EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

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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.

This is our recommended approach to COVID-19 based on the best (and most recent) available literature including the Shanghai Management Guideline for COVID. We should not re-invent the wheel, but learn from the experience of others around the world. It is important to recognize that COVID-19 does not cause your “typical ARDS”… this disease must be treated differently and it is likely we are exacerbating this situation by causing ventilator induced lung injury. This is a very fluid situation; therefore, we will be updating the guideline as new information emerges. Please check on the EVMS website for updated versions of this protocol.

EVMS COVID website: https://www.evms.edu/covid-19/medical_information_resources/
Short url: evms.edu/covidcare

Dr. AB (NYC).

“We have zero success for patients who were intubated. Our thinking is changing to postpone intubation to as long as possible, to prevent mechanical injury from the ventilator. These patients tolerate arterial hypoxia surprisingly well. Natural course seems to be the best.”

This is not your “typical ARDS”. Mechanical Ventilation may be doing harm. We need to think of alternative treatment strategies.
**A few General thoughts:**

1. We are all inhabitants of the same planet and we are all in this together. The medical community needs to get off their “high pedestal” and act decisively and immediately; there is no time to lose. Patients are dying needlessly.

2. 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 will just go away. Our goal, therefore, should be to reduce the mortality in those who are at greatest risk of dying. This requires those at risk to diligently “social distance” themselves. Once they become infected, we should treat aggressively to prevent disease progression.

3. The course of the disease is quite predictable. Acute respiratory failure occurs on day 6-8 concomitant with the cytokine storm and hypercoagulable state. In those patients requiring supplemental oxygen, we need to be very aggressive to prevent disease progression and mechanical ventilation. Once intubated, the mortality is high.

4. This is not your “typical” ARDS... but something else (weird). Chest CT shows bilateral, discreet, irregular, multilobar infiltrates and not the typical dependent air-space consolidation (“sponge lung”) characteristic of “typical” ARDS. Physiologically “COVID-19 ARDS” is different; our preliminary data suggests that lung water (EVLWI) is normal or only marginally increased (therefore by definition this is **NOT ARDS**). Furthermore, lung compliance is quite good yet there is severe hypoxia (due to shunting). This suggest microvascular and/or macrovascular disease... or some other alternative explanation. In addition, pulmonary embolism appears to be very common in these patients and may be the cause of sudden death.

5. It is important to stress that there is no known drug/treatment that has been proven to improve the outcome of COVID. This, however, does not mean we should adopt a nihilist approach. Furthermore, it is likely that there will not be a single “magic bullet” to cure COVID-19. Rather, we should be using multiple drugs/interventions that have synergistic and overlapping biological effects, that are **safe, cheap and “readily” available.** The impact of COVID-19 on middle- and low-income countries will be enormous; these countries will not be able to afford expensive designer molecules.

6. Preliminary data suggests that chloroquine and hydroxychloroquine decrease the duration of viral shedding. In addition, chloroquine has favorable immunomodulating properties including inhibition of PAI-1 expression. These agents are now FDA approved for the treatment of COVID-19. These agents (if available) could be used to mitigate/curtail the spread of this virus and could be used in elderly patients with comorbidities at risk of progression and death.

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

8. Ascorbic acid has numerous proven biological properties (anti-inflammatory, anti-oxidant, immune enhancing, antiviral) that are likely to be of benefit in patients with COVID-19 disease. Furthermore, it is important to stress that ascorbic acid has proven synergistic effects when combined with corticosteroids. Therefore, steroids are recommended in patients with COVID-19 and respiratory failure. The benefit of ascorbic acid (without corticosteroids) in patients with severe respiratory failure appears to be limited. While the optimal dose of ascorbic acid is unknown, we suggest 3 g IV q 6 hourly. It should be noted that in the presence of free iron (released from ferritin) ascorbic acid may potentially have pro-oxidant effects. Therefore, the trends in CRP and ferritin need to be closely monitored; in those patients who ferritin AND CRP are increasing, reducing the dose to 1.5g q 6 hourly should be considered.
9. Very recent data suggests that in addition to being a potent anti-oxidant, melatonin may have direct antiviral effects against COVID-19. In healthy people, melatonin levels plummet after the age of 40 years. This may partly explain the increased risk of death in patients with COVID-19 who are over the age of 40. Melatonin may therefore have a role in both the prevention and treatment of COVID-19.

10. Vitamin D has important immune-enhancing effects. Much of the population, especially the elderly have sub-optimal vitamin D levels, particularly during the winter months. Low vitamin D levels have been shown to increase the risk of developing viral upper respiratory tract infections. Therefore, prophylactic vitamin D should be considered especially in the elderly.

11. Quercetin is a plant phytochemical. Experimental and early clinical data 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. This readily available and cheap plant-derived compound may play a role in the prophylaxis of COVID-19 in high risk populations.

**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, especially amongst the most vulnerable citizens in our community; i.e. those over the age of 60 years and those with medical comorbidities. While there is no high level evidence that this cocktail is effective; it is cheap, safe and should be readily available. So what is there to lose?

- **Vitamin C** 500 mg BID
- **Zinc** 75-100 mg/day (acetate, gluconate or picolinate; do not use for more than 2 months)
- **Quercetin** 500-1000 mg/day
- **Melatonin** (slow release): Begin with 0.3mg and increase as tolerated to 1-2 mg at night
- **Vitamin D3** 1000-4000 u/day (optimal dose unknown; likely that those with baseline low 25-OH vitamin D and those > 40° latitude will benefit the most)

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

- **Vitamin C** 500mg BID
- **Zinc** 75-100 mg/day
- **Quercetin** 500-1000 mg/day
- **Melatonin** 6-12 mg at night (the optimal dose is unknown)
- **Vitamin D** 1000-4000 u/day
- **Enoxaparin** 40-60mg day (if not contraindicated; dose adjust with CrCl < 30ml/min)
- 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.**
- **Avoid non-invasive ventilation**
- T/f EARLY to the ICU for increasing respiratory signs/symptoms.
Respiratory symptoms (SOB; hypoxia: admit to ICU):

1. Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly until extubated and for at least 4 days and up to 7 days (see dosage adjustment above and caution with POC glucose testing).
3. Anticoagulation. COVID-19 results in a hypercoagulable state with pulmonary micro- and macrovascular disease playing a role in the hypoxia/pulmonary shunting. 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). The use of half-dose rTPA has also been suggested: 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation.
4. Thiamine 200mg q 12 (PO or IV).
5. Azithromycin 500 mg day 1 then 250 mg for 4 days (has immunomodulating properties including downregulating IL-6; in addition Rx of concomitant bacterial pneumonia).
6. Melatonin 6-12 mg at night (the optimal dose is unknown).
7. Zinc 75-100 mg daily.
8. 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).
9. Broad-spectrum antibiotics 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 reported to be uncommon (however, this may not be correct).

10. Maintain EUVOLEMIA (this is not non-cardiogenic pulmonary edema).
11. Early norepinephrine for hypotension. While the angiotenin II agonist Giapreza ™ has a limited role in septic shock, this drug may uniquely be beneficial in patients with COVID-19 (downregulates ACE-2).
12. Optional: Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit. Statins have been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. Statins have pleotrophic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1.
13. Optional: Tocilizumab (if available) may have a role in cytokine storm (specific IL-6 inhibitor).

14. Steroids:
   a. This topic is controversial. However, the only study on the use of corticosteroids and COVID (from Wuhan) demonstrates a marked mortality reduction with methylprednisolone (60mg daily). Steroids together with vitamin C maybe necessary to down-regulate the cytokine storm.
   b. During the early viral replicative stage, best to avoid.
   c. During the hyperimmune/hypercoagulable phase (day 6-8 onward) in patients with hypoxia: Hydrocortisone 50mg IV q 6 for 4 days is recommended (together with ascorbic acid)
   d. Patients may evolve into an HLH/cytokine vortex phase, marked by increasing ferrin, CRP, IL-6 and worsening oxygenation. These patients may benefit from high dose methylprednisolone. (dose ?? 200-500 mg q 12).
15. Consider plasma exchange for cytokine storm/HLH picture (see steroids below). The use of CVVH filters that remove cytokines should also be considered.

16. Escalation of respiratory support (steps); **Try to avoid intubation if at all possible**
   - Accept “permissive hypoxemia” (keep O2 Saturation > 86%)
   - N/C 1-6 L/min
   - High Flow Nasal canula (HFNC) up to 60-80 L/min
   - Trial of inhaled Flolan (epoprostenol)
   - Attempt proning (cooperative proning)
   - Intubation ... by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
   - Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible
   - Moderate sedation to prevent self-extubation
   - Trial of inhaled Flolan (epoprostenol)
   - Prone positioning
   - ?? ECMO < 60 yrs and no severe commodities/organ failure.

   There is widespread concern that using HFNC could increase the risk of viral transmission. There is, however, no solid evidence to support this fear.

   CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

17. Monitoring
   - Daily: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Mg, CRP and Ferritin are good biomarkers and track disease severity.
   - 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.
   - Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients)
   - 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

Try to avoid intubation if possible

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

High flow nasal cannula
- Accept permissive hypoxemia (O₂ Saturation > 86%)
- Titrate FiO₂ 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 Pa02/Fi02 ratio <150.

VV-ECMO
- Indications remain unclear.
- Early discussion with ECMO center or team may be advisable.
Typical CT scan of “COVID-9 ARDS”
CTPA of 44 COVID + patient (with no risk factor for DVT/PE) presenting with severe tachycardia
**Covid-19 shedding**

No. of samples positive for SARS-CoV-2 by RT-PCR/ total no. of samples in aggregated studies (%)

**Nasopharyngeal swabs:** 31/35 (88.6%)
- Ju X et al, Lancet, 2020
- Kubo J et al, medRxiv, 2020
- Chen P et al, Lancet

**Conjunctival swabs:** 2/188 (1.1%)
- Ju X et al, medRxiv, 2020
- Zhang X et al, medRxiv, 2020
- Jin Y et al, medRxiv, 2020

**Sputum:** 48/49 (97.9%)
- Pan Y et al, Lancet Infect Dis, 2020
- Kubo J et al, medRxiv, 2020
- Chen P et al, Lancet, 2020
- Lin C et al, medRxiv, 2020
- Chen J et al, Lancet, 2020

**Throat swabs:** 45/75 (60%)
- Pan Y et al, Lancet Infect Dis, 2020
- Kubo J et al, medRxiv, 2020
- Chen P et al, Lancet, 2020
- Lin C et al, medRxiv, 2020
- Wu J et al, Lancet Infect Dis, 2020
- Chen J et al, Clin Infect Dis, 2020
- Chen P et al, Lancet, 2020

**Post. throat saliva:** 31/35 (88.6%)

**Oral swabs:** 7/15 (46.7%)
- Pan Y et al, Lancet Infect Dis, 2020
- Chen P et al, Lancet, 2020
- Lin C et al, medRxiv, 2020
- Wu J et al, Lancet Infect Dis, 2020
- Chen J et al, Clin Infect Dis, 2020
- Chen P et al, Lancet, 2020

**Stool:** 34/48 (70.8%)

**Anal swabs:** 16/78 (20.5%)

**Rectal swabs:** 4/23 (17.4%)
- Cui P et al, medRxiv, 2020
- Chen Y et al, Emerg Microbes Infect
- Pan Y et al, Lancet Infect Dis, 2020
- Tu KH et al, Lancet Infect Dis, 2020
- Kubo J et al, medRxiv, 2020
- Lin C et al, medRxiv, 2020
- Xu C et al, UCI, 2020
- Wang Z et al, JAMA, 2020
- Huang R et al, AJKD, 2020

**Urine:** 0/76 (0%)
- Pan Y et al, Lancet Infect Dis, 2020
- Tu KH et al, Lancet Infect Dis, 2020
- Kubo J et al, medRxiv, 2020
- Xu C et al, UCI, 2020
- Wang Z et al, JAMA, 2020
- Huang R et al, AJKD, 2020

**Blood:** 20/162 (12.3%)
- Chen J et al, Emerg Microbes Infect
- Tu KH et al, Lancet Infect Dis, 2020
- Kubo J et al, medRxiv, 2020
- Xu C et al, UCI, 2020
- Wang Z et al, JAMA, 2020
- Huang R et al, AJKD, 2020
- Chen J et al, Lancet, 2020
- Chen P et al, Lancet, 2020
- Wu J et al, Lancet, 2020

**Vaginal swabs:** 0/35 (0%)
- Cui P et al, medRxiv, 2020

Found on Internet, source unknown (thank you, author)

Yadi Zhou¹, Yuan Hou¹, Jiayu Shen¹, Yin Huang¹, William Martin² and Feixiong Cheng¹,²,³
Proposed mechanism of hypercoagulable state.

Found on Internet, source unknown (thank you, author)