

# EVMS

MEDICAL GROUP

## 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) literature. We should not re-invent the wheel but learn from the experience of others. This is a very dynamic 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/](https://www.evms.edu/covid-19/medical_information_resources/)  
Short url: [evms.edu/covidcare](https://www.evms.edu/covidcare)

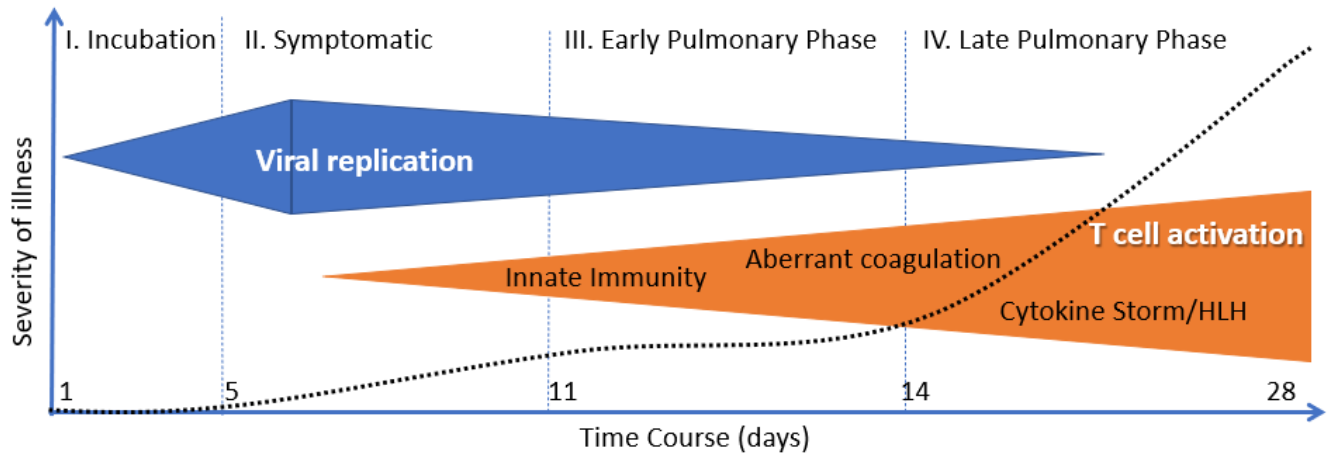
**“If what you are doing ain’t working, change what you are doing”**



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.”

**Figure 1. The course of COVID-19 and General Approach to treatment**



	Time Course (days)			
	1 - 5	5 - 11	11 - 14	14 - 28
Ground-glass infiltrates	+                      ++                      +++                      ++++			
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 95%		Progressive hypoxia
Treatment approach	Antiviral Rx		Anti-inflammatory: Immune Suppressive Rx	
Potential therapies	? Remdesivir		?MP 40mg/day	Methylprednisolone 40mg q 12
		Enoxaparin 40-60 mg/day		Enoxaparin 1mg/kg s/c q 12
	? Hydroxychloroquine 400/200 5 days			
	Vitamin C 500mg PO BID			Vitamin C 3g Iv q 6

### ***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. While there is no high level evidence that this cocktail is effective; it is cheap, safe and widely available.

- Vitamin C 500 mg BID and? Quercetin 250-500 mg BID
- Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1-2 months, reduce the dose to 30-50 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).

### ***Mildly Symptomatic patients (at home):***

- Vitamin C 500 mg BID 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 1000-4000 u/day
- *Optional:* ASA 81 -325 mg/day
- *Optional:* Hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days

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

- Vitamin C 500mg BID 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 1000-4000 u/day
- Enoxaparin 40-60 mg daily
- *Optional:* Methylprednisolone 40 mg daily
- *Optional:* Hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days
- *Optional:* Remdesivir, only available in clinical trials
- N/C 2L /min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use “Spinhaler” or MDI and spacer if required.
- Avoid non-invasive ventilation
- T/f EARLY to the ICU for increasing respiratory signs/symptoms.

**Respiratory symptoms (SOB; hypoxia- requiring N/C  $\geq$  4 L min: admit to ICU):**

**Essential Treatment (dampening the STORM)**

1. Methylprednisolone 80 mg loading dose then 40mg q 12 hourly for at least 7 days and until transferred out of ICU. Alternative approach: Hydrocortisone 50 mg q 6 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 (see below).
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. Alternative approach: Half-dose rTPA: 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.

Note: Early termination of ascorbic acid and corticosteroids will likely result in a rebound effect (see Figure 2).

**Additional Treatment Components (the Full Monty)**

4. Melatonin 6-12 mg at night (the optimal dose is unknown).
5. 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).
6. *Optional:* 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).
7. *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 pleotropic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1
8. 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).
9. Maintain *EUVOLEMIA* (this is not non-cardiogenic pulmonary edema). Due to the prolonged “symptomatic phase” with flu-like symptoms (6-8 days) patients may be volume depleted. Cautious rehydration with 500 ml boluses of Lactate Ringers may be warranted, ideally guided by non-invasive hemodynamic monitoring. Diuretics should be avoided unless the patient has obvious intravascular volume overload.
10. 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).

11. Escalation of respiratory support (steps); **Try to avoid intubation if at all possible**, (see Figure 3)

- Accept “permissive hypoxemia” (keep O<sub>2</sub> Saturation > 84%)
- 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 repositioning-proning; see Figure)
- 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. Keep driving pressures < 15 cmH<sub>2</sub>O.
- 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 evidence to support this fear. HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

A sub-group of patients with COVID-19 deteriorates very rapidly. Intubation and mechanical ventilation may be required in these patients.

12. **Treatment of secondary HLH** (increasing Ferritin, CRP and transaminases)

- “High dose corticosteroids.” Methylprednisolone 120 mg q 8 hourly for at least 3 days, then wean accruing to CRP, IL-6, Ferritin etc (see Figure 4).
- Tocilizumab (IL-6 inhibitor) as per dosing guideline.
- Consider plasma exchange

13. **Monitoring**

- Daily: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP, IL-6 and Ferritin track disease severity closely. Thromboelastogram (TEG) on admission 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.
- Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg<sup>++</sup> (torsades is uncommon in monitored ICU patients)
- No routine CT scans, follow CXR and chest ultrasound.
- Follow ECHO closely; Pts develop a severe cardiomyopathy.

#### 14. Post ICU management

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

Figure 2. Premature discontinuation of corticosteroids and IV vitamin C (after 4 day) and the effect of reinitiation of this combination on the CRP 9clinical course followed CRP profile.

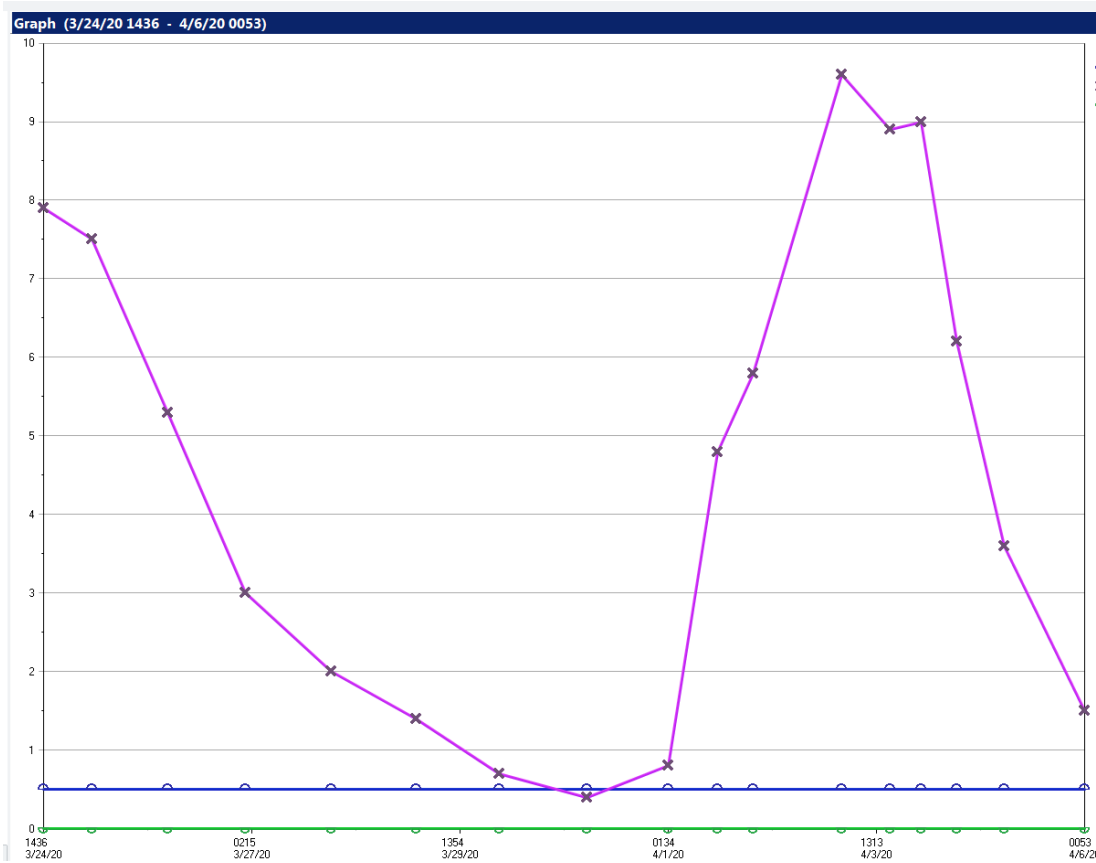


Figure 3.

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

**Try to avoid intubation if possible**

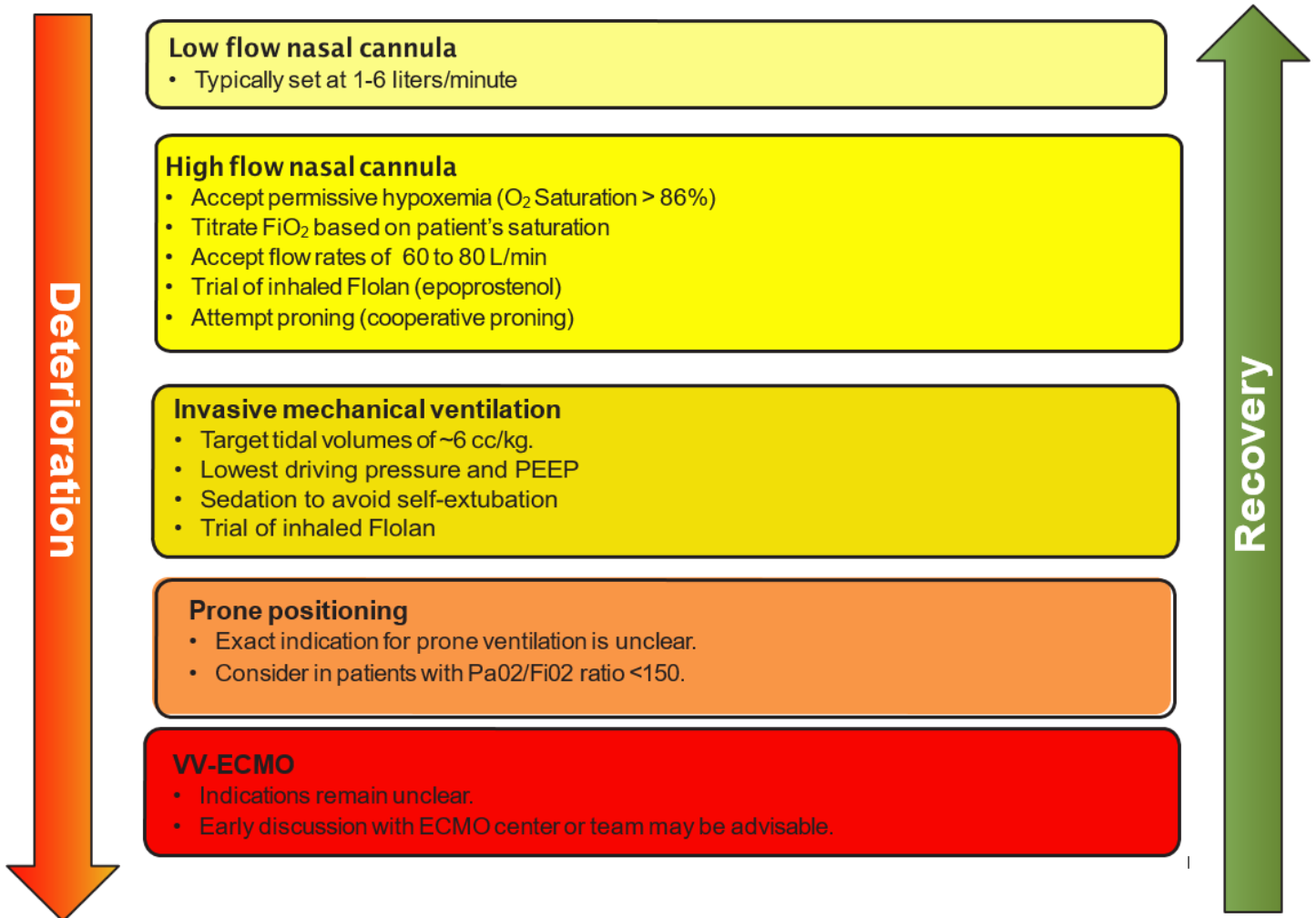
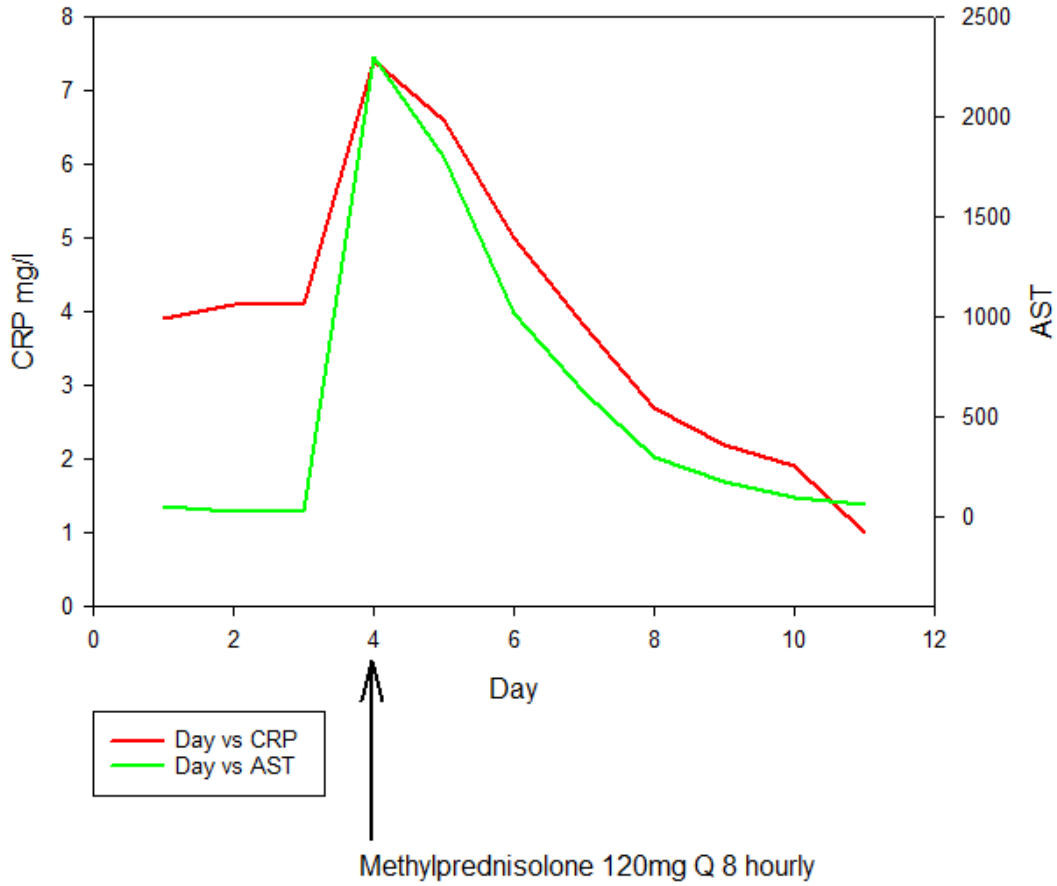


Figure 4. Secondary HLH Rx with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)





## Scientific Rational for Treatment Protocol

Three core pathologic processes lead to multi-organ failure and death in COVID-19:

- 1) **Hyper-inflammation (“Cytokine storm”)** – a dysregulated immune system whose cells infiltrate and damage multiple organs, namely the lungs, kidneys, and heart. It is now widely accepted that SARS-CoV-2 causes aberrant T lymphocyte activation resulting in a “cytokine storm.”.
- 2) **Hyper-coagulability (increased clotting)** – the dysregulated immune system damages the endothelium and activates blood clotting, causing the formation of micro and macro blood clots. These blood clots impair blood flow.
- 3) **Severe Hypoxemia (low blood oxygen levels)** –lung inflammation caused by the cytokine storm, together with microthrombosis in the pulmonary circulation severely impairs oxygen absorption resulting in oxygenation failure.

The above pathologies are not novel, although the combined severity in COVID-19 disease is considerable. Our long-standing and more recent experiences show consistently successful treatment if traditional therapeutic principles of early and aggressive intervention is achieved, before the onset of advanced organ failure. It is our collective opinion that the historically high levels of morbidity and mortality from COVID-19 is due to a single factor: the widespread and inappropriate reluctance amongst intensivists to employ anti-inflammatory and anticoagulant treatments, including corticosteroid therapy *early in the course of a patient’s hospitalization*. It is essential to recognize that it is not the virus that is killing the patient, rather it is the patient’s overactive immune system. The flames of the “cytokine fire” are out of control and need to be extinguished. Providing supportive care (with ventilators that themselves stoke the fire) and waiting for the cytokine fire to burn itself out simply does not work... this approach has FAILED and has led to the death of tens of thousands of patients.

The systematic failure of critical care systems to adopt corticosteroid therapy resulted from the published recommendations against corticosteroids use by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the American Thoracic Society (ATS) amongst others. A very recent publication by the Society of Critical Care Medicine and authored one of the members of our group (UM), identified the errors made by these organizations in their analyses of corticosteroid studies based on the findings of the SARS and H1N1 pandemics. Their erroneous recommendation to avoid corticosteroids in the treatment of COVID-19 has led to the development of myriad organ failures which have overwhelmed critical care systems across the world.

Our treatment protocol targeting these key pathologies has achieved near uniform success, *if begun within 6 hours* of a COVID19 patient presenting with shortness of breath or needing  $\geq$  4L/min of oxygen. If such early initiation of treatment could be systematically achieved, the need for mechanical ventilators and ICU beds will decrease dramatically.

It is important to recognize that “COVID-19 pneumonia” does not cause ARDS. These patients have normal lung compliance with near normal lung water (as measured by transpulmonary thermodilution). Treating them with early intubation and the ARDNSnet treatment protocol will cause the disease you are trying to prevent i.e. ARDS. These patients tolerate hypoxia remarkable well, without an increase in blood lactate concentration nor a fall in central venous oxygen saturation. We therefore suggest the liberal use of HFNC, with frequent patient repositioning (proning) and the acceptance of “permissive hypoxemia”. However, this approach entails close patient observation.

Further, it is important to recognize that COVID-19 present with a variety of phenotypes, likely dependent on genetic heterogeneity, age, and co-morbidities (these are illustrated in Figure 5). COVID-19 patients may develop a “thrombophilic phenotype” presenting with severe thrombo-embolic disease with little evidence of lung parenchymal involvement. This suggests that mildly symptomatic patients may benefit from anticoagulation.

Finally, it is important to acknowledge that there is no known drug/treatment that has been proven unequivocally to improve the outcome of COVID-19. This, however, does not mean we should adopt a nihilist approach and limit treatment to “supportive care”. 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.

Figure 5a.

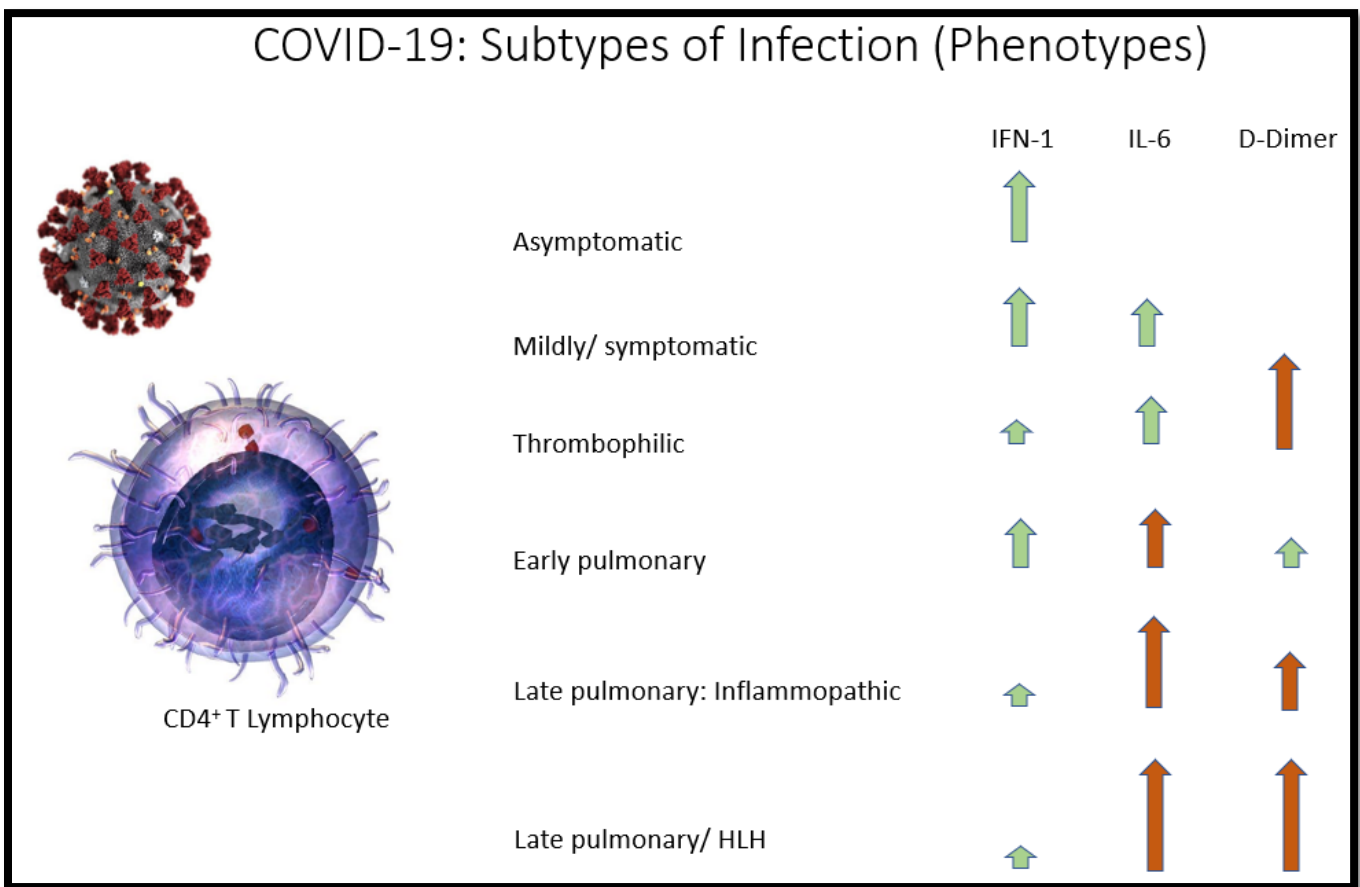


Figure 5b

## Factors Determining COVID Phenotypes

- Age
- Genotype
  - Inflammopathic, Thrombophilic, Adaptative, etc
- Co-morbidities
- Baseline immunological competence
- Vitamin D status (latitude)
- ? Vitamin C and Zinc status
- Unknown confounders