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. This is a very dynamic situation; therefore, we update the guideline as new information emerges. Please check the EVMS website for updated versions of this protocol.

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

MATH+
Hospital Treatment Protocol for COVID-19

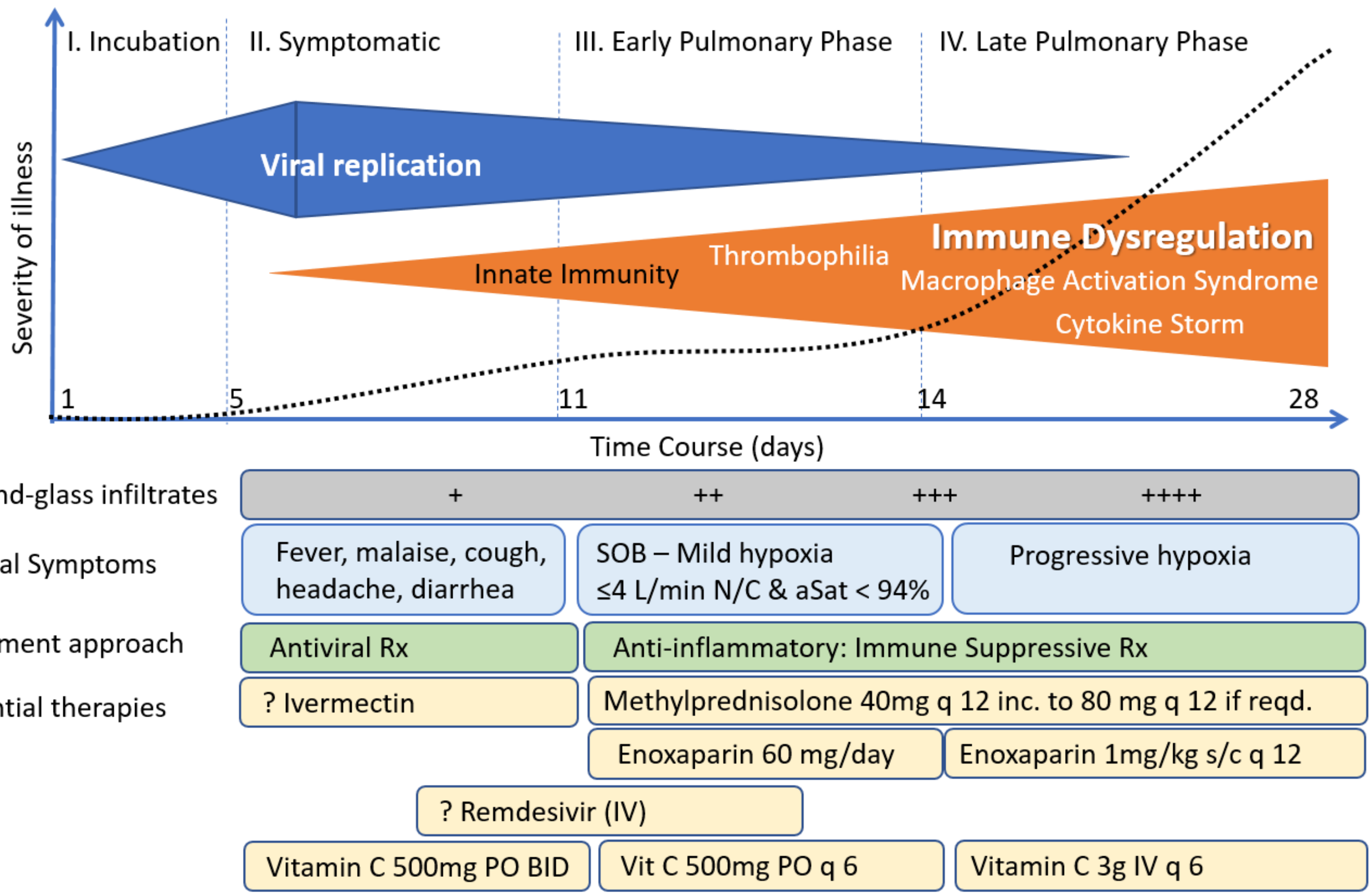
Intravenous **M**ethylprednisolone
High Dose Intravenous **A**scorbic Acid *(Vitamin C)*
Thiamine *(Vitamin B1)*
Full Dose Low Molecular Weight **H**eparin
+
Zinc, Vitamin D, Famotidine, Magnesium & Melatonin

FLCCC Working Group

Frontline Covid19 Critical Care Working Group
Covid19CriticalCare.com

FLCC website: https://covid19criticalcare.com/

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



THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL

Prophylaxis

While there is extremely limited data, the following "cocktail" may have a role in the prevention/mitigation of COVID-19 disease. This cocktail is cheap, safe, and widely available.

- Vitamin C 500 mg BID and Quercetin 250-500 mg BID [1-7]
- Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1 month, reduce the dose to 30-50 mg/day. [1,8-12]
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night [13-16]
- Vitamin D3 1000-4000 u/day [17-24]
- *Optional:* Famotidine 20-40mg/day [25]

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:* Ivermectin 150-200 ug/kg (single dose) [26-28]
- In symptomatic patients, monitoring with home pulse oximetry is recommended. Ambulatory desaturation < 94% should prompt hospital admission. [29]
- *Not recommended:* chloroquine and hydroxychloroquine. The use of these agents is extremely controversial. Notwithstanding, the retraction of the Lancet paper,[30] there is a paucity of data to support the use of these drugs. [31-35] It is possible that the efficacy of these drugs requires the co-administration of Zinc. [36,37]

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 [38-47] Consider increasing the dose to 1mg/kg q 12 hourly in those with a high D-Dimer or an increasing D-Dimer (see Xa monitoring below)
- Methylprednisolone 40 mg q 12 hourly ; increase to 80 mg q 12 hourly in patients with progressive symptoms and increasing CRP. [48-54]
- Famotidine 40 mg daily (20 mg in renal impairment)
- *Optional: Remdesivir,* 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [55,56] This agent has been reported to reduce time to recovery (based on an ordinal scale). [56] 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.

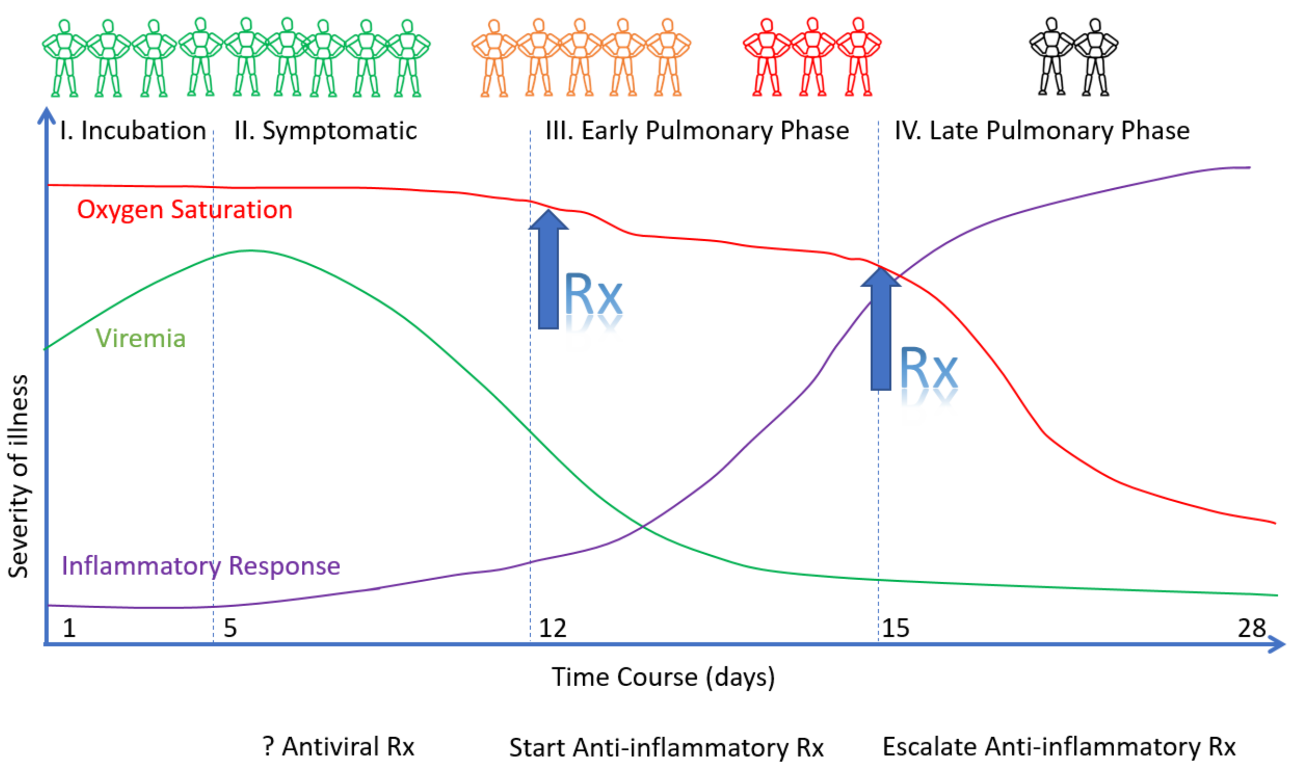
Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU):

Essential Treatment (dampening the STORM); MATH +

1. ***Methylprednisolone*** 80 mg loading dose then 40 mg 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. [48-54]
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). [57-65]
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). [38-47] Heparin is suggested with CrCl < 15 ml/min. Due to augmented renal clearance patients may have reduced anti-Xa activity despite standard dosages of LMWH.[66] We therefore recommend monitoring anti-Xa activity in underweight and obese patients, those with chronic renal failure and in those patients with an increasing D-dimer, aiming for an anti-Xa activity of 0.6-1.1 IU.ml.

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 40 mg daily (20 mg in renal impairment)
6. Vitamin D 2000-4000 u PO daily
7. Thiamine 200 mg IV q 12 hourly [67-71]
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). [72-74]
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). [75]
10. *Optional:* Simvastatin 80 mg/day. Of theoretical but unproven benefit. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [76] Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. In addition, statins decrease expression of PAI-1. Due to serious drug-drug interactions with drugs including amiodarone, amlodipine, erythromycin, *azithromycin,* telithromycin, verapamil, diltiazem, cyclosporin, HIV protease inhibitors, etc, atorvastatin 80 mg is preferred.
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. It should however be appreciated that despite the cytokine storm vasodilatory shock is distinctly uncommon in uncomplicated COVID-19 (not complicated by bacterial sepsis).

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 O_2 saturations ($ScvO_2$) in patents with low arterial O_2 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) [77,78]
    - 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_2O.
    - 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

- High dose corticosteroids; 120 -250 mg methylprednisolone q 6-8 hourly
- Plasma exchange [79-81]. Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy as well as in patients with severe MAS. Patients may require up to 5 exchanges. FFP is required for the exchange; giving back "good humors" appears to be more important than taking out "bad humors".
- In patients with a large dead-space ventilation i.e. high $PaCO_2$ despite adequate minute ventilation consider "Half-dose rTPA" to improve pulmonary microvascular blood flow; 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.[82,83]
- Siltuximab and Tocilizumab (IL-6 inhibitors).[84,85] These agents should only be considered once the above measures have failed.
- Convalescent serum; the role and timing of convalescent serum are uncertain. [86-89] COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [90]
- CVVH with cytokine absorbing/filtering filters [91] This treatment strategy appears to have a very limited role.
- Janus Kinase inhibitors downregulate cytokine expression and may have a role in this disease. [92-94]
- ?? ECMO < 60 yrs. and no severe comorbidities/organ failure [95]. 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 likely serve 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). [96,97]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and increasing CRP. [98]
- "*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

- On admission: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg.
- Daily: *CRP, Ferritin, D-Dimer and PCT*. CRP and Ferritin track disease severity closely (although ferritin tends to lag behind CRP). Early high CRP levels are closely associated with the degree of pulmonary involvement and the CT score. [99]
- Thromboelastogram (TEG) in patients with high D-dimer 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. [100,101]
- Monitor QTc interval if using azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients)
- No routine CT scans, follow CXR and chest ultrasound.
- ECHO as clinically indicated; Pts may 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 days) and the effect of reinitiation of this combination on the CRP profile.

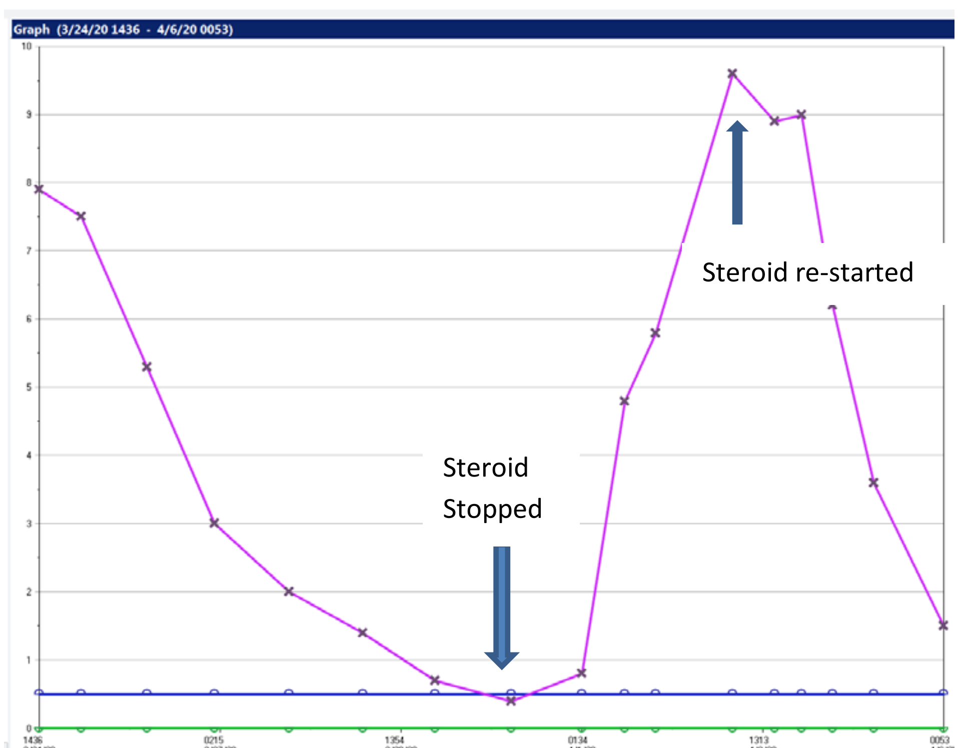


Figure 4.

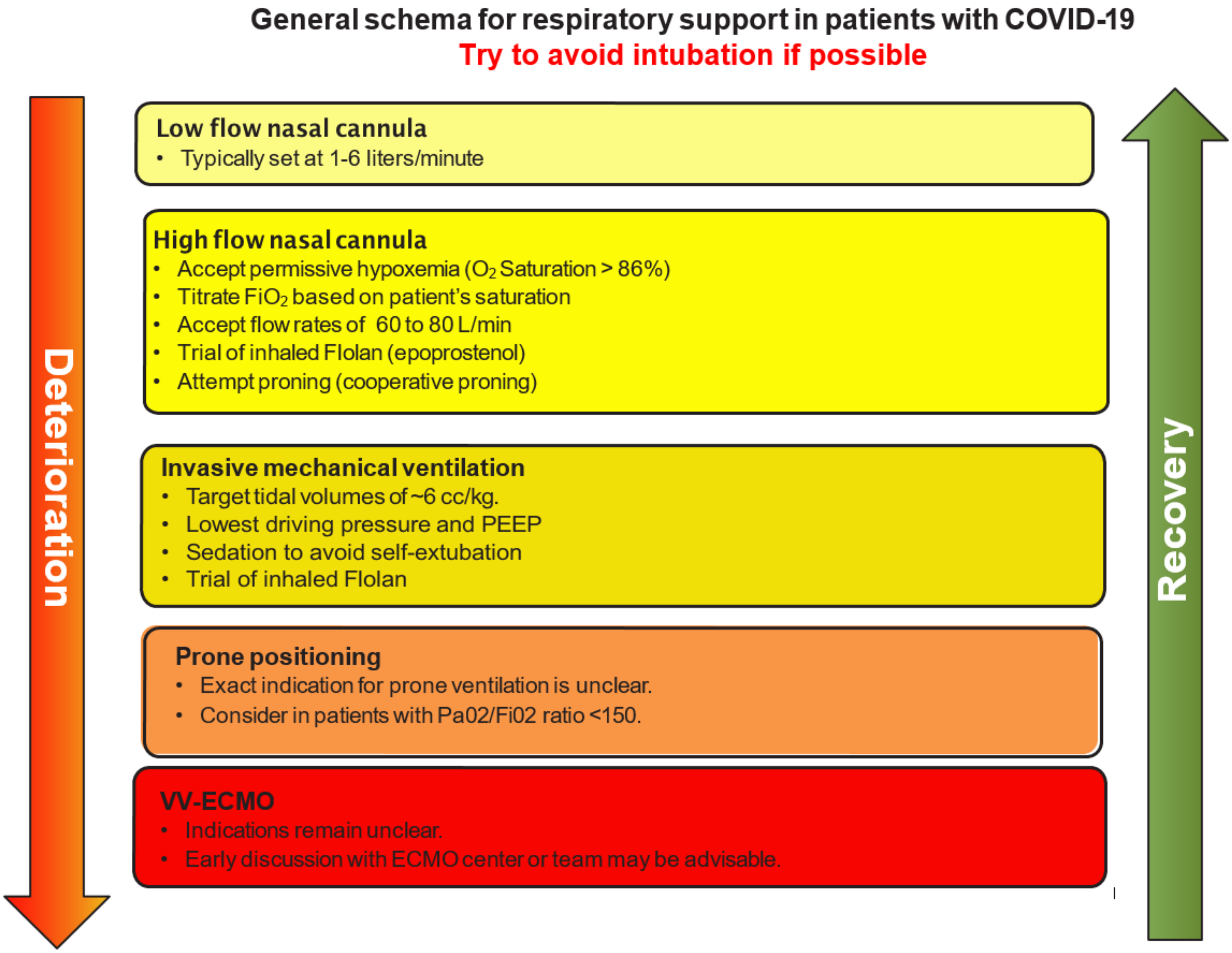
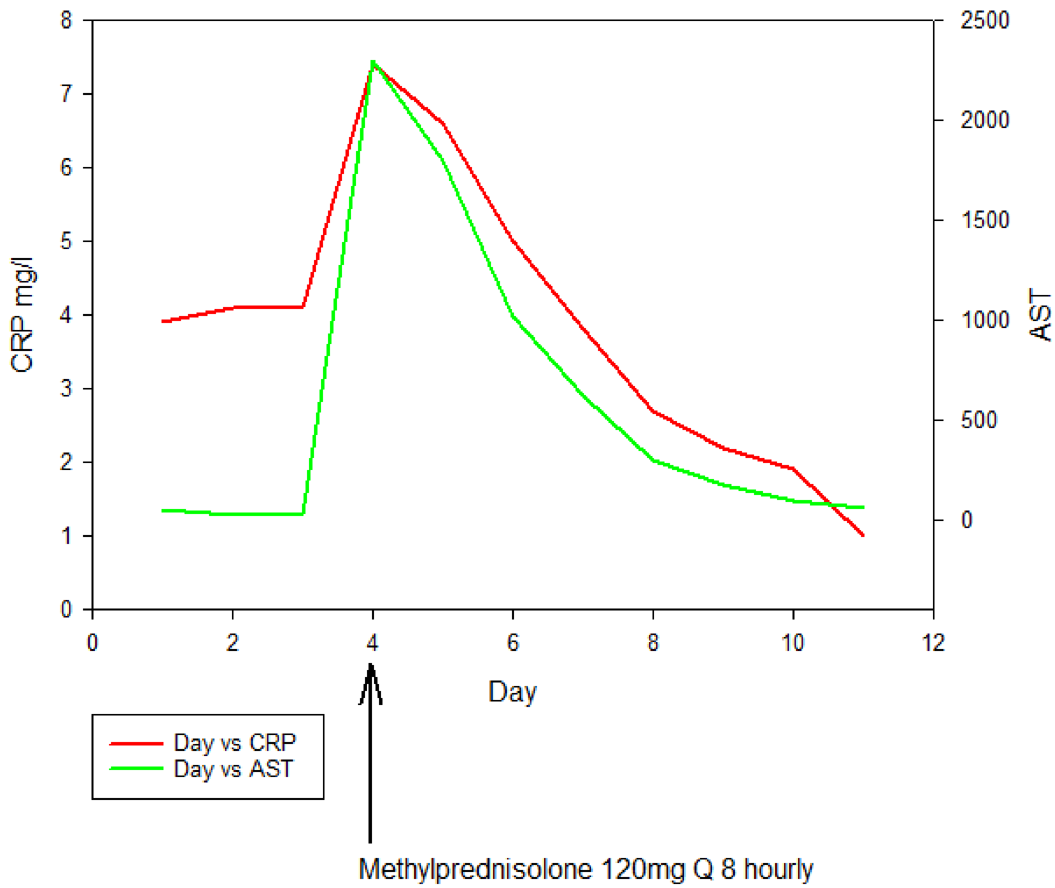

General schema for respiratory support in patients with COVID-19
Try to avoid intubation if possible
Deterioration
Recovery
Low flow nasal cannula
• Typically set at 1-6 liters/minute
High flow nasal cannula
• Accept permissive hypoxemia (O_2 Saturation > 86%)
• Titrate FiO_2 based on patient's saturation
• 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.

Figure 5. SARS-CoV-2 induced Macrophage Activation Syndrome (MAS) treated with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)



Key Concepts of the EVMS Treatment Protocol

This is a very complex disease; many of the mysteries are still unravelling. However, a number of concepts are key to the management of this "treatable disease." They include:

1. Patients transition through a number of different phases (clinical stages). The treatment of each phase is distinct ... this is critically important (see Figures 1 & 2).
2. As patients progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are twofold.
    a. Early treatment is ESSENTIAL to a good outcome (this is critical)
    b. Treatment in the late pulmonary phase may require escalation of the dose of corticosteroids, as well as the use of salvage methods (i.e. plasma exchange).
2. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on genetic heterogeneity, blood type, sex and androgen status, age, viral load, immunological and nutritional status, and co-morbidities (see Figure 6).[51,102-107] The phenotype at presentation likely determines the optimal approach to treatment.
3. COVID-19 is a treatable disease; it is inappropriate to limit therapy to "supportive care" alone. Furthermore, it is likely that there will not be a single "magic bullet" to treat 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.
4. The pulmonary phase is characterized by immune dysregulation, [85,92,94,96,97,105,108-116] a pulmonary microvascular injury (endothelialitis),[116-119] with activation of clotting and a pro-coagulant state together with the characteristics of an organizing pneumonia.
5. It should be noted that SARS-CoV-2 as compared to all other respiratory viruses, upregulates cytokines and chemokines while at the same time down regulating the expression of Interferon alpha (the hosts primary antiviral defence mechanism). [96,109] This factor is critical to understanding the treatment of COVID-19 organizing pneumonia. (see Figure 7).[109]
6. THIS is NOT ARDS (at least initially). The initial pulmonary phase neither looks like, smells like nor is ARDS.[120-122] The ground glass infiltrates are peripheral and patchy, and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS".[123] Extravascular lung water index (EVLWI) is normal or only slightly increased; this by definition excludes non-cardiogenic pulmonary edema (ARDS). Lung compliance is normal (this excludes ARDS). Patients are PEEP unresponsive. Treating patients as if they ARDS is a very dangerous approach. The hypoxia is due to severe ventilation/perfusion mismatch likely due to the microvascular narrowing, thrombosis and vasoplegia.

7. The core principles of the pulmonary phase (MATH+) is the use of anti-inflammatory agents to dampen the "cytokine storms" together with full anticoagulation to limit the microvascular and macrovascular clotting and supplemental oxygen to help overcome the hypoxia.

8. 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 8). 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.[107,124-127] 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.
9. The combination of steroids and ascorbic acid (vitamin C) is essential. Both have powerful synergistic anti-inflammatory actions. [58] Vitamin C protects the endothelium from oxidative injury.[59,128-130] Furthermore, vitamin C Increases the expression of interferon-alpha (this is critical) ([4] while corticosteroids (alone) decease expression of interferon-alpha. [131-134] It should however be noted that when corticosteroids are used in the pulmonary phase (and not in the viral replicative phase) they do not appear to increase viral shedding.
10. Notwithstanding the very important and impressive results of the Recovery-Dexamethasone study, methylprednisolone is the corticosteroid of choice for the pulmonary phase of COVID-19. This is based on pharmacokinetic data (better lung penetration),[135] genomic data specific for SARS-CoV-2,[136] and a long track record of successful use in inflammatory lung diseases.
11. For prophylaxis and treatment of the early symptomatic phase, we suggest the combination of Quercetin (a plant polyphenol), Vitamin C and Zinc. This is based on intriguing basic-science data, which indicates that:
    a. Zinc is essential for innate and adaptive immunity.[9] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[8]
    b. Quercetin has direct viricidal properties against a range of viruses, including SARS-CoV-2.[2,6] In addition, quercetin acts as a zinc ionophore. [137]
    c. Vitamin C improves the potency of Quercetin and its antiviral activity.[2]
12. It should also be noted that Vitamin D may be a very powerful prophylactic and treatment strategy against COVID-19. [17-24] Vitamin D deficiency explains, in part, the enormous geographic variation in mortality of this disease.

Figure 6. COVID-19 Subtypes of Infections (Phenotypes)

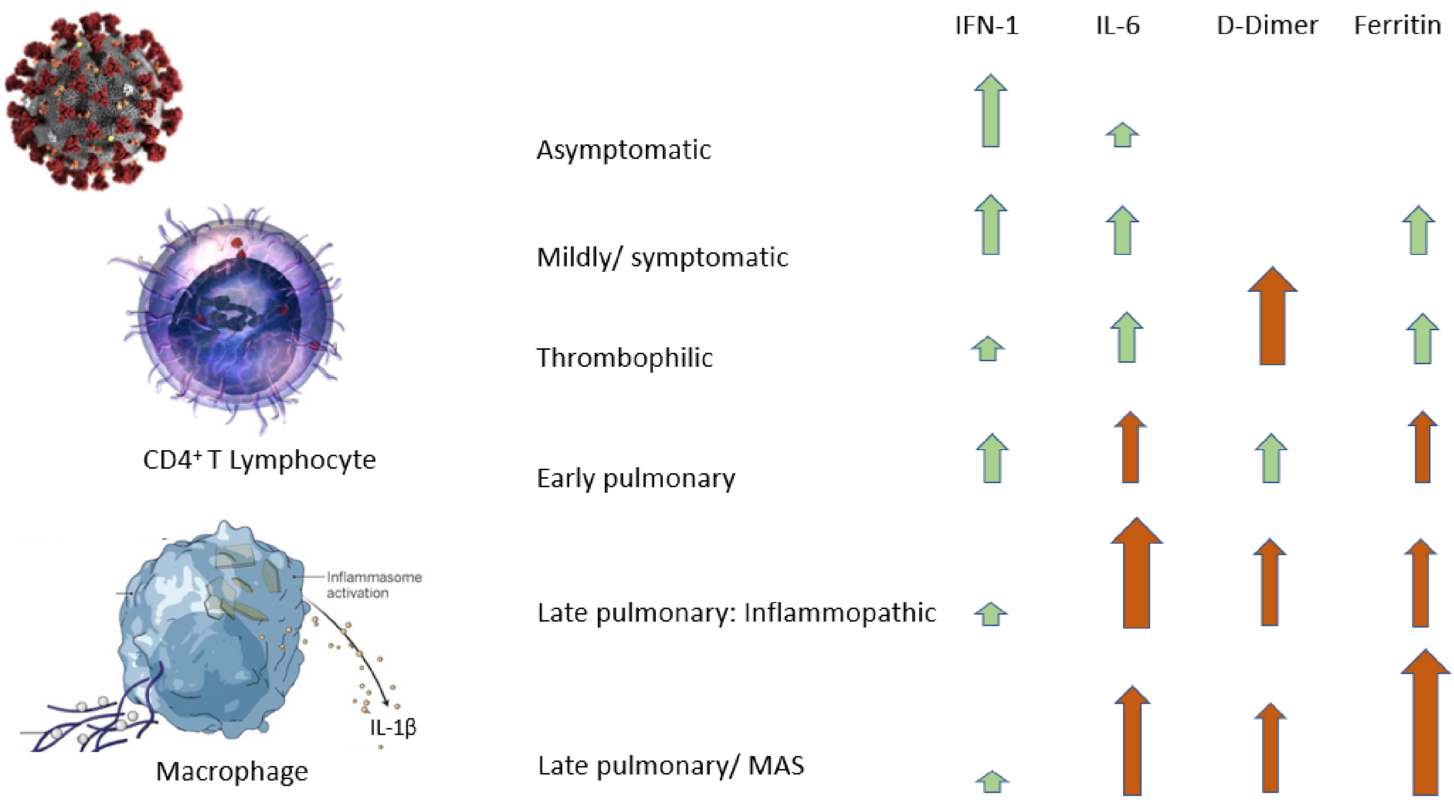
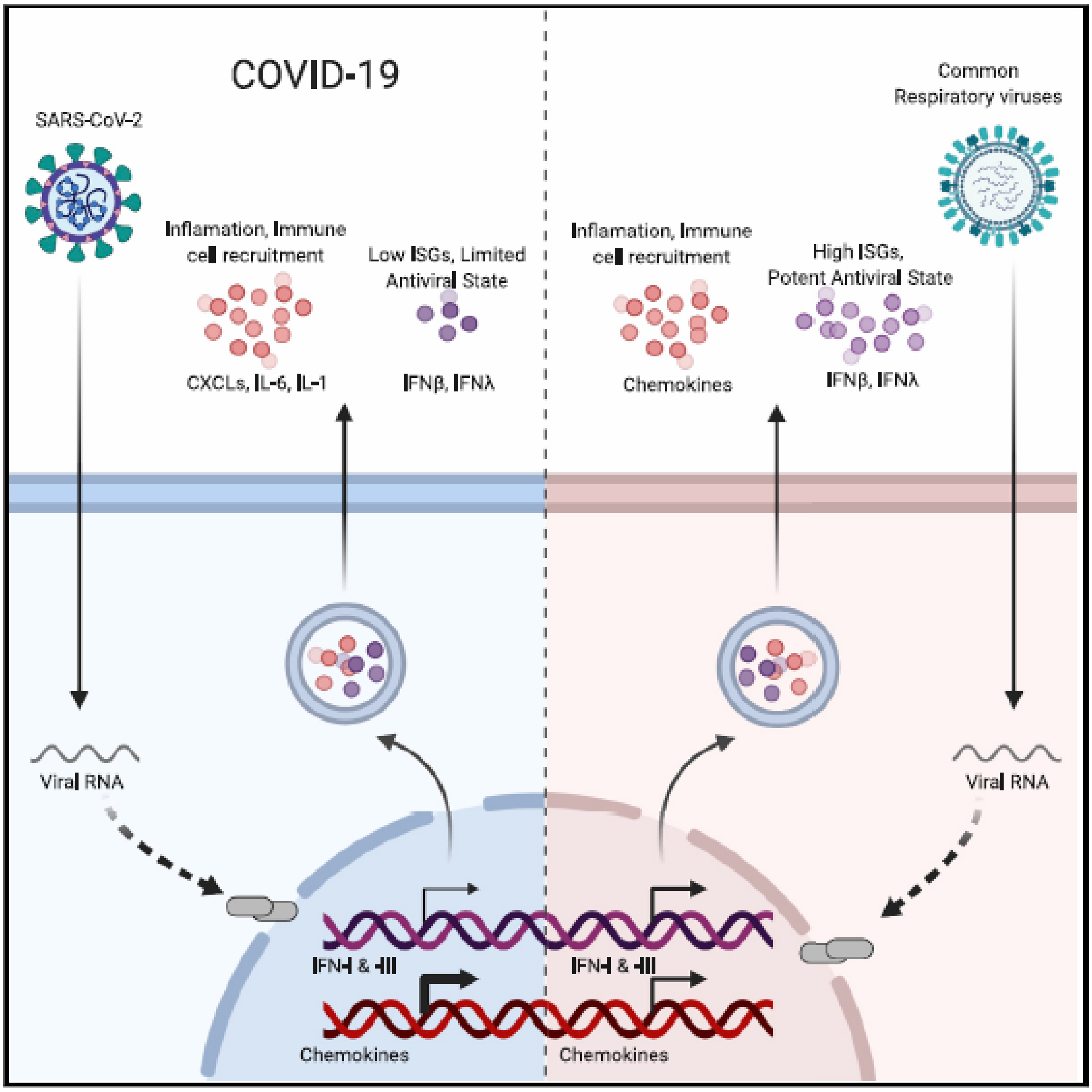


Figure 7. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. [109] Open Access Publication with permission.



Scientific Rationale for MATH+ Treatment Protocol (pulmonary phase)

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." [85,92,94,96,97,105,108,110-115]
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. Clotting activation may occur directly due to increased expression of Factor Xa as well as endothelial injury with the release of large aggregates of van Willebrand factor. These blood clots impair blood flow. [38-47,118,119,138,139]
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 longstanding 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 hospitalists and 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. [90,94] 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.

"If what you are doing ain't working, change what you are doing"- PEM

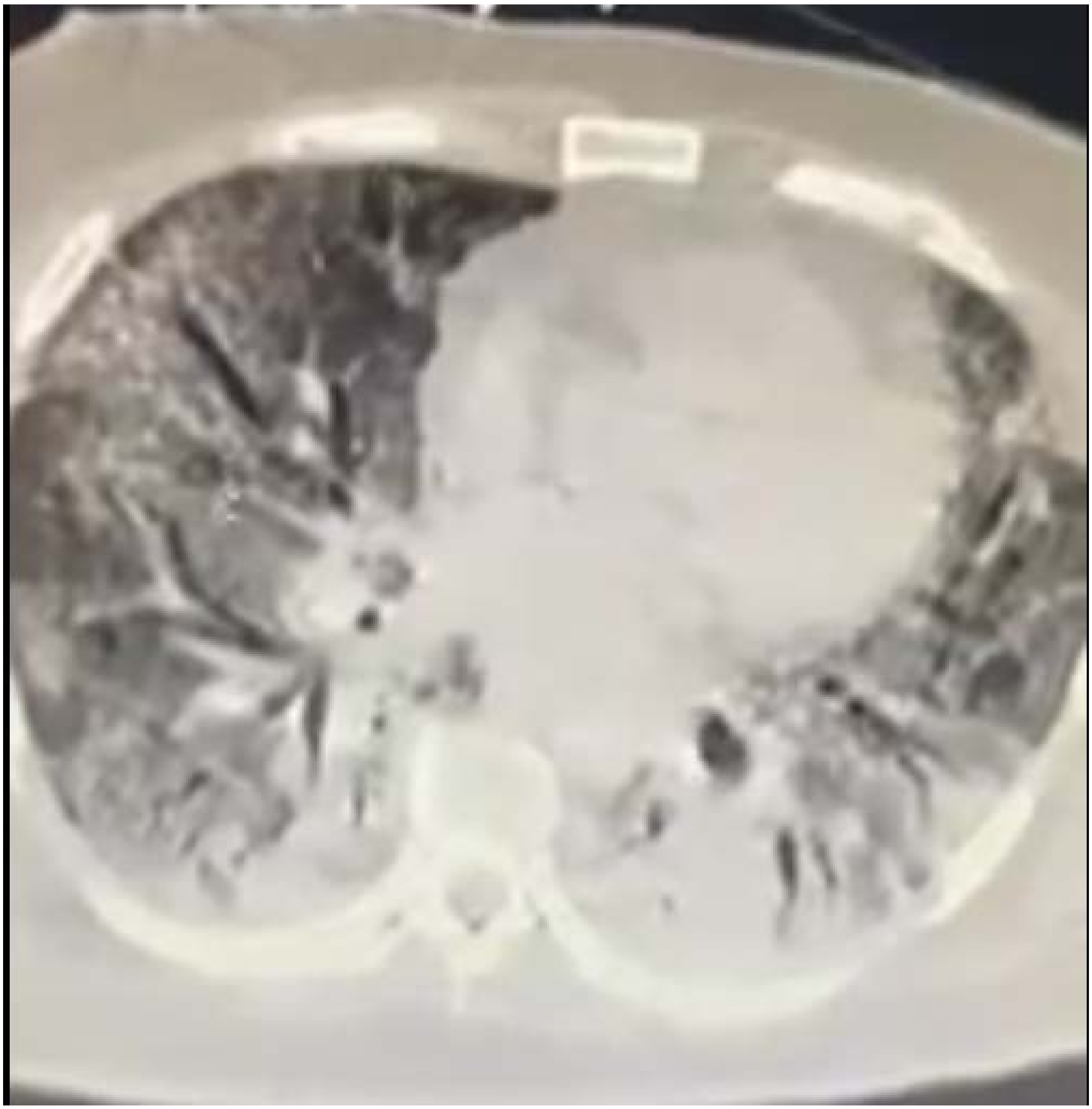
The systematic failure of critical care systems to adopt corticosteroid therapy resulted from the published recommendations against corticosteroids use by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), Infectious Diseases Association of America (IDSA) among 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.[48,140] 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 and led to excess deaths. The recently announced results of the RECOVERY-DEXAMETHASONE study provides definitive and unambiguous evidence of the lifesaving benefits of corticosteroids and strong validation of the MATH + protocol. The RECOVERY-DEXAMETHASONE study, randomized 2104 patients to receive dexamethasone 6 mg (equivalent to 32 mg methylprednisolone) once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomized to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021).

There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14). The results of this study STRONGLY support the EVMS protocol, which recommends the use of corticosteroids for the "pulmonary phase" of COVID-19. It should be noted that we would consider the non-titratable 'fixed" dose of dexamethasone used in the RECOVERY-DEXAMETHASONE study to be very low. Furthermore, as indicated above, we consider methylprednisolone to be the corticosteroid of choice for the treatment of COVID-19 pulmonary disease.

Our treatment protocol targeting the key pathologic processes has achieved near uniform success, *if begun within 6 hours* of a COVID-19 patients presenting with shortness of breath and/or arterial desaturation and requiring supplemental oxygen. If such early initiation of treatment could be systematically achieved, the need for mechanical ventilators and ICU beds will decrease dramatically. The systematic used of the MATH+ protocol in 2 hospital in the USA has reduced the hospital mortality from COVID-19 to approximately 3.5%

Front Line COVID-19 Critical Care Working Group

Figure 8. 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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