

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/
Short url: [evms.edu/covidcare](https://www.evms.edu/covidcare)

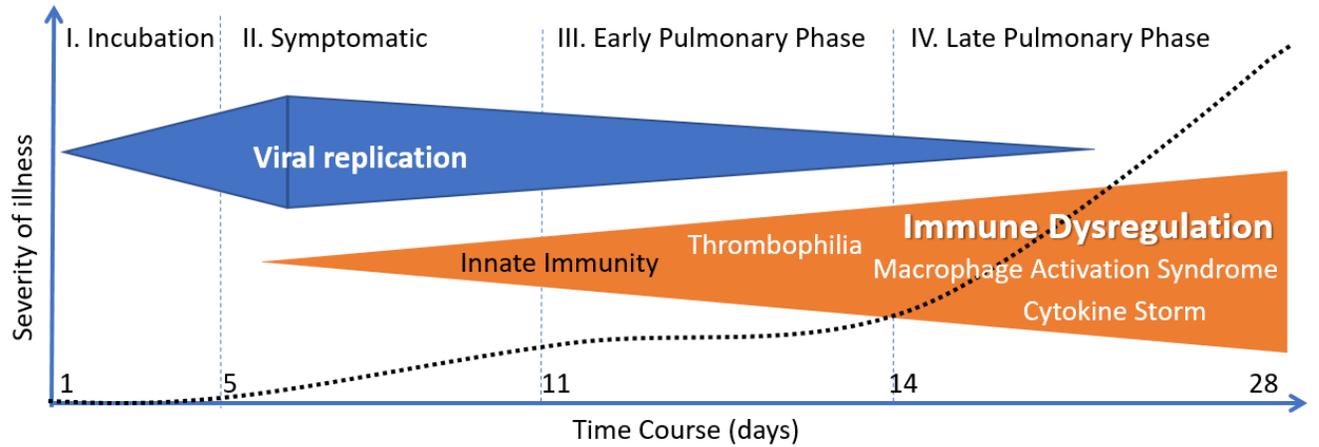
“If what you are doing ain’t working, change what you are doing”



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)			
	+	++	+++	++++
Ground-glass infiltrates				
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia	
Treatment approach	Antiviral Rx	Anti-inflammatory: Immune Suppressive Rx		
Potential therapies	? Ivermectin	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.		
	?? HCQ 400/ 200 5 days	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12	
	? Remdesivir (IV)			
	Vitamin C 500mg PO BID	Vit C 500mg PO q 6	Vitamin C 3g IV q 6	

THIS IS A STEROID RESPONSIVE DISEASE: HOWEVER, TIMING IS CRITICAL

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 [1-5]
- Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1 month, reduce the dose to 30-50 mg/day. [1,6-9]
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night [10-13]
- Vitamin D3 1000-4000 u/day [14-20]
- *Optional:* Famotidine 20-40mg/day [21]
- *Optional/uncertain:* Once weekly chloroquine/hydroxychloroquine may have a role in prophylaxis in high risk subgroups i.e. health care workers, residents of nursing homes, etc. Ongoing studies are testing this hypothesis.

Symptomatic patients (at home):

- Vitamin C 500 mg 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:* ASA 81 -325 mg/day
- *Optional:* Famotidine 20-40mg/day
- *Optional:* Hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days [22]. Recent evidence suggests that HCQ has no role in the treatment of COVID-19 in hospitalized patients.[23] However, the potential role of HCQ in early symptomatic patients (prior to hospitalization) is unknown.
- *Optional:* Ivermectin 150-200 ug/kg (single dose) [24,25]
- In symptomatic patients, monitoring with home pulse oximetry is recommended. Ambulatory desaturation < 94% should prompt hospital admission

Mildly Symptomatic patients (on floor):

- Vitamin C 500 mg 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 [26-30]
- Methylprednisolone 40 mg q 12 hourly ; increase to 80 mg q 12 hourly in patients with progressive symptoms and increasing CRP. [31-35]
- Famotidine 40mg daily (20 mg in renal impairment)
- *Optional: Remdesivir*, 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [36,37] This agent has been reported to reduce time to recovery (based on an ordinal scale). [37] The benefit of this agent on patient centered outcomes is unclear.

- *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).
- Avoid Nebulization and Respiratory treatments. Use “Spinhaler” or MDI and spacer if required.
- Avoid CPAP or BiPAP
- T/f EARLY to the ICU for increasing respiratory signs/symptoms and arterial desaturation.

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

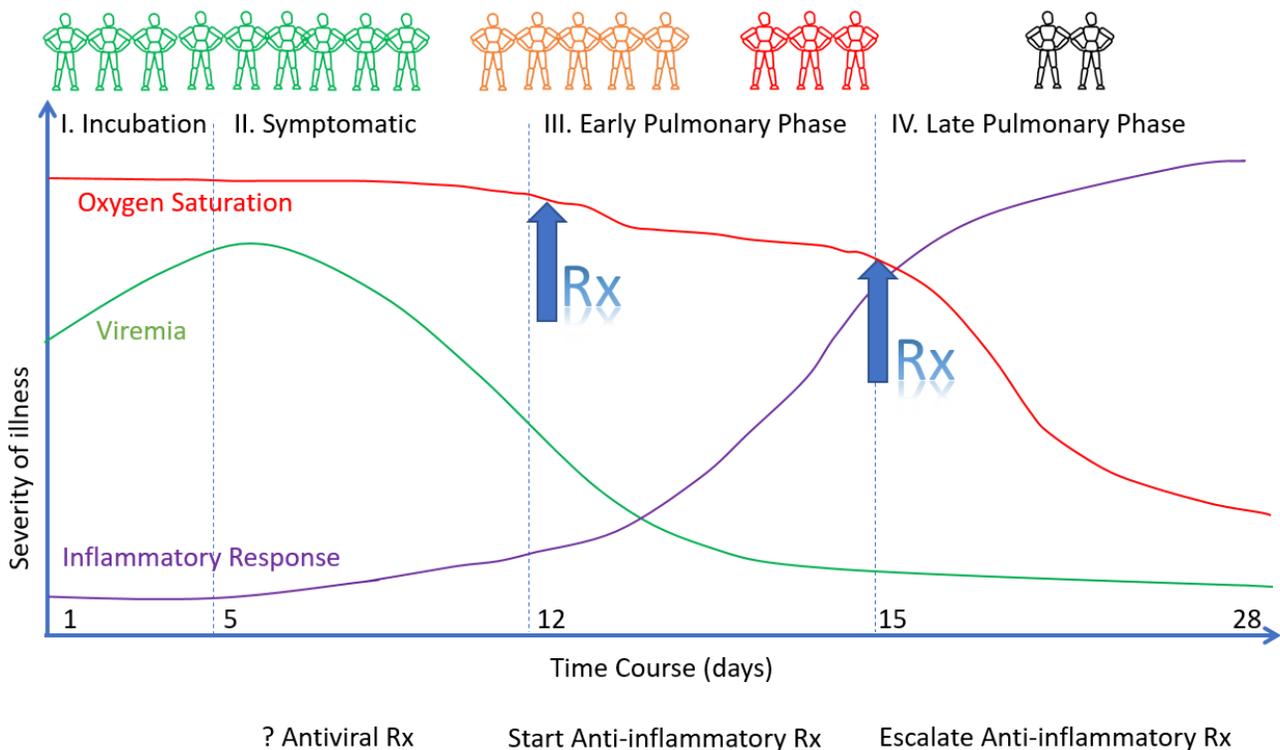
Essential Treatment (dampening the STORM)

1. Methylprednisolone 80 mg loading dose then 40mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 12 hourly, then titrate down as appropriate. [31-35]
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). [38-46]
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). [26-30] 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: A falling SaO2 despite respiratory symptoms should be a trigger to start anti-inflammatory treatment (see Figure 2).

Note: Early termination of ascorbic acid and corticosteroids will likely result in a rebound effect with clinical deterioration (see Figure 3).

Figure 2. Timing of the initiation of anti-inflammatory therapy



Additional Treatment Components (the Full Monty)

4. Melatonin 6-12 mg at night (the optimal dose is unknown).
5. Famotidine 40mg daily (20 mg in renal impairment)
6. Vitamin D 2000-4000 u PO daily
7. Thiamine 200 mg IV q 12 hourly
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). [47-49]
9. *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). [50]
10. *Optional*: Simvastatin 80 mg/day. Of theoretical but unproven benefit. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [51] Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1.
11. *Optional*: Remdesivir. The role of this agent in patients with more advanced pulmonary involvement appears to be limited.
12. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy). Due to the paradox of hyper-inflammation and immune suppression (a major decrease of HLA-DR on CD14 monocytes) secondary bacterial infection is not uncommon.
13. 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. Avoid hypovolemia.
14. Early norepinephrine for hypotension.
15. Escalation of respiratory support (steps); **Try to avoid intubation if at all possible**, (see Figure 4)
 - Accept “permissive hypoxemia” (keep O₂ Saturation > 84%); follow venous lactate and Central Venous O₂ saturations (ScvO₂) in patents with low arterial O₂ saturations
 - 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)
 - 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 cmH₂O.
 - Moderate sedation to prevent self-extubation
 - Trial of inhaled Flolan (epoprostenol)
 - Prone positioning.

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.

16. Salvage Treatments

- Plasma exchange [52-54]. Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy. Patients may require up to 5 exchanges.
- High dose corticosteroids; 120mg methylprednisolone q 6-8 hourly
- Siltuximab and Tocilizumab (IL-6 inhibitors) [55,56]
- Convalescent serum; the role and timing of convalescent serum are uncertain. [57-59]
- CVVH with cytokine absorbing/filtering filters [60]
- ?? ECMO < 60 yrs. and no severe commodities/organ failure [61]. Unlike “typical ARDS” patients do not progress into a resolution phase. Rather, patients with COVID-19 progress to a severe fibro-proliferative phase and ventilator dependency. ECMO in these patients would serve very little purpose.

17. Treatment of Macrophage Activation Syndrome (MAS)

- A sub-group of patients will develop MAS. This appears to be driven by SARS-CoV-2 induced inflammasome activation and increased IL-1 β production (see Figure 5). [62,63]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and increasing CRP. [64]
- “*High dose corticosteroids.*” Methylprednisolone 120 mg q 6-8 hourly for at least 3 days, then wean according to Ferritin, CRP, AST/ALT (see Figure 6). Ferritin should decrease by at least 15% before weaning corticosteroids.
- Consider plasma exchange.
- Anakinra (competitively inhibits IL-1 binding to the interleukin-1 type I receptor) can be considered in treatment failures.

18. 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 (although ferritin tends to lag behind CRP). Early CRP levels are closely associated with the degree of pulmonary involvement and the CT score. [65] 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⁺⁺ (torsades is uncommon in monitored ICU patients)
- No routine CT scans, follow CXR and chest ultrasound.
- Follow ECHO closely; Pts develop a severe cardiomyopathy.

19. Post ICU management

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

Figure 3. Premature discontinuation of corticosteroids and IV vitamin C (after 4 day) and the effect of reinitiation of this combination on the CRP profile.

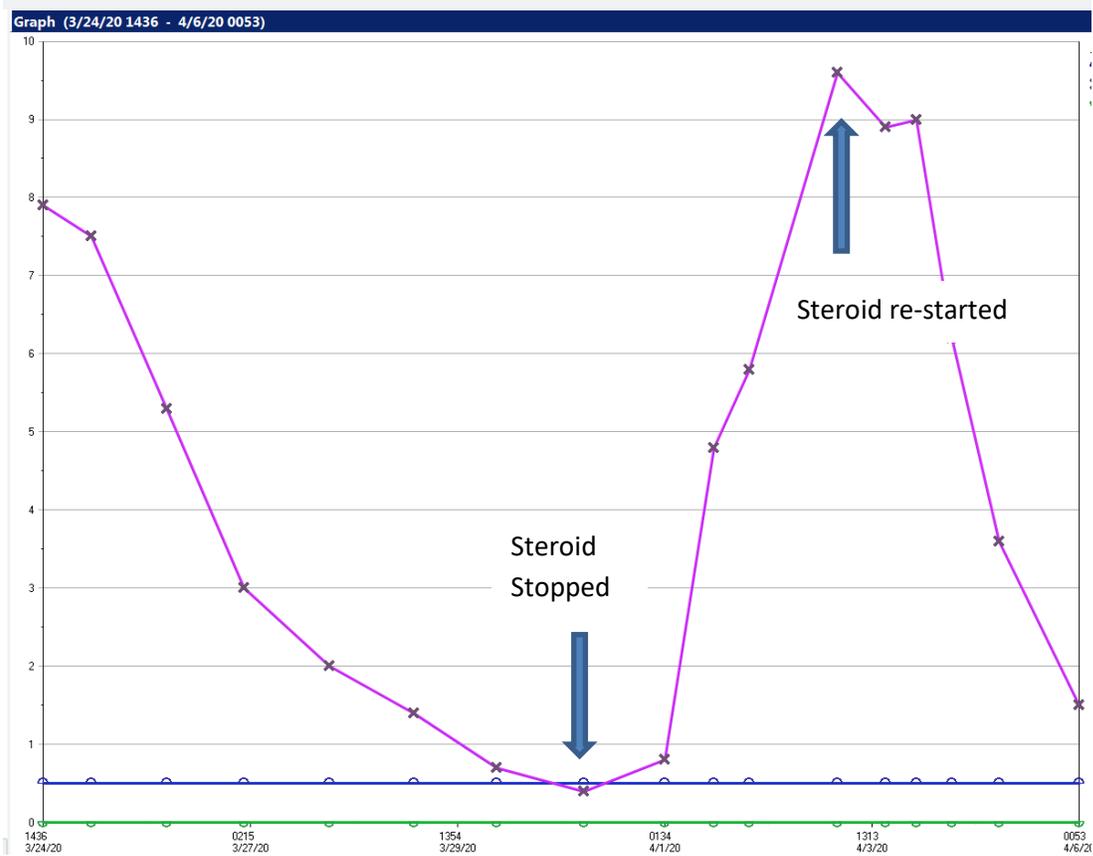


Figure 4.

General schema for respiratory support in patients with COVID-19

Try to avoid intubation if possible

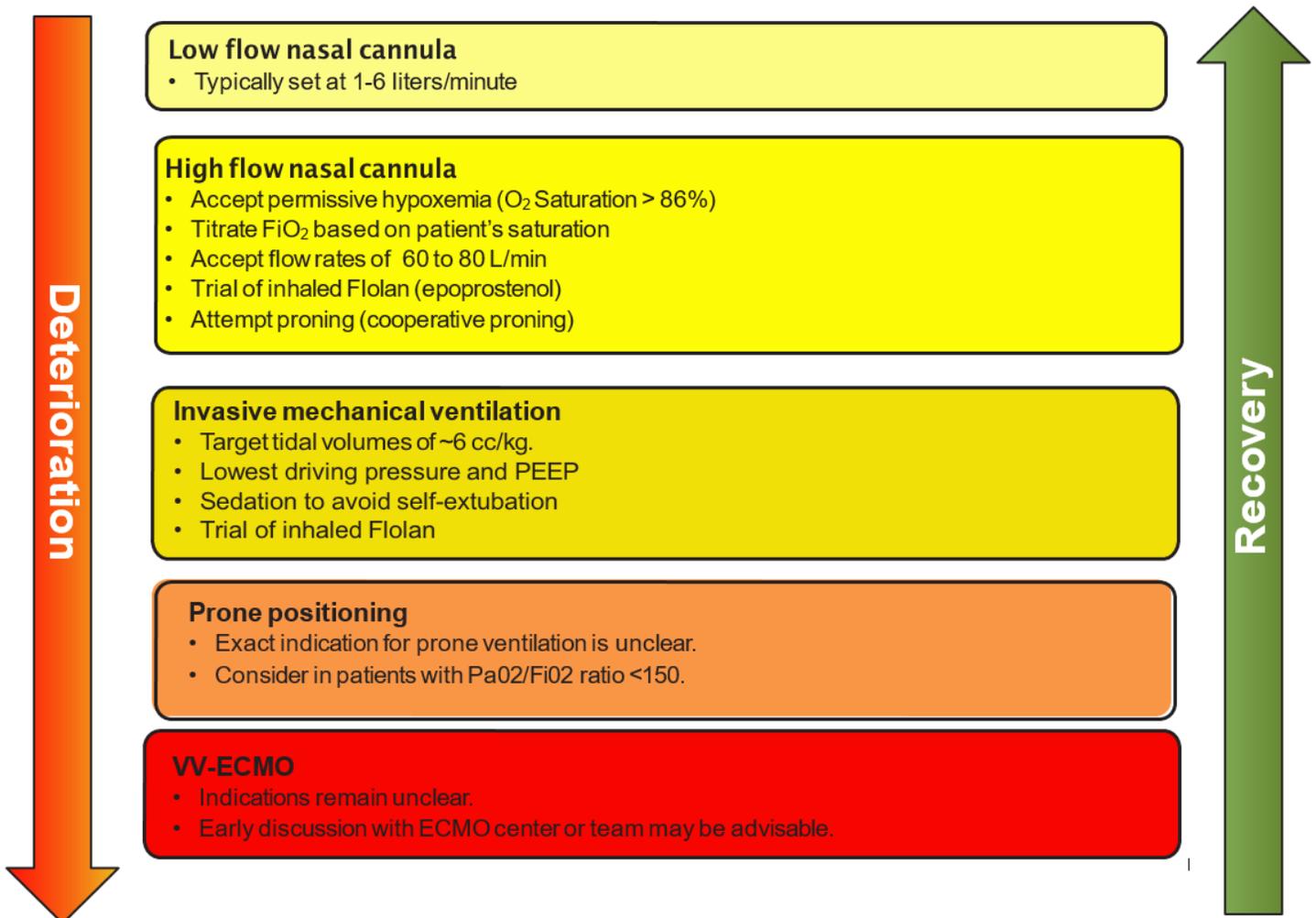


Figure 5. COVID-19 Subtypes of Infections (Phenotypes)

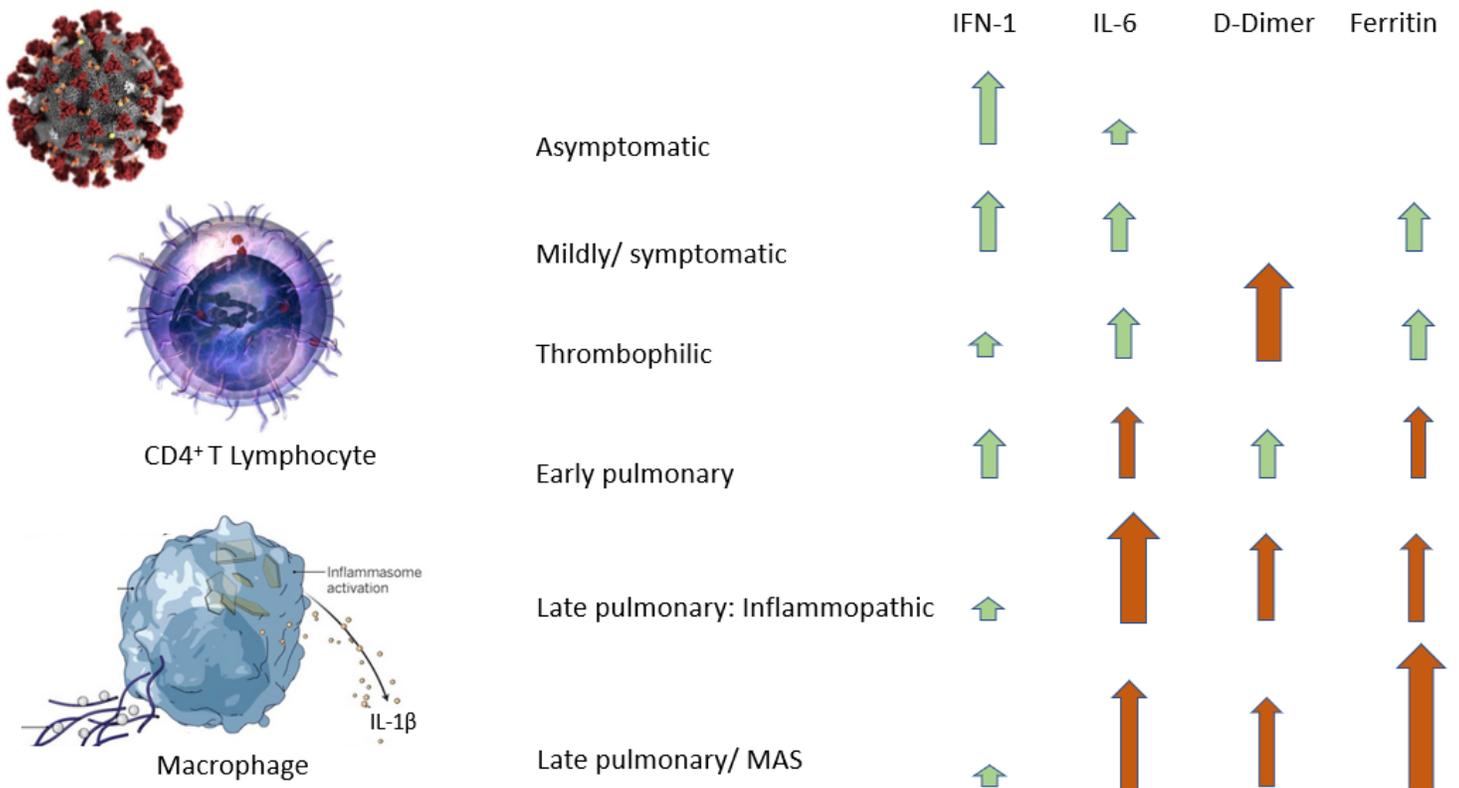
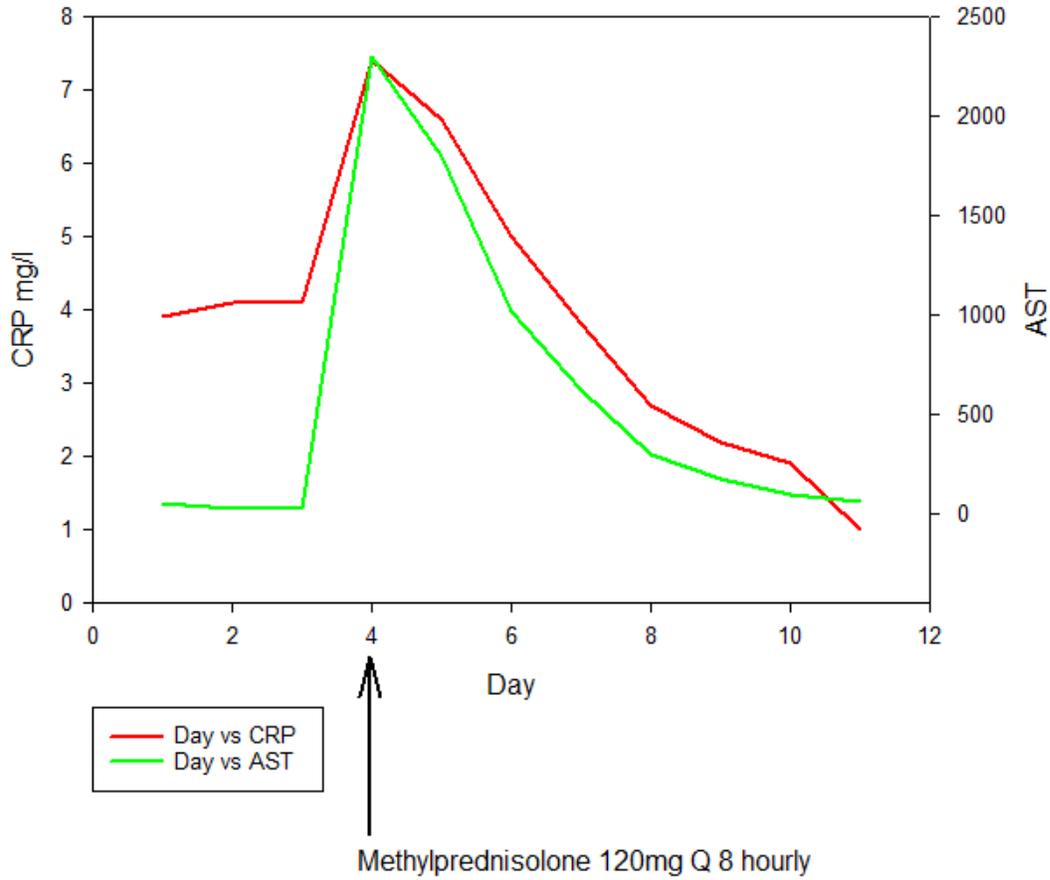


Figure 6. SARS-CoV-2 induced Macrophage Activation Syndrome (MAS) treated with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)



Scientific Rational for MATH+ 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 and macrophage activation resulting in a “cytokine storm.” [56,62,63,66-74]
- 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. [26,27,29,75-79]
- 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. [71] 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), Infectious Diseases Association of America (IDSA) amongst others. A very recent publication by the Society of Critical Care Medicine and authored one of the members of the Front Line COVID-19 Critical Care (FLCCC) 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.[31,80] 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. The initial phase of “oxygenation failure” is characterized by normal lung compliance, with poor recruitability and near normal lung water (as measured by transpulmonary thermodilution). This is the “L phenotype” as reported by Gattolini and colleagues. [81-84] Treating these patients 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.

Patients in whom the cytokine storm is not “dampened” will progress into the “H phenotype” characterized by poor lung compliance, severe oxygenation failure and PEEP recruitability (see Figure 7). Progression to this phase is exacerbated by ventilator induced lung injury (VILI). The histologic pattern of the “H Phenotype” is characterized by an acute fibrinous and organizing pneumonia (AFOP), with extensive intra-alveolar fibrin deposition called fibrin “balls” with absent hyaline membranes. Corticosteroids seem to be of little benefit in established AFOP. High dose methylprednisolone should be attempted in the “early phase” of AFOP, however many patients will progress to irreversible pulmonary fibrosis with prolonged ventilator dependency and ultimately death. [85,86]

It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on genetic heterogeneity, age, viral load, immunological and nutritional status, and comorbidities (see 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. Furthermore, Vitamin D insufficiency exacerbates the cytokine storm and likely increases the risk of death.

Finally, it is important to acknowledge that there is no known therapeutic intervention that has unequivocally been proven 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.

Front Line COVID-19 Critical Care Working Group

Figure 7. The consequences of “steroid” avoidance”. CT scan after 23 days of “supportive care” demonstrating the late fibroproliferative (irreversible) phase of COVID-19 lung disease (Image kindly provide by Dr. Pierre Kory, from NYC).



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