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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.

An 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 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 to "socially" isolate themselves. 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 !L-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).
12. Optional: Consider full anticoagulation with hepatin/enoxaparin in patients with rapidly increasing D-dimer.
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, 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
- Daily: PCT, CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer.
- 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

Deterioration

Recovery

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 Fi02 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. 6-15 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 Pa02/Fi02 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