clinical study and not recommended for use outside of clinical trials."

Warner C. Greene, MD, PhD, of the Gladstone Institutes and the University of California San Francisco, agreed that before widely administering quercetin to patients with COVID-19, it should be tested in a well-controlled clinical trial.

Although Greene told *MedPage Today* in an email that quercetin can also act as a free radical scavenger with antioxidant effects, he said he was "not overly optimistic about quercetin as a potent antiviral for SARS-CoV-2 in patients."

**The Next HCQ?**

Lowe compared the recent attention quercetin is receiving to the early popularity of hydroxychloroquine, which showed promise in preclinical studies and was endorsed by President Donald Trump. Ultimately, hydroxychloroquine was shown to have no survival benefit and in fact trended toward an increased risk of death among COVID-19 patients.

"Twenty years from now, when we're remembering these COVID days, there are still going to be people with websites talking about how hydroxychloroquine could have saved someone if they had only done X, Y, and Z," Lowe said. "I don't think we are going to see any amazing therapies like this popping up."

In an email to *MedPage Today,* Mark Cushman, PharmD, PhD, of Purdue University College of Pharmacy in West Lafayette, Indiana, said the analogy to hydroxychloroquine was "not unrealistic" as both agents are proposed to have similar mechanisms and inhibit the virus from entering cells.

"Quercetin is not a good candidate for drug development because it is metabolically unstable and it lacks potency in *in vitro* experiments," Cushman wrote. "The next step would be to demonstrate anti-SARS-CoV-2 activity in an animal model, but that would not likely lead to promising results because of the two factors listed in the previous sentence."

Lowe agreed, noting that the pharmacokinetics of quercetin show it "disappears in human dosing like a snowflake hitting a pancake griddle."