EVMS
MEDICAL GROUP

# EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

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This is our recommended approach to COVID-19 based on the best (and most recent) literature. 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

Disclaimer: The information provided in this protocol is primarily to provide information to physicians on a protocol that we found to be highly effective in damping down the hyper-inflammatory cytokine "storm" that is the cause of mortality and morbidity in COVID-19. Our guidance should only be used by medical professionals in formulating their approach to COVID-19. Patients should always consult with their physician before starting any medical treatment.

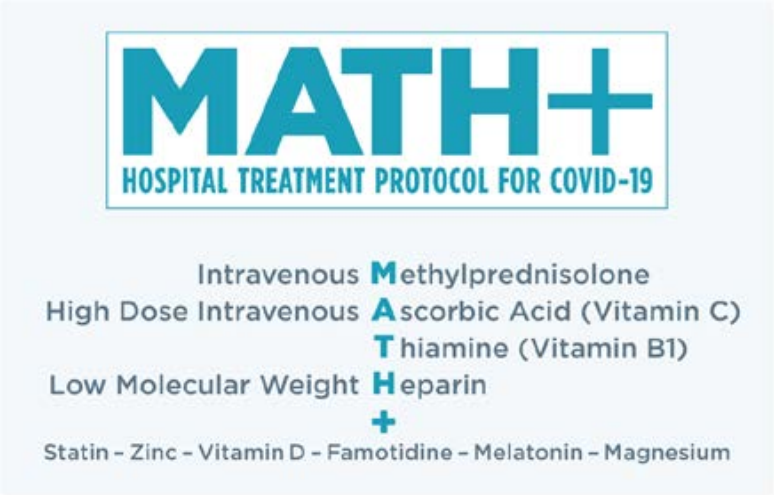


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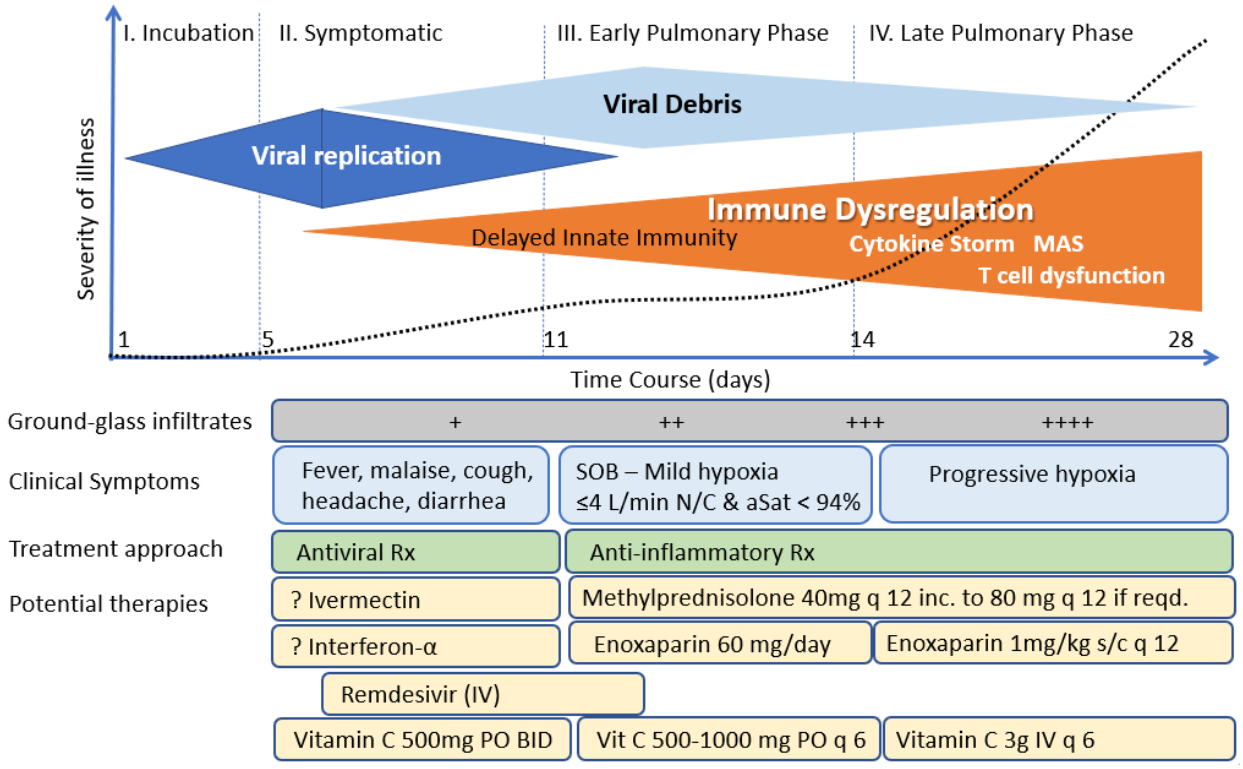
**Figure 1. The course of COVID-19 and General Approach to treatment**




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

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

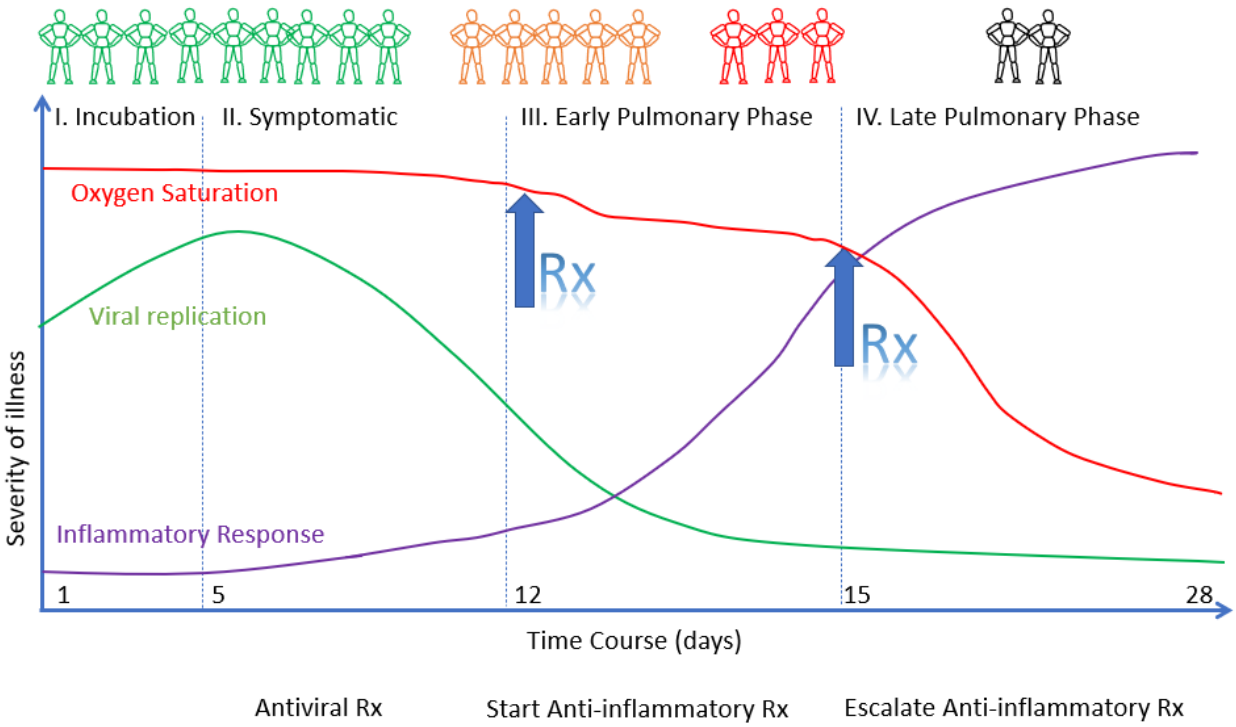


**Figure 3. Time course of laboratory tests for COVID-19**

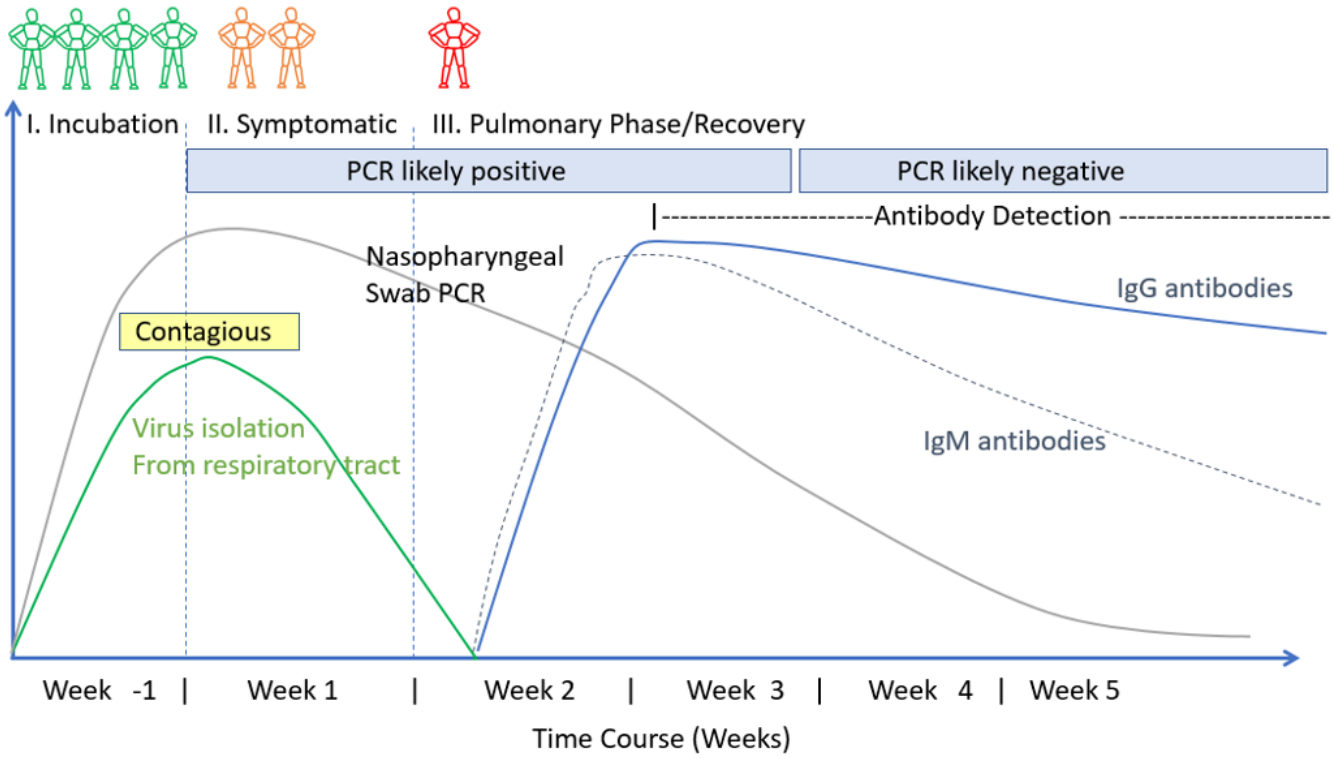
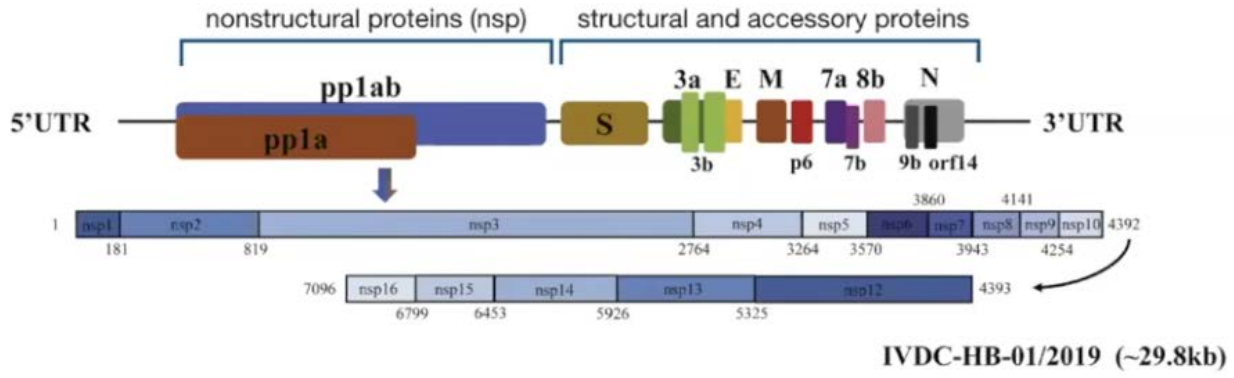



**Figure 4. SARS-Co-V-2 RNA genome**



***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 inexpensive, safe, and widely available. It should be noted that a recent publication suggests that melatonin my reduce the risk of COVID-19 infection, [1] while many papers suggest that Vitamin D deficiency increases the risk of infection and is associated with a significantly worse outcome. [2-14]

- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night [1,15-19]
- Vitamin D3 1000-3000 u/day. Note RDA (Recommended Daily Allowance) is 800-1000 u/day. The safe upper-dose daily limit is likely < 4000 u/day. [2-14,20]
- Vitamin C 500 mg BID (twice daily) and Quercetin 250 mg daily [10,11,21-30] Note that prolonged high dose quercetin has very rarely been associated with hypothyroidism. [31,32] Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored.
- Zinc 50-75 mg/day (elemental zinc). After 1 month, reduce the dose to 30-50 mg/day. [10,11,21,28,33-37]
- Famotidine 20-40 mg/day [38-41]
- *Optional/Experimental:* Interferon-α nasal spray for health care workers [42]
- *Optional:* Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561)

***Symptomatic patients at home*** **(for the duration of acute symptoms)**

- Vitamin C 500 mg BID and Quercetin 250-500 mg BID
- Zinc 75-100 mg/day (elemental zinc)
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 2000-4000 u/day
- ASA 81 -325 mg/day (unless contraindicated). ASA has antiinflammatory, antithrombotic, and antiviral effects.[43,44] Platelet activation may play a major role in propagating the prothrombotic state associated with COVID-19. [45]
- Famotidine 40 mg BID (reduce dose in patients with renal dysfunction) [38-41]
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved or chewed. Omega-3 fatty acids have anti-inflammatory properties and play an important role in the resolution of inflammation. In addition, omega-3 fatty acids may have antiviral properties. [10,46-49]
- *Optional:* Ivermectin 150-200 ug/kg orally (dose can be repeated on day 2) [50-55]
- *Optional:* Interferon-α/β s/c, nasal spray or inhalation. [42,56-58] It should be noted that Zinc potentiates the effects of interferon.[59,60]
- In symptomatic patients, monitoring with home pulse oximetry is recommended (due to asymptomatic hypoxia). The limitations of home pulse oximeters should be recognized, and validated devices are preferred.[61] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[61] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [62] The following guidance is suggested: [61]
    - Use the index or middle finger; avoid the toes or ear lobe
    - Only accept values associated with a strong pulse signal
    - Observe readings for 30-60 seconds to identify the most common value
    - Remove nail polish from the finger on which measurements are made
    - Warm cold extremities prior to measurement

- *Not recommended:* Hydroxychloroquine (HCQ). The use of HCQ is extremely controversial.[63] The best scientific evidence to date suggests that HCQ has no proven benefit for post exposure prophylaxis, for the early symptomatic phase and in hospitalized patients. [64-76] According to a recent press release of unpublished data from the double-blind placebo-controlled RECOVERY trial in the United Kingdom, HCQ has no mortality benefit in hospitalized patients with COVID-19. Considering the unique pharmacokinetics of HCQ, it is unlikely that HCQ would be of benefit in patients with COVID-19 infection (it takes 5-10 days to achieve adequate plasma and lung concentrations).[73,77-79] However, even in those patients with therapeutic blood levels HCQ failed to reduce viral shedding.[73] Furthermore, a recent in-vitro experiment demonstrated that chloroquine and hydroxychloroquine had no antiviral activity in lung cells infected with SARS-CoV-2. [80] It should be noted that the failed HCQ studies did not include Zinc, and it is possible that the efficacy of HCQ requires the co-administration of Zinc. [81,82] However, the benefit derived from the co-administration of Zinc may be due to the effects of zinc alone. Finally, it should be recognized that those studies which are widely promoted to support the use of HCQ are profoundly methodologically flawed.[83-86]
- *Not recommended:* Systemic or inhaled corticosteroids *(*budesonide). In the early symptomatic (viral replicative phase), corticosteroids may increase viral replication and disease severity.[87] An OpenSAFELY analysis in patients with COVID-19 demonstrated a higher risk of death in COPD and asthmatic patients using high dose ICS. [88] The role of ICS in the pulmonary phase is unclear as patients require systemic corticosteroids to dampen the cytokine storm, with ICS having little systemic effects.

***Mildly Symptomatic patients (on floor/ward in hospital):***

- Vitamin C 500-1000 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 20 000 – 60 000u single oral dose. Calcifediol 200 -500 ug is an alternative. [89] This should be followed by 20 000u D3 (or 200ug calcifediol) weekly until discharged from hospital. Calcifediol is more efficiently absorbed, achieves 1,25 OH vitamin D levels quicker and is three times more potent than vitamin D3. [90,91] However, it is important to note that the optimal dose of vitamin D in the acute setting is unknown.[92,93] Very high doses may paradoxically block the vitamin D receptor.
- Enoxaparin 60 mg daily [55,94-107] 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 and then 125mg q 12 hourly in patients with progressive symptoms and increasing CRP. There is now overwhelming and irrefutable evidence that corticosteroids reduce the risk of death in patients with the pulmonary phase of COVID-19 i.e those requiring supplemental oxygen or higher levels of support. [108-120] The role of inhaled corticosteroids (budesonide) is unclear and appears to be rather limited.
- Famotidine 40 mg BID (20 -40 mg/day in renal impairment). [38-41]
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily.
- *Optional: Ivermectin 150-200 ug/kg (dose can be repeated on day 2)* [50-55]
- *Optional:* Remdesivir, 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [121,122] This agent has been reported to reduce time to recovery (based on an ordinal scale) in patients NOT REQUIRING OXYGEN (i.e. not in pulmonary phase). [122,123] The benefit of this agent on patient centered outcomes is unclear. [124,125]

- *Optional:* Interferon-α/β s/c, nasal spray or inhalation. [42,56-58] The late administration of interferon is not likely to be effective.[126]
- 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.
- T/f EARLY to the ICU for increasing respiratory signs/symptoms, increasing oxygen requirements and arterial desaturation.

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

**Essential Treatment (dampening the STORM); MATH + [127]**

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 125mg q 12 hourly), then titrate down as appropriate. [108-120] Pulse methylprednisolone 250 -500mg mg/day may be required.[118] As depicted in Table 1, methylprednisolone is the corticosteroid of choice.
2. ***Ascorbic acid (Vitamin C***) 3g IV q 6 hourly for at least 7 days and/or until transferred out of ICU. [25,128-138]. Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport and it is difficult to achieve adequate levels with PO administration. However, if IV Vitamin C is not available, attempts should be made to administer PO vitamin C at a dose of 1g every 4-6 hours.
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). There is now good evidence that high intensity anticoagulation reduces mortality of hospitalized patients with COVID-19. [94,96,97,99-107,139] 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.[140] 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 and the requirement for supplemental oxygen 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 5).

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

4. Melatonin 6-12 mg at night (the optimal dose is unknown).
5. Famotidine 40 mg BID (20-40 mg/day in renal impairment) [38-41]
6. Vitamin D3 20 000 – 60 000u single oral dose. Calcifediol 200 -500 ug is an alternative. This should be followed by 20 000u D3 (or 200ug calcifediol) weekly until discharged from hospital.
7. Thiamine 200 mg IV q 12 hourly [141-146] Thiamine may play a role in dampening the cytokine storm. [142]
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). [147-149]
9. Atorvastatin 80 mg/day. Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. In addition, statins decrease expression of PAI-1. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [150] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[151-154] Due to numerous drug-drug interactions simvastatin should be avoided.
10. *Optional:* Vascepa, Lovaza or DHA/EPA 4g day (see above).
11. *Optional:* Remdesivir. The role of this agent in patients with more advanced pulmonary involvement appears to be very limited. [122]

12. *Not recommended:* The role of azithromycin in the treatment of COVID-19 is controversial. The best information to date suggests that azithromycin is of no benefit.[155,156]
13. 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 and T cell dysfunction) secondary bacterial and fungal infection is not uncommon. [157]
14. 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.

**Table 1: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone- Number Need to Treat (NNT)**

| PUBLISHED RCT's/COHORT STUDIES OF CORTICOSTEROID THERAPY IN COVID-19 | | ABSOLUTE DIFFERENCE IN MORTALITY RATE (Rx Group vs. Control Group) | ESTIMATED NUMBER NEEDED TO TREAT TO SAVE ONE LIFE |
|---|---|---|---|
| METHYLPREDNISONE - HOSPITAL PATIENTS (Edalatifard et al, Italy) | | 5.9% vs. 42.9% | 2.7 |
| METHYLPREDNISONE - ICU PATIENTS (Confalonieri et al, Italy) | | 7.2% vs. 23.3% | 6.2 |
| METHLPREDNISONE - HOSPITAL PATIENTS, (Fadel et al, USA) | | 13.6% vs. 26.3% | 7.8 |
| METHYLPREDNISONE- ARDS PATIENTS (Wu C et al - China) | | 46.0% vs.61.8% | 6.3 |
| METHYLPREDNISONE - Pts on oxygen - (Fernandez-Cruz, Spain) | | 13.9% vs. 23.9% | 10.0 |
| CoDEX – DEXAMETHASONE – MECHANICAL VENTILATION | | 56.3% vs. 61.5% | 19.2 |
| RECOVERY TRIAL (DEXAMATHASONE) | PTS ON OXYGEN | 23.3% vs. 26.2% | 28.6 |
| RECOVERY TRIAL (DEXAMATHASONE) | PTS ON MV | 29.3% vs. 41.4% | 8.4 |
| HYDROCORTISONE-CAPE-COVID - ICU Patients (Dequin et al France) | | 14.7% vs. 27.4% | 7.9 |
| HYDROCORTISONE - REMAP-CAP - ICU patients | | 28% vs. 33% | 20.0 |

15. Early norepinephrine for hypotension. It should however be appreciated that despite the cytokine storm, vasodilatory shock is distinctly uncommon in uncomplicated COVID-19 (when not complicated by bacterial sepsis). This appears to be due to the fact that TNF-α which is "necessary" for vasodilatory shock is only minimally elevated.
16. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible,*** (see Figure 6)
    - 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) [158,159]
    - 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.

17. **Salvage Treatments**
    - High dose bolus corticosteroids; 250-500 mg/day methylprednisolone [116,118]
    - Plasma exchange [160-166]. 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.[167,168]

***Salvage treatments of unproven benefit.***

- Siltuximab and Tocilizumab (IL-6 inhibitors).[169,170] The results of the Roche™ tocilizumab study were recently published as a Preprint. [171] In this study tocilizumab did not improve clinical status or mortality at day 28 as compared to placebo. It should be noted that Il-6 inhibitors may increase the risk of opportunistic infections. [172] IL-6 is required for a normal antibody response.
- Convalescent serum: the role and timing of convalescent serum are uncertain. [173-176] COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [177] Furthermore, giving antibodies directed against SARS-CoV-2 appears pointless when the virus is DEAD.
- Janus Kinase inhibitors downregulate cytokine expression and may have a role in this disease. [178-180]

- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [181-184] It should however be recognized that unlike all the medications in the MATH+ protocol, pirfenidone and nintedanib have complex side-effects and drug interactions and should be prescribed by pulmonary physicians who have experience with these drugs.
- CVVH with cytokine absorbing/filtering filters [185] This treatment strategy appears to have a very limited role.
- ECMO [186,187]. 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.

18. **Treatment of Macrophage Activation Syndrome (MAS)**
    - A sub-group of patients will develop MAS, particularly those patients with severe COVID-19 disease.[188] While the pathophysiology of MAS in the setting of COVID-19 is unclear this appears to be driven by SARS-CoV-2 induced inflammasome activation and increased IL-18 production as well as increased GM-CSF and INFγ production. [189-192] The role of IL-1 and IL-6 in the pathogenesis of MAS is unclear.
    - A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multi-system organ failure.[193]
    - "*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 7). Ferritin should decrease by at least 15% before weaning corticosteroids.
    - Consider plasma exchange.
    - The role of inhibition of IL-1 (Anakinra) and IFNγ (emapalumab) is unclear (NCT04324021).

19. **Monitoring**
    - On admission: Procalcitonin (PCT), CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic marker. A PCT is essential to rule out coexisting bacterial pneumonia.
    - 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. [194]
    - 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. [195,196]
    - Monitor QTc interval if using azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients) Avoid azithromycin with other QTc prolonging drugs. [197]
    - No routine CT scans, follow CXR and chest ultrasound.
    - ECHO as clinically indicated; Pts may develop a severe "septic" cardiomyopathy.

20. **Post ICU management**
    a. Enoxaparin 40-60 mg s/c daily
    b. Methylprednisolone 40 mg day, then wean slowly (follow CRP)
    c. Vitamin C 500 mg PO BID
    d. Melatonin 3-6 mg at night
    e. Vascepa, Lovaza or DHA/EPA 4g day (important for resolution of inflammation)

21. **Post Hospital Discharge management**
    a. Patients have an increased risk of thromboembolic events post-discharge. [198] Extended thromboprophylaxis (? with a DOAC) should be considered in high risk patients. Risk factors include:[199]
        i. Increased D dimer (> 2 times ULN)
        ii. Increased CRP (> 2 times ULN) [200]
        iii. Age > 60
        iv. Prolonged immobilization
    b. The *post-COVID-19 syndrome*, is characterized by prolonged malaise, headaches, generalized fatigue, painful joints, dyspnea, chest pain and cognitive dysfunction. [201-203] Approximately 10% of patients experience prolonged illness after Covid-19. The p[ost-COVID-19 syndrome may persistent for months after the acute infection and almost half of patients report reduced quality of life. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[188] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [204] Similar to patients who have recovered from septic shock, [205] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the post-COVID-19 syndrome. Consequently, A CRP should be measured prior to discharge and a tapering course of corticosteroids should be considered in those with an elevated CRP. It should be noted that much like omega-3 fatty acids corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4.[206] Other interventions that should be considered include:
        i. Vascepa, Lovaza or DHA/EPA 4g day; important for resolution of inflammation by inducing resolvin production. [48,49]
        ii. Atorvastatin 40mg daily (increase resolvin synthesis) [207]
        iii. Continue melatonin for its antioxidant properties and stabilization of the circadian rhythms.
        iv. Multivitamin with adequate vitamin D.
    c. *Post-COVID-19 pulmonary fibrosis.* An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [181-184] however additional data is required before this therapy can be more generally recommended.

**Figure 5. Premature discontinuation of corticosteroids and IV vitamin C (after 4 day) and the effect of reinitiation of this combination on the CRP profile.**

**Figure 6.**

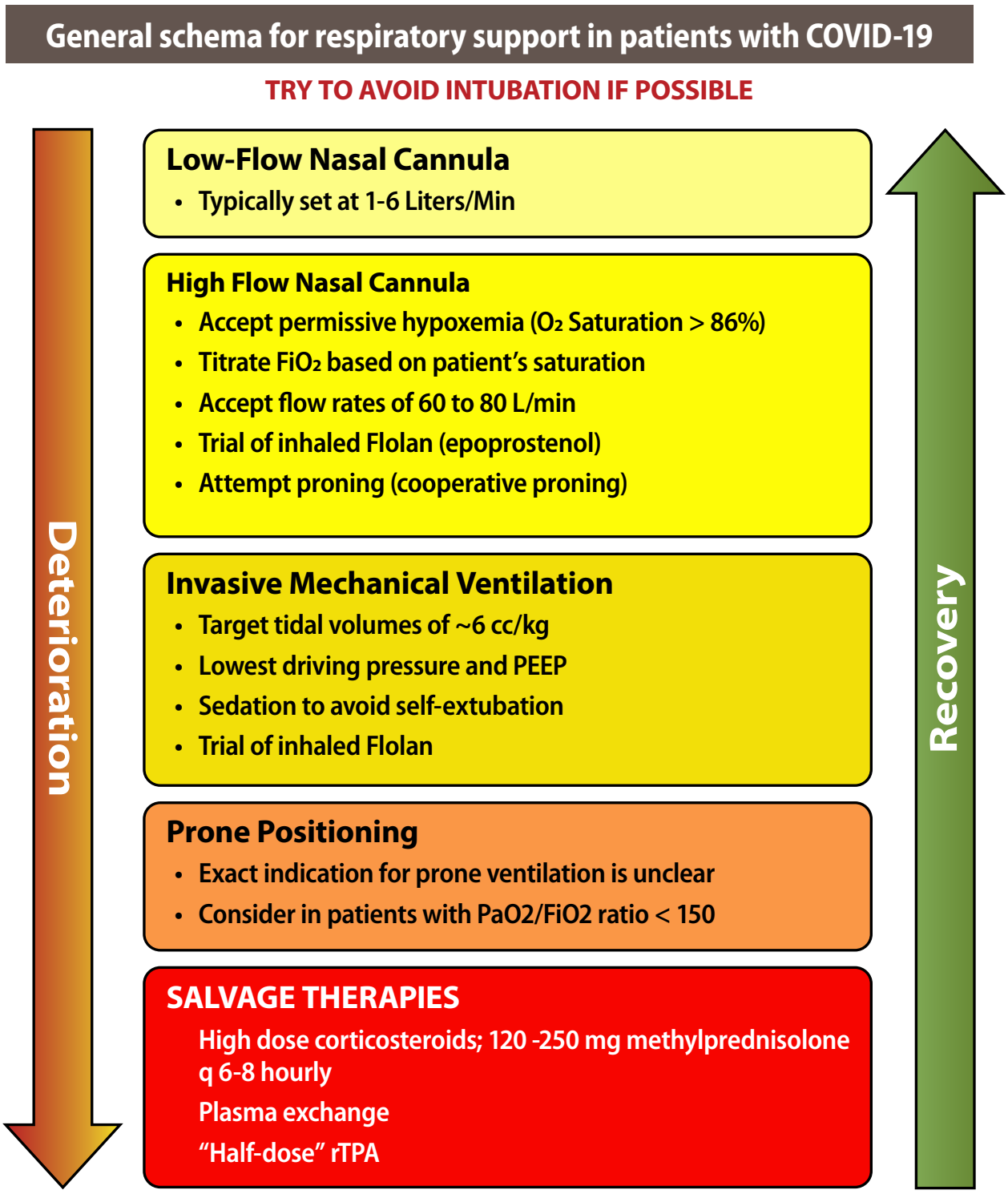
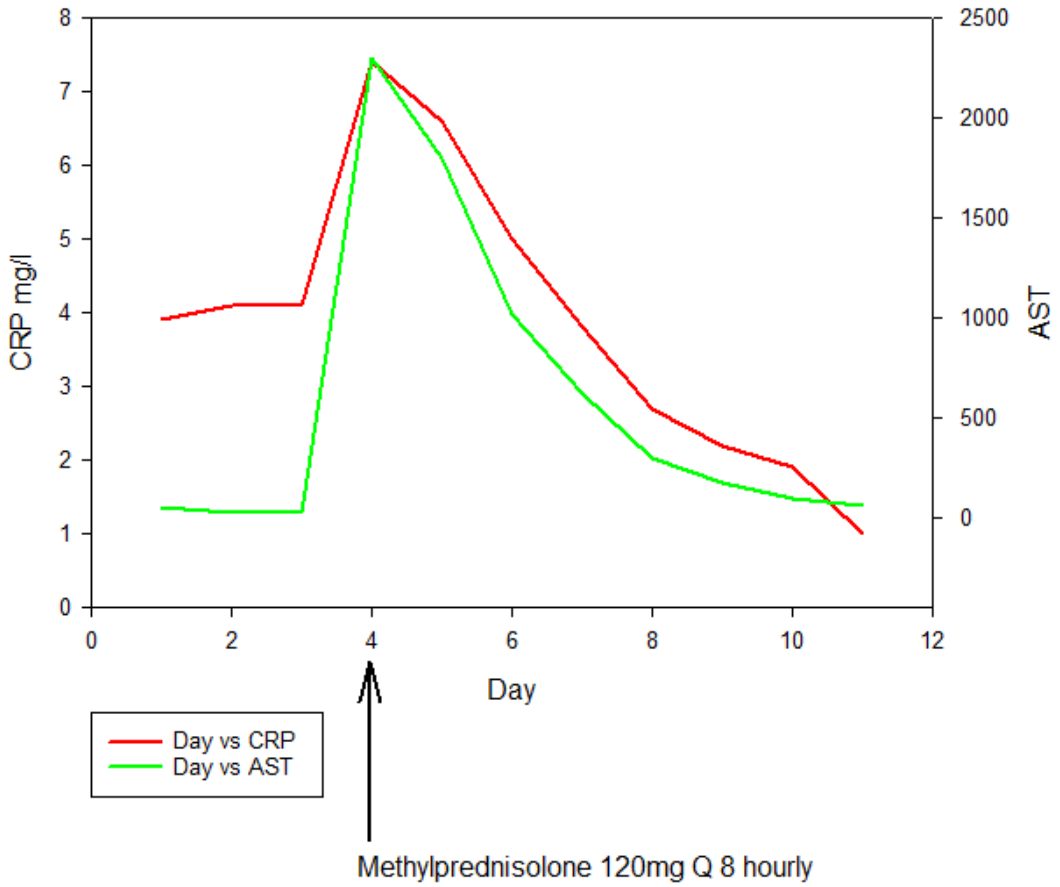

General schema for respiratory support in patients with COVID-19
TRY TO AVOID INTUBATION IF POSSIBLE
Deterioration
Recovery
Low-Flow Nasal Cannula
• Typically set at 1-6 Liters/Min
High Flow Nasal Cannula
• Accept permissive hypoxemia ($O_2$ Saturation > 86%)
• Titrate $FiO_2$ based on patient's saturation
• 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 PaO2/FiO2 ratio < 150
SALVAGE THERAPIES
High dose corticosteroids; 120 -250 mg methylprednisolone q 6-8 hourly
Plasma exchange
"Half-dose" rTPA

**Figure 7. 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

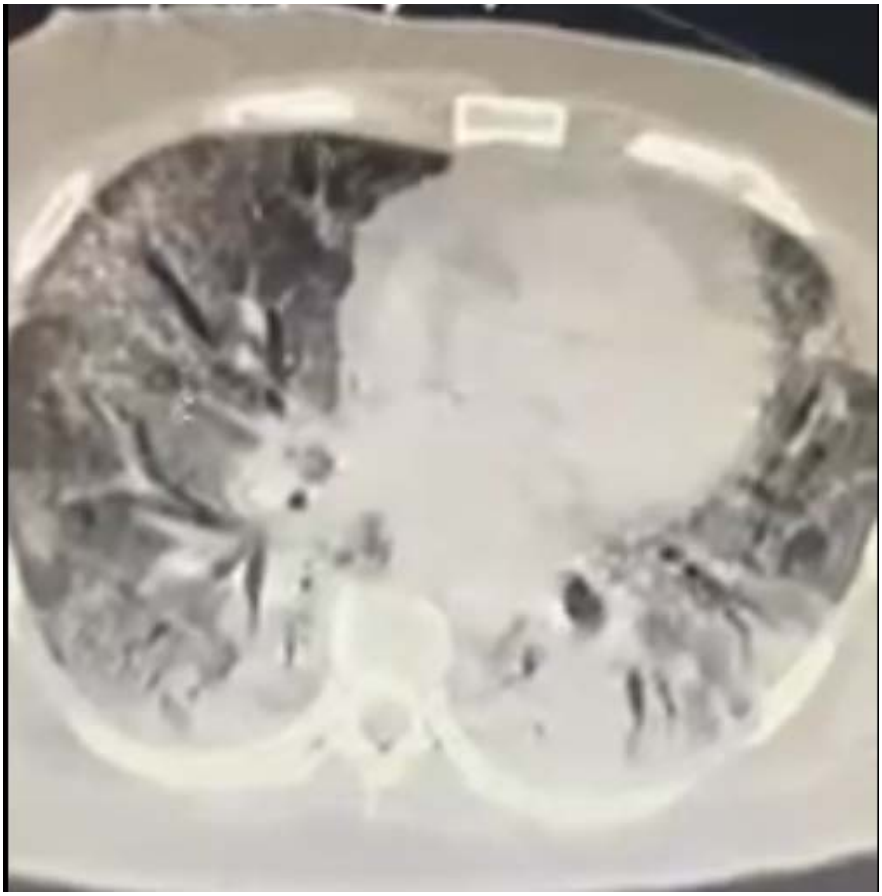
This is a very complex disease; many of the mysteries are still unravelling. However, a number of concepts are key to the management of this "treatable disease; they include.

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. Antiviral therapy is likely to be effective only during the viral replicative phase whereas anti-inflammatory therapy is expected to be effective during the pulmonary phase and possibly the post-COVID-19 phase. While Remdesivir is a non-specific antiviral agent that targets RNA viruses, it is likely that agents specifically designed to target SARS-CoV-2 will be developed.
3. The SARS-CoV-2 PCR remains positive for at least 2 weeks following detection of whole virus (by culture, See figure 3). Patients who progress to the pulmonary phase are usually PCR positive despite cessation of viral replication (and are therefore less likely to be infectious).
4. Due to the imperfect sensitivity of the PCR test as many as 20% of patients who progress to the pulmonary phase will be PCR negative (even on repeat testing). At symptom onset PCR will be positive in approximately 60% of patients; maximal positivity rate is on day 8 (post infection) when 80% of patients will be positive (see Figure3). [208]
5. Symptomatic patients are likely to be infectious during a narrow window starting 2-3 days before the onset of symptoms and to up to 6 days after the onset of symptoms (see Figure 3).[209]
6. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, genetic heterogeneity mutations and polymorphisms, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[111,210-219] The phenotype at presentation determines the prognosis and impacts the optimal approach to treatment.
7. The pulmonary phase is characterized by immune dysregulation, [170,178,180,188,191,192,213,220-228] a pulmonary microvascular injury (vasculopathy),[188,228-231] with activation of clotting and a pro-coagulant state together with the characteristics of an organizing pneumonia. [232,233]
8. Endothelial damage and an imbalance of both innate and adaptive immune responses, with aberrant macrophage activation, plays a central role in the pathogenesis of the severe COVID-19 Disease. [188]
9. As patients, progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are twofold.
    a. Early treatment (of the pulmonary phase) is ESSENTIAL to a good outcome.
    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). However, patients who present in the late pulmonary phase may have progressed to the irreversible pulmonary fibroproliferative phase (see Figure 8).
10. The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to "supportive care" alone. Furthermore, it is unlikely that there will be a single "silver bullet" to treat severe COVID-19 disease. Rather, patients will require treatment with multiple drugs/ interventions that have synergistic and overlapping biological effects. Repurposed FDA approved drugs that are safe, inexpensive, and "readily" available are likely to have a major therapeutic effect on this disease. The impact of COVID-19 on middle- and low-income countries is enormous; these countries are not able to afford expensive propriety "designer" molecules.
11. The radiographic and pathological finding of COVID-19 lung disease are characteristic of a secondary organizing pneumonia (and not ARDS). [232,234,235]

12. THIS is NOT ARDS (at least initially). The initial pulmonary phase neither looks like, smells like nor is ARDS.[236-238] The ground glass infiltrates are peripheral and patchy, [234] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS".[239] 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.
13. 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.
14. The pulmonary phase of COVID-19 is characterized by PROLONGED immune dysregulation that may last weeks or even months. The early and abrupt termination of anti-inflammatory agents will likely result in rebound inflammation (see Figure 5).[240]
15. 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). [131,155] Low innate antiviral defenses and high pro-inflammatory mediators contribute to ongoing and progressive lung injury.
16. 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 or minimal hyaline membranes.[215,235,241-243] 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.
17. An unknown percentage of patients with COVID-19 present with "silent hypoxia" with a blunted respiratory response. This phenomenon may be related to involvement of chemoreceptors of the carotid bodies and/or brain stem dysfunction,[244,245] and necessitates pulse oximetry in symptomatic patients managed at home (as discussed above).
18. It should be recognized that LWMH has non-anticoagulant properties that are likely beneficial in patients with COVID-19, these include anti-inflammatory effects and inhibition of histones.[246] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[247,248] as well as viral replication [55,95]. Most importantly LWWH inhibits heparanase (HPSE).[249] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[249] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [250]
19. Due to the ease of administration, greater anti-Xa activity and better safety profile we prefer low molecular weight heparin (LMWH) to unfractionated heparin (UFH).
20. The combination of steroids and ascorbic acid (vitamin C) is essential. Both have powerful synergistic anti-inflammatory actions. [129,137] Vitamin C protects the endothelium from oxidative injury.[130,251-253] Furthermore, vitamin C Increases the expression of interferon-alpha [24] while corticosteroids (alone) decease expression of this important protein. [254-257] It should 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 or decrease the production of type specific antibodies. [113,258] It is likely that heparin (LMWH) acts synergistically with corticosteroids and vitamin C to protect the endothelium and treat the endothelialitis of severe COVID-19 disease.
21. 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),[259] genomic data specific for SARS-CoV-2,[260] and a long track record of successful use in inflammatory lung diseases.

22. 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.[34] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[33]
    b. Quercetin has direct viricidal properties against a range of viruses, including SARS-CoV-2. [22,27,30] In addition, quercetin acts as a zinc ionophore. [261]
    c. Vitamin C improves the potency of Quercetin and has antiviral activity.[22]
23. It should also be noted that Vitamin D may be a very powerful prophylactic and treatment strategy against COVID-19. [2-9] Vitamin D deficiency explains, in part, the enormous geographic variation in mortality of this disease. [4,262]

**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).**



## 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 the lungs as well as other organs including the heart and bone marrow. It is now widely accepted that SARS-CoV-2 causes aberrant T lymphocyte and macrophage activation resulting in a "cytokine storm." [170,178,180,191,192,213,220,222-227] In addition, post-mortem examination has demonstrated features of the "macrophage activation syndrome", with hemophagocytosis and a hemophagocytic lymphohistiocytosis-like disorder.[188]
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.[45] These blood clots impair blood flow. [96,97,99-107,230,231,263,264] It should be noted that the thrombotic microangiopathy appears to target predominantly the pulmonary and cerebral circulation. [188]
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 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. [177,180,188,245] Autopsy studies have demonstrated minimal viral cytopathic effects.[188,245] 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 (early in this pandemic) resulted from the published recommendations against corticosteroids use by the World Health Organization (as recent as May 27th 2020) [265,266]. This recommendation was then perpetuated by the Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), Infectious Diseases Association of America (IDSA) amongst others. A publication 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.[108,267] 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 published results of the RECOVERY-DEXAMETHASONE study provide definitive and unambiguous evidence of the lifesaving benefits of corticosteroids and strong validation of the MATH + protocol. It should be recognized that corticosteroids are the only therapy proven to reduce the mortality in patients with COVID-19.[125] 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.[87] 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/MATH+ 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. The benefit of methylprednisolone in improving respiratory function, ventilator dependency and mortality has been confirmed in a number of observational studies, [109,110,116,258,268-270] as well as a randomized controlled study.[118] It should be recognized that the mortality benefit with methylprednisolone was not replicated in a recent Brazilian RCT. [240] However, in this study methylprednisolone was started relatively late (day 13 after symptom onset), but most importantly was stopped on day 5. This failed study reinforces the concept of early and prolonged treatment with methylprednisolone titrated to the patient's clinical response. In patients at high risk of Strongyloides infection, screening and/or treatment of this parasite with ivermectin is suggested prior to treatment with corticosteroids.[271]

Our treatment protocol targeting the key pathologic processes has been highly successful, *if begun within 6 hours* of a COVID19 patient 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.

***Further resources:***

The reader is referred to the large autopsy series by Bruce and colleagues which clearly outlines the pathophysiology of severe COVID-19 disease.[188]

The scientific rationale for the MATH + protocol is reviewed in this paper.[127]

In this U-tube video, Professor Britt Glaunsinger, PhD provides an outstanding review on the molecular virology of SARS-CoV-2: https://www.youtube.com/watch?v=DQVpHyvz4no

Lecture by Paul Marik, MD reviewing clinical aspects of COVID-19. https://youtu.be/bJZcDBTEGio

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