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Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

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The COVID-19 (SARS-2-Cov) pandemic, first reported in Wuhan, China, is now spreading to many continents and countries, causing a severe public health burden. Currently, there is no vaccine or specific antiviral drug for this deadly disease. A quick, deployable and accessible, effective and safe treatment is urgently needed to save lives and curtail the spreading. Acute respiratory distress syndrome (ARDS) is a key factor of fatality. Significantly increased oxidative stress due to rapid release of free radicals and cytokines is the hallmark of ARDS which leads to cellular injury, organ failure and death. Early use of large dose antioxidants, such as vitamin C (VC) may become an effective treatment for these patients. Clinical studies also show that high-dose oral VC provides certain protection against viral infection. Neither intravenous nor oral administration of high-dose VC is associated with significant side-effects. Therefore, this regimen should be included in the treatment of COVID-19 and used as a preventative measure for susceptible populations such as healthcare workers with higher exposure risks.

Coronaviruses and influenza are among the pandemic viruses that can cause lethal lung injuries and death from ARDS [1-3]. Viral infections could evoke “cytokine storm” that leads to lung capillary endothelial cell activation, neutrophil infiltration and increased oxidative stress (reactive oxygen and nitrogen species). ARDS, characteristic of severe hypoxemia, is usually accompanied by uncontrolled inflammation, oxidative injury and damage to the alveolar-capillary barrier [4]. Increased oxidative stress is a major insult in pulmonary injury including acute lung injury (ALI) and ARDS, two clinical manifestations of acute respiratory failure with substantially high morbidity and mortality [5,6].

In a report of 29 patients with COVID-19 pneumonia, 27 (93%) showed increased hsCRP, a marker of inflammation and oxidative stress [7]. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. VC, an important component of the cellular antioxidant system [8], is beneficial to critical care management [9]. Cytokine storm is observed in both viral and bacterial infections [3] and results in increased oxidative stress via a common and non-specific pathway. Since the prevention and management of oxidative stress could be realized by large dose of antioxidants, this approach may be applicable to COVID-19 with intravenous high-dose VC based on the outcome of three previous clinical studies involving a total of 146 patients with sepsis [10].

Hemila and colleagues reported that various high-dose intravenous VC infusions (e.g., 200 mg/kg body weight/day, divided into 4 doses) shortened the intensive care unit (ICU) stay by
97.8% [11], accompanied by a significant reduction in the mortality rate [12]. Such an experience was reproduced among patients ill with severe influenza [13,14]. Indeed, dietary antioxidants (VC and sulforaphane) were shown to decrease oxidative stress induced acute inflammatory lung injury in patients receiving mechanical ventilation [15]. In addition, oral VC (e.g., 6 g daily) was able to reduce viral infection risk [16] or to improve symptoms [17].

High-dose intravenous VC has also been successfully used in the treatment of 50 moderate to severe COVID-19 patients in China. The doses used varied between 2 g and 10 g per day, given over a period of 8 to 10 hours. Additional VC bolus may be required among patients in critical conditions. The oxygenation index was improving in real time and all the patients eventually cured and were discharged [18]. In fact, high-dose VC has been clinically used for several decades and a recent NIH expert panel document states clearly that this regimen (1.5 g/kg body weight) is safe and without major adverse events [19].

Because the development of efficacious vaccines and antiviral drugs takes time, VC and other antioxidants are among currently available agents to mitigate COVID-19 associated ARDS. Given the fact that high-dose VC is safe, healthcare professionals should take a close look at this opportunity. Obviously, well-designed clinical studies are absolutely needed to develop standard protocols for bedside use.

References


18. Shanghai Expert Panel, cited on Mar 23, 2020 (http://mp.weixin.qq.com/s?__biz=MzA3Nzk5Mzc5MQ==&mid=2653620168&idx=1&sn=2352823b79a3cc42e48229a0c38f65e0&chksm=84962598b3e1ac8effb763e3ddb4858435de7aa947a8f41790e8df2bca34c20e6f6a64cd191#rd).

URGENT! Please circulate as widely as possible. It is crucial that every pulmonologist, every critical care doctor and nurse, every hospital administrator, every public health official receive this information immediately.

Folks: I have updated our approach to COVID-19 based on the best (and most recent) available literature and the Shanghai Management Guideline for COVID. We should not re-invent the wheel, but learn from others experience.

A few General thoughts:

1. It is likely that 40-80% of the population across the world will become infected with this virus. It is therefore unrealistic for us to expect this is will just go away. Our goal should therefore to reduce the mortality in those who are at greatest risk of dying. This requires that those at risk “socially” isolate themselves and then once they become infected we should treat aggressively to prevent disease progression.

2. The course of the disease is quite predictable. Acute respiratory failure occurs on day 6-8 (due to cytokine storm) In those patients requiring supplemental oxygen we need to be very aggressive to prevent progression to ARDS. Once ARDS develops the mortality is high.

3. It is likely that there will not be a single “magic bullet” to cure COVID-19. Rather we should be using multiple drugs that have synergistic and overlapping biological effects, that are, safe, cheap and could be made readily available. The impact on middle and low income countries will be enormous; these countries will not be able to afford expensive designer molecules.

4. Preliminary data suggest that chloroquine and hydroxychloroquine decrease the duration of viral shedding. These agents (if available) could be used to mitigate/curtail the spread of this virus. They may be used in elderly patients with comorbidities at risk of progression and death.

5. Zinc (Zn++) inhibits viral RNA dependent RNA polymerase (replicase). Chloroquine and hydroxychloroquine are potent Zn ionophores that increase intracellular Zn concentrations.

6. Quercetin is a plant phytochemical. Experimental and early clinical data (published in high impact journals) suggests that this compound has broad antiviral properties (including against coronavirus) and acting at various steps in the viral life cycle. Quercetin is a potent inhibitor of heat shock proteins (HSP 40 and 70) which are required for viral assembly.

7. It is not clear if the dose of Vitamin C should be reduced to 6 g/day in patients with very high ferritin levels. In patients with high ferritin, free iron is released form ferritin under hypoxic condition, and this may have a prooxidant effect in combination with Vitamin C. Monitor ferritin
and CRP; if both going up consider reducing dose to 6g/day (see below) and increasing dose of corticosteroids.

8. We are all inhabitants of the same planet, we are in this together and we need to act decisively, and right now.

**Prophylaxis**

While there is limited data, Vitamin C (500 mg BID), Zn (75-100 mg/day) and Quercetin (500-1000 mg/day) may have a role in high-risk populations (i.e. all of those on this planet).

**Mildly symptomatic patients (on floor):**

- Vitamin C (500mg BID) and Zn (75-100 mg/day) and Quercetin (500-1000 mg/day).
- Observe closely
- N/C 2L /min if required (max 6L/min; however, consider early t/f to ICU for escalation of care)
- Avoid Nebulization and Respiratory treatments. Use MDI if required
- NO Bagging
- NO NIV, CPAP, BiPAP or Hi-flow
- T/f to ICU for increasing respiratory signs/symptoms

**Respiratory symptoms (SOB; hypoxia: admit to ICU):**

1. Chloroquine 500mg PO BID for 7-10 days or hydroxychloroquine 400mg BiD day 1 followed by 200mg BID for 4 days.
2. Vitamin C 3g IV q 6 hourly until extubated and for at least 4 days up to 10 days (see dosage adjustment below).
3. Thiamine 200mg q 12 (PO or IV)
4. Azithromycin 500mg day 1 then 250mg for 4 days
5. Melatonin 6mg at night
6. Zn 75-100mg daily
7. Broad spectrum antibiotics only if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy)
   Co-infection with other viruses appears to be uncommon, however a full respiratory viral panel is still recommended; superadded bacterial infection is uncommon on presentation (may develop with prolonged ventilation). Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (increases the cytokine storm and prolongs Qtc)
10. Optional: Tocilizumab (if available) may have a role in cytokine storm (specific IL-6 inhibitor)
11. Optional: Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit.. may have a role in the hyper-inflammatory ARDS phenotype (typical of COVID-19)

13. Escalation of respiratory support (steps)
   a. N/C 1-6 l/min
b. High Flow up to 30 L/min  
c. **Intubation** ... By Expert intubator; Rapid sequence. No Bagging; Full PPE,  
d. Volume protective ventilation following ARDSnet table  
e. **APRV**  
f. Prone positioning  
g. ??? ECMO < 60yrs and no severe commodities/organ failure. Plasma exchange should be considered before ECMO; see below.

There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, there is no solid evidence to support this fear. CPAP/BiPAP may be used in select patients; notably those with COPD exacerbation or heart failure.

14. Consider plasma exchange for cytokine storm/HLH picture (see steroids below)  
The use of CVVH filters that remove cytokines should also be considered.

15. **Steroids:**  
This topic is controversial. However, the only study on steroids and COVID (from Wuhan) demonstrates a marked mortality reduction with methylprednisolone (60mg daily)  
- During the early viral replicative stage; probably best to avoid.  
- During the hyperimmune phase (day 6-8 onward).... Hydrocortisone 50mg q 6 for 4 days may be given on a case by case basis and based on features of ARDS and high CRP (lung injury is due to cytokine storm)  
- Pts may evolve into an HLH/cytokine vortex phase, marked by increasing ferrin, IL-6 and worsening oxygenation. These patients may benefit from high dose methylprednisolone. (dose ?? 200-500 mg q 12)

16. **Monitoring**  
- Seems like CRP and Ferritin are good biomarkers and tracks disease severity  
- IL-6 at baseline and ? every 3-4 days  
- Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++  
- No routine CT scans, follow CXR and chest ultrasound;  
- Follow ECHO closely; Pts develop a severe cardiomyopathy.
General schema for respiratory support in patients with COVID-19

Low flow nasal cannula
- Typically set at 1-6 liters/minute

High flow nasal cannula (with limitation in the flow rate)
- Titrate FiO2 based on patient’s saturation.
- Avoid very high flow rates (e.g. perhaps flow rates between 15-30 liters/minute could be reasonable??) This isn’t truly “high flow” - yet it allows administration of high levels of FiO2 in a comfortable fashion.
- If a commercial high-flow cannula isn’t available, a standard nasal cannula can be set at higher rates if clinically tolerated (e.g. 5-15 liters/minute). This may be uncomfortable and cause nasal dryness, but it’s not dangerous. Other options include venturi masks and non-rebreather facemasks.

Invasive mechanical ventilation
- Target tidal volumes of ~6 cc/kg.
- Permissive hypercapnia may be useful to allow for lung-protective settings.
- May use conventional lung-protective ventilation strategies or APRV.

Prone positioning
- Exact indication for prone ventilation is unclear.
- Proning is a font-line therapy for refractory hypoxemia, but it’s unclear whether it is beneficial in all patients with PaO2/FiO2 ratio <150.

VV-ECMO
- Indications remain unclear.
- Early discussion with ECMO center or team may be advisable.

Source: The Internet Book of Critical Care, by @PulmCrit
March 24, 2020

Governor Andrew M. Cuomo
New York State

Dear Governor Cuomo:

Re: URGENT: COVID treatment protocol. **Patients are dying needlessly.**

I do not think the WH task force are being entirely honest with the American public. Furthermore, the amount of misinformation and the mixed messaging is causing panic and anxiety. While Dr. Fauci is a highly respected scientist, he is not on the front lines and does not take care of critically sick patients.

While it is true that there is no definitive treatment for COVID-19 there is substantial information on treatments that could be of potential benefit. Many of these are FDA approved drugs with an extremely good safety profile. In addition, simple interventions such as Vitamin C, Quercetin, Zinc and melatonin hold great promise in the mitigation of this disease; however as big Pharma will not profit from these agents, it gets no attention. The use of these drugs for COVID-19 are supported by experimental and pre-clinical studies published in the most respected peer reviewed Journals (available on request). In addition, they are cheap and safe; so what does one have too loose.

Dr. Fauci and others are promoting the idea of performing randomized controlled trials (RCTs). I believe that it is unethical to do such trials. How can you offer patients a placebo when testing a drug that you believe may have clinical efficacy? Every patient needs to get the best treatment we can offer; we would expect no less for our loved ones. Furthermore, once these trials are eventually completed we will all be dead, or the pandemic will be over! This does not mean we should not be studying the impact of these interventions; detailed observational studies can provide very useful information.

I am reaching out to you as I pains me to see what is happening in the USA and across the world. While I am usually very modest, this is not a time for modesty. As the most published (and influential) clinician/researcher in critical care in the USA, I believe that I have the scientific and clinical background to understand how to treat these patients and what is possible.

Please see our treatment algorithm attached. I have tried to contact the NIH, CDC, Dr Fauci etc etc. however no one will return my e-mails or calls. I would be happy to discuss this with you personally. I can be reached 24/7 on my cell: 757-544-8512.

Kindly,

Paul Marik, MD, FCCM. FCCP, FRCP.