

EVMS

MEDICAL GROUP

EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

Developed and updated by [Paul Marik, MD](#)
Chief of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School, Norfolk, VA
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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](https://www.evms.edu/covidcare)

Disclaimer: The information provided in this protocol is primarily to educate 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.

MATH+ Hospital Treatment Protocol for COVID-19

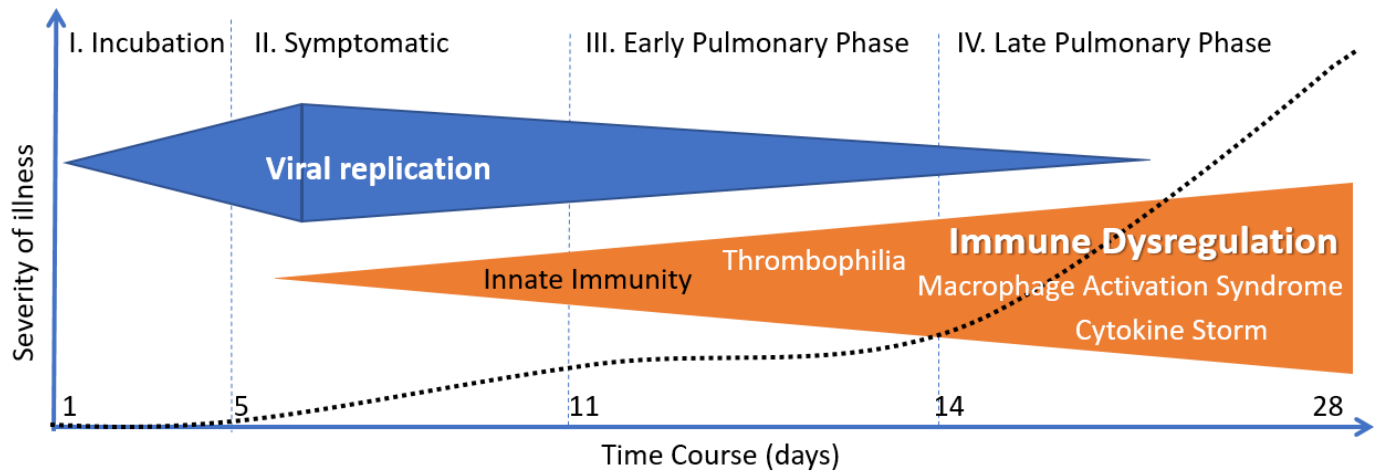
Intravenous **M**ethylprednisolone
High Dose Intravenous **A**scorbic Acid (Vitamin C)
Thiamine (Vitamin B1)
Full Dose Low Molecular Weight **H**eparin
+
Zinc, Vitamin D, Famotidine, Magnesium & Melatonin



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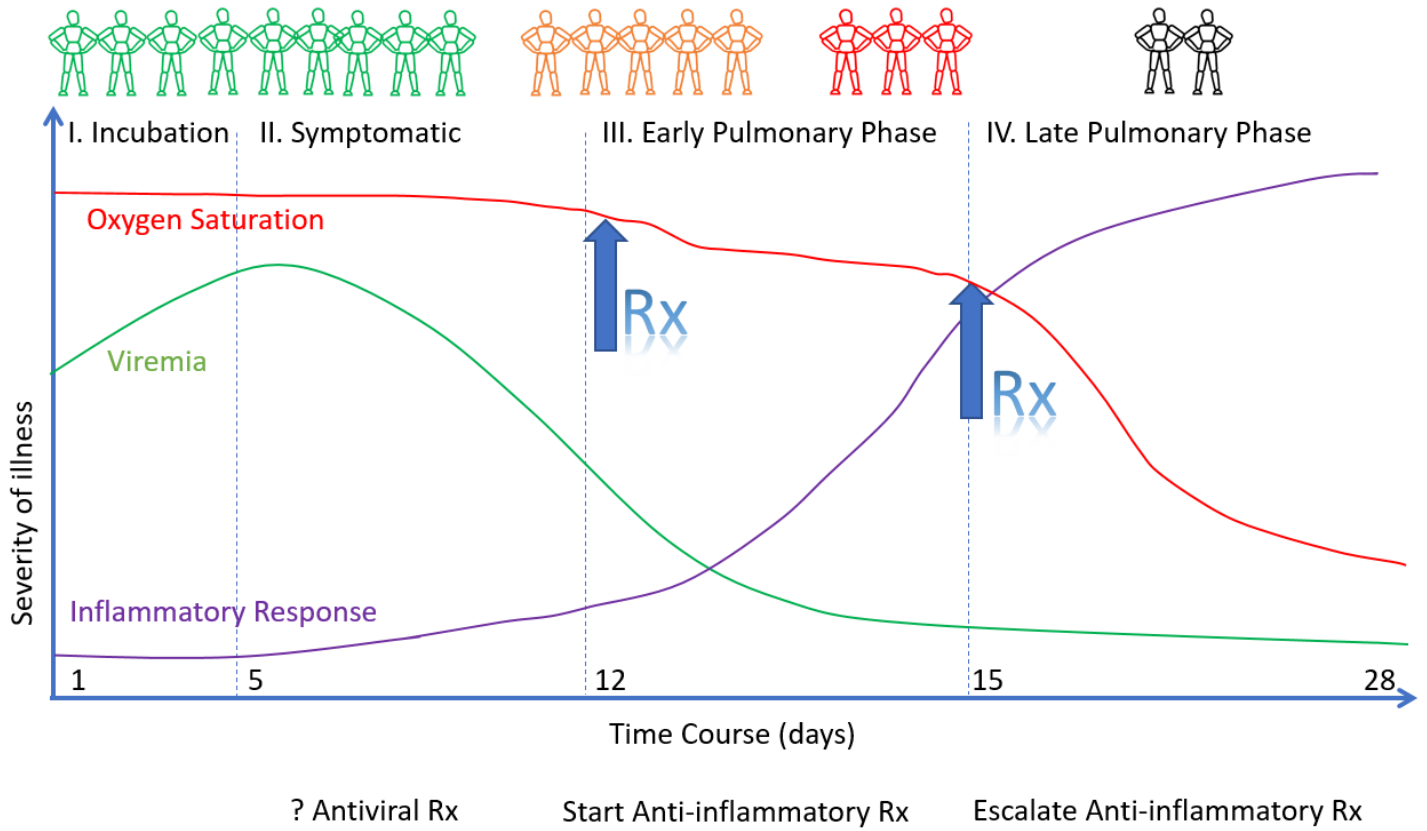
Figure 1. The course of COVID-19 and General Approach to treatment



	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.		Enoxaparin 1mg/kg s/c q 12
		Enoxaparin 60 mg/day		
		? 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**

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



Prophylaxis

While there is extremely limited data, the following “cocktail” may have a role in the prevention/mitigation of COVID-19 disease. It should however be noted that a recent publication suggests that melatonin may reduce the risk of COVID-19 infection.[1] This cocktail is cheap, safe, and widely available.

- Vitamin C 500 mg BID (twice daily) and Quercetin 250-500 mg BID [2-8]
- Zinc 50-75 mg/day (elemental zinc). Zinc lozenges are preferred. After 1 month, reduce the dose to 30-50 mg/day. [2,9-13]
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night [1,14-17]
- Vitamin D3 2000-4000 u/day [18-25]
- *Optional:* Famotidine 20-40 mg/day [26]

Symptomatic patients (at home):

- 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)
- *Optional:* Famotidine 20-40 mg/day
- *Optional:* Ivermectin 150-200 ug/kg orally (dose can be repeated on day 2) [27-31]
- In symptomatic patients, monitoring with home pulse oximetry is recommended. Baseline or ambulatory desaturation < 94% should prompt hospital admission. [32]
- *Not recommended:* Hydroxychloroquine (HCQ). The use of HCQ is extremely controversial.[33] The best scientific evidence to date suggest that HCQ has no proven benefit for post exposure prophylaxis, for the early symptomatic phase and in hospitalized patients. [34-39] It should be noted that these studies did not include Zinc, and it is possible that the efficacy of HCQ requires the co-administration of Zinc. [40,41] However, considering the unique pharmacokinetics of HCQ, it is unlikely that HCQ is of benefit (takes about 10 days to achieve adequate plasma and lung concentrations).[42-44] The benefit derived from the co-administration of Zinc may be due to the effects of zinc alone. This is however, a very “volatile” situation, so stay tuned.

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 4000 u/day
- Enoxaparin 60 mg daily [31,45-54] 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. [55-61] The role of inhaled corticosteroids (budesonide) is unclear and appears to be rather limited.
- Famotidine 40 mg daily (20 mg in renal impairment)
- *Optional:* Ivermectin 150-200 ug/kg (dose can be repeated on day 2)

- *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.
- *Optional:* Remdesivir, 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [62,63] This agent has been reported to reduce time to recovery (based on an ordinal scale). [63] The benefit of this agent on patient centered outcomes is unclear.
- 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 \geq 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 125mg q 12 hourly), then titrate down as appropriate. [55-61]
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). [64-72]. Oral absorption is limited by saturable transport and it is difficult to achieve adequate levels with PO administration. However, unfortunately, IV Vitamin C is not available in many hospitals; in this situation 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). [45-54] 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.[73] 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).

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 4000 u PO daily
7. Thiamine 200 mg IV q 12 hourly [74-78]
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). [79-81]
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. [82]
Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[83,84]
Due to numerous drug-drug interactions simvastatin should be avoided.

10. *Optional*: Vascepa, Lovaza or DHA/EPA 4g day (see above).
11. *Optional*: Azithromycin 500 mg day 1 then 250 mg for 4 days (has immunomodulating properties including downregulating IL-6; has anti-viral properties and in addition, Rx of concomitant bacterial pneumonia). [31,85] The benefit of azithromycin in COVID-19 is however unproven.
12. *Optional*: Remdesivir. The role of this agent in patients with more advanced pulmonary involvement appears to be limited.
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) secondary bacterial infection is not uncommon.
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.
15. 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). This appears to be due to the fact TNF- α which is only moderately elevated in COVID-19, is “necessary” for vasodilatory shock.
16. 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) [86,87]
 - 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.

17. Salvage Treatments

- High dose corticosteroids; 120 -250 mg methylprednisolone q 6-8 hourly
- Plasma exchange [88-90]. 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 PaCO₂ 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.[91,92]
- Janus Kinase inhibitors downregulate cytokine expression and may have a role in this disease. [93-95]
- Convalescent serum; the role and timing of convalescent serum are uncertain. [96-99] COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [100]

Salvage treatments of unproven benefit.

- Siltuximab and Tocilizumab (IL-6 inhibitors).[101,102] Roche™ recently announced the results of the COVACTA study, which demonstrated that Tocilizumab did not improve patient outcome.
- Convalescent serum: the role and timing of convalescent serum are uncertain. [96-99] COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [100]
- CVVH with cytokine absorbing/filtering filters [103] This treatment strategy appears to have a very limited role.
- ECMO [104]. 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. This appears to be driven by SARS-CoV-2 induced inflammasome activation and increased IL-1 β production (see Figure 5). [105,106]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and increasing CRP. [107]
- “*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. [108,109]

19. Monitoring

- On admission: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. D-dimer is the most important prognostic marker.
- 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. [110]
- 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. [111,112]
- 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.

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

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.

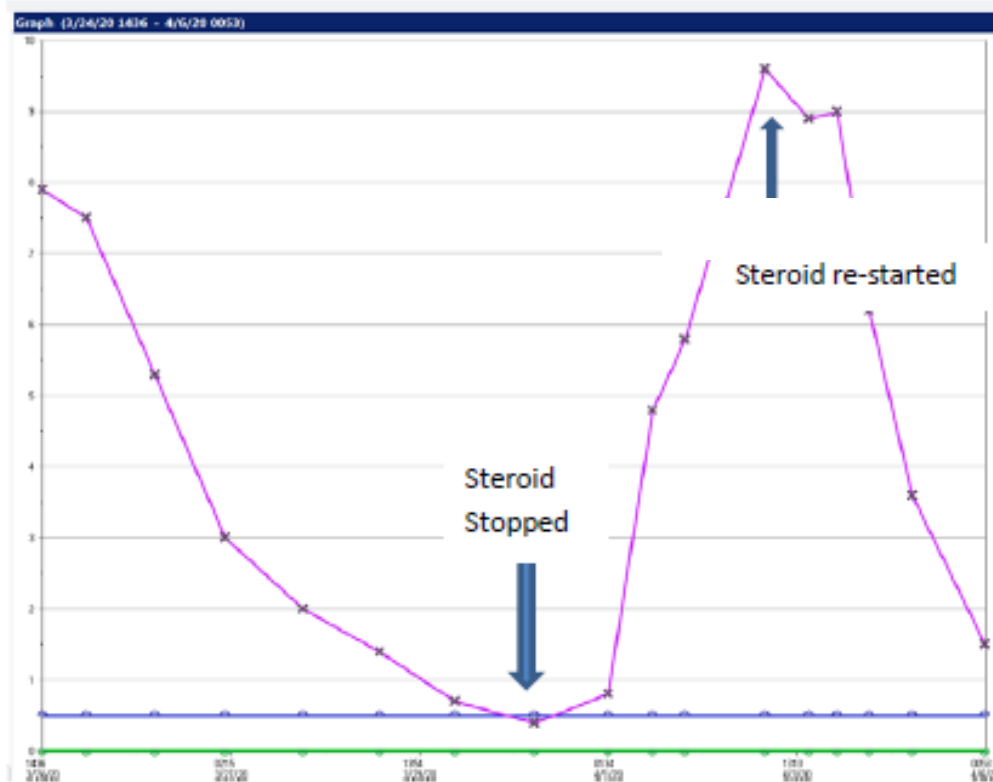


Figure 4.

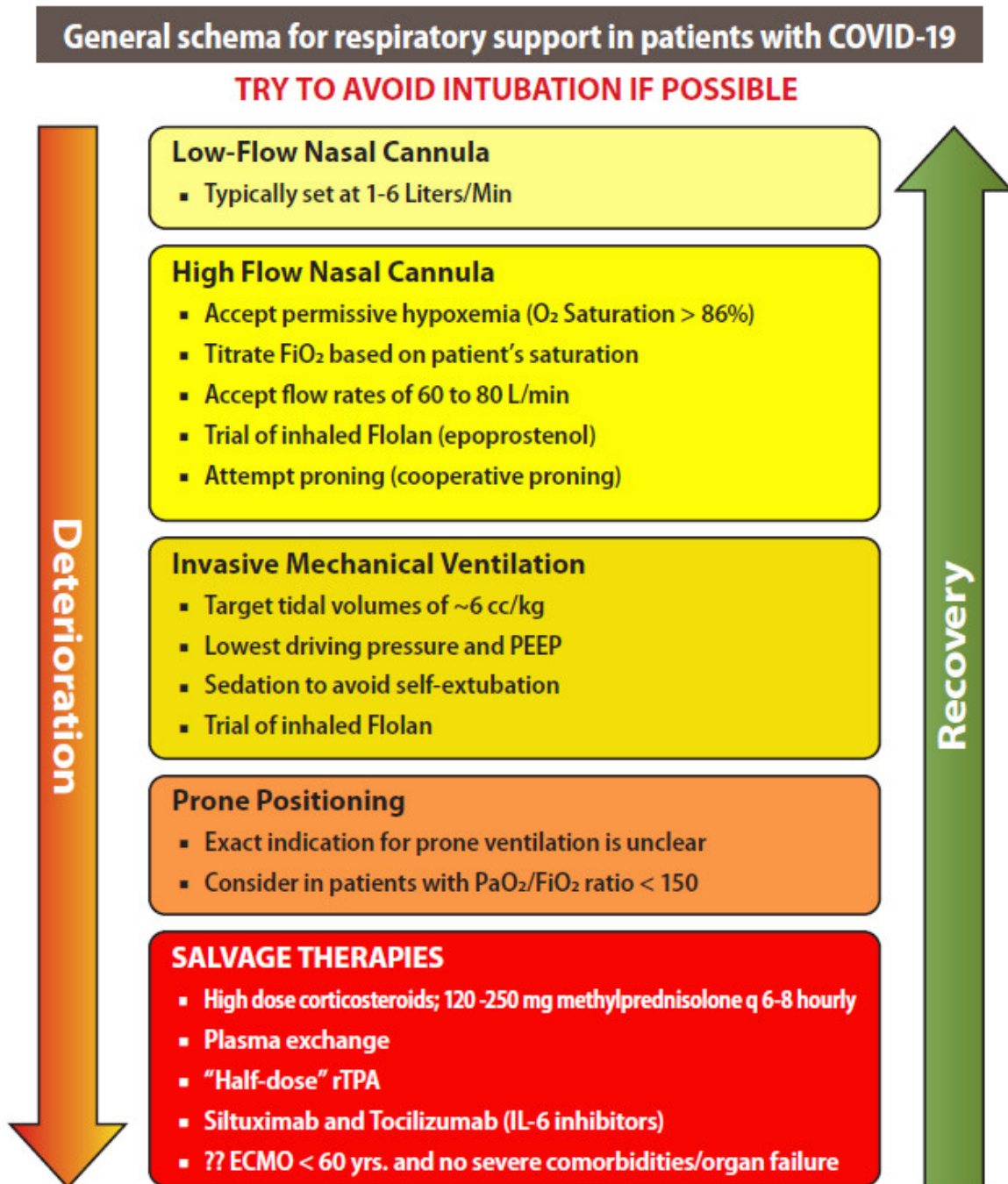
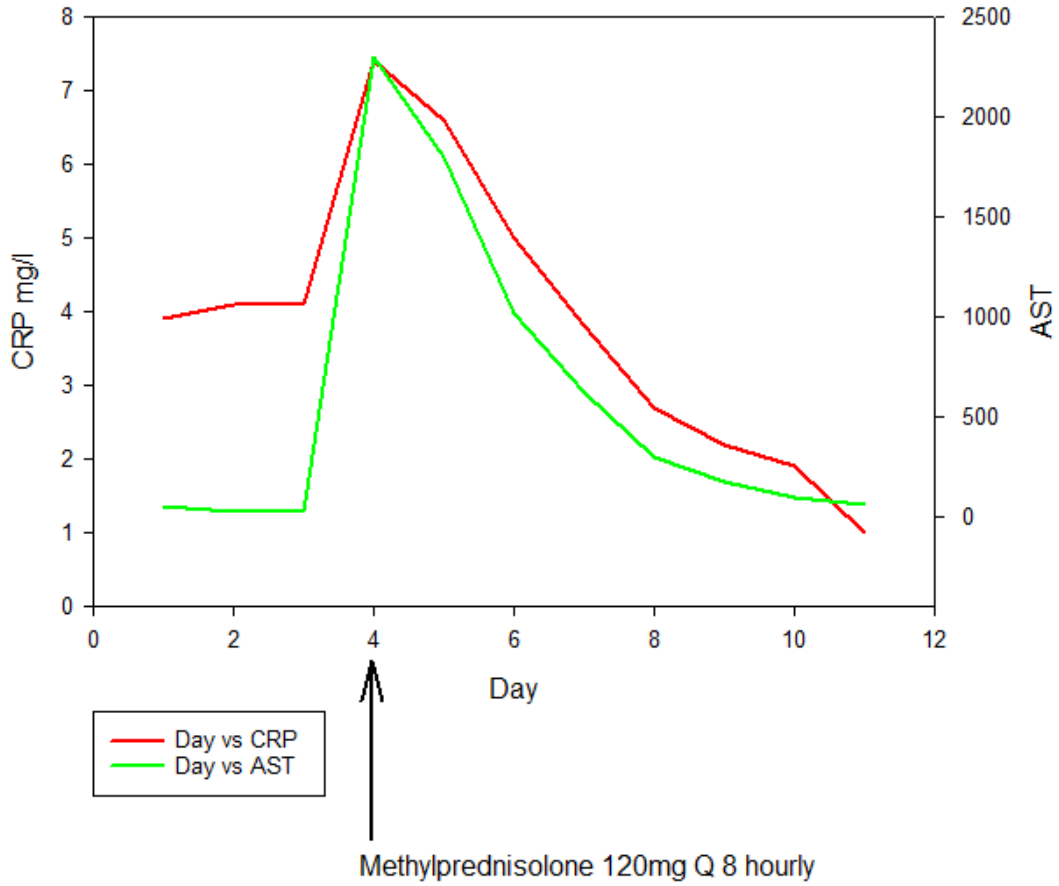


Figure 5. SARS-CoV-2 induced Macrophage Activation Syndrome (MAS) treated with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)



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).[58,113-118] 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, [93,95,102,105,106,116,119-127] a pulmonary microvascular injury (endothelialitis),[127-130] 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). [105,120] This factor is critical to understanding the treatment of COVID-19 organizing pneumonia. (see Figure 7).[120]
6. THIS is NOT ARDS (at least initially). The initial pulmonary phase neither looks like, smells like nor is ARDS.[131-133] The ground glass infiltrates are peripheral and patchy, and do not resemble the dependent air space consolidation (sponge/baby lung) seen with “typical ARDS”. [134] 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.[118,135-138] 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. [65] Vitamin C protects the endothelium from oxidative injury.[66,139-141] Furthermore, vitamin C increases the expression of interferon-alpha (this is critical) ([5] while corticosteroids (alone) decrease expression of interferon-alpha. [142-145] 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 or decrease the production of type specific antibodies.
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),[146] genomic data specific for SARS-CoV-2,[147] 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.[10] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[9]
 - b. Quercetin has direct viricidal properties against a range of viruses, including SARS-CoV-2.[3,7] In addition, quercetin acts as a zinc ionophore. [148]
 - c. Vitamin C improves the potency of Quercetin and has antiviral activity.[3]
12. It should also be noted that Vitamin D may be a very powerful prophylactic and treatment strategy against COVID-19. [18-25] Vitamin D deficiency explains, in part, the enormous geographic variation in mortality of this disease.

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

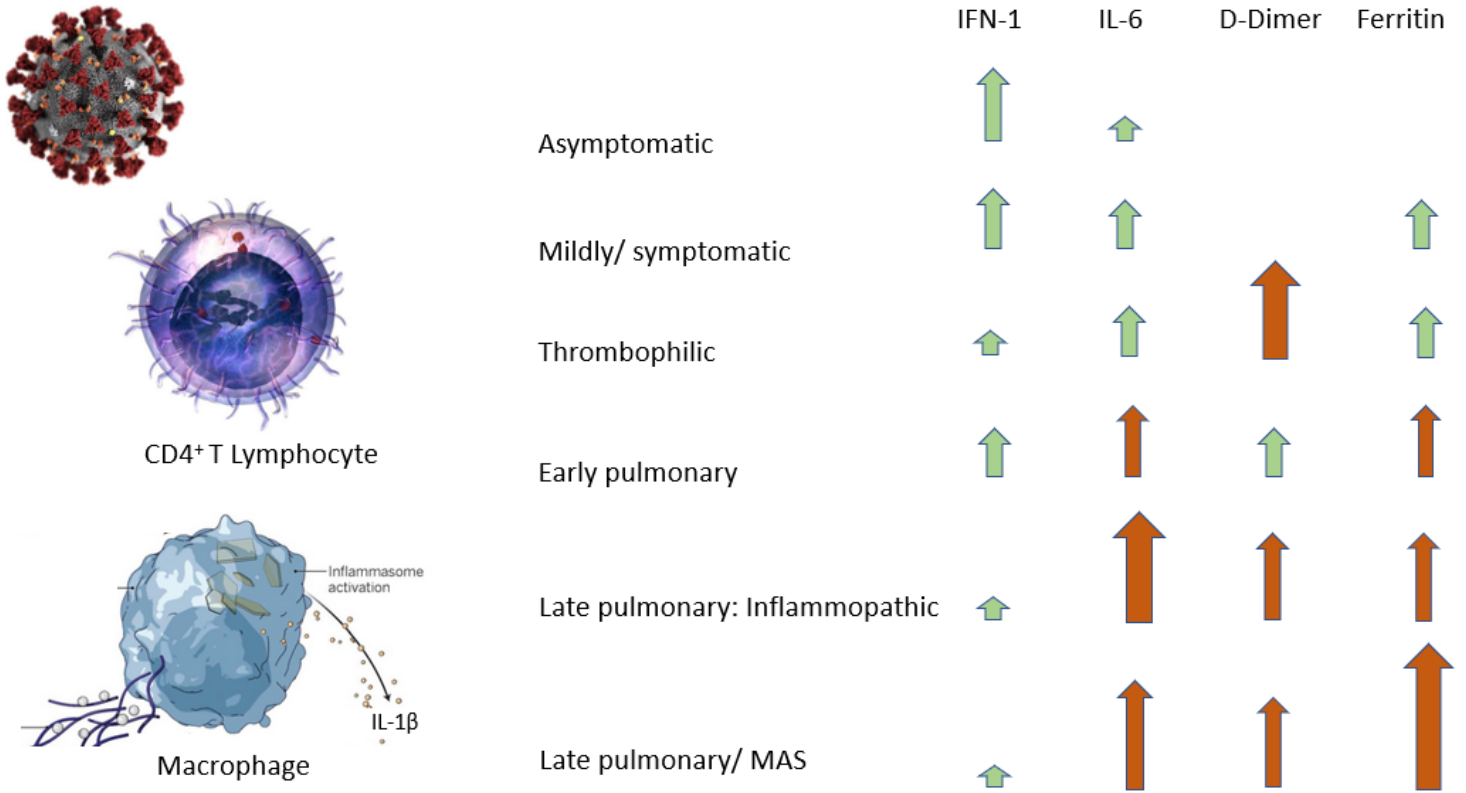
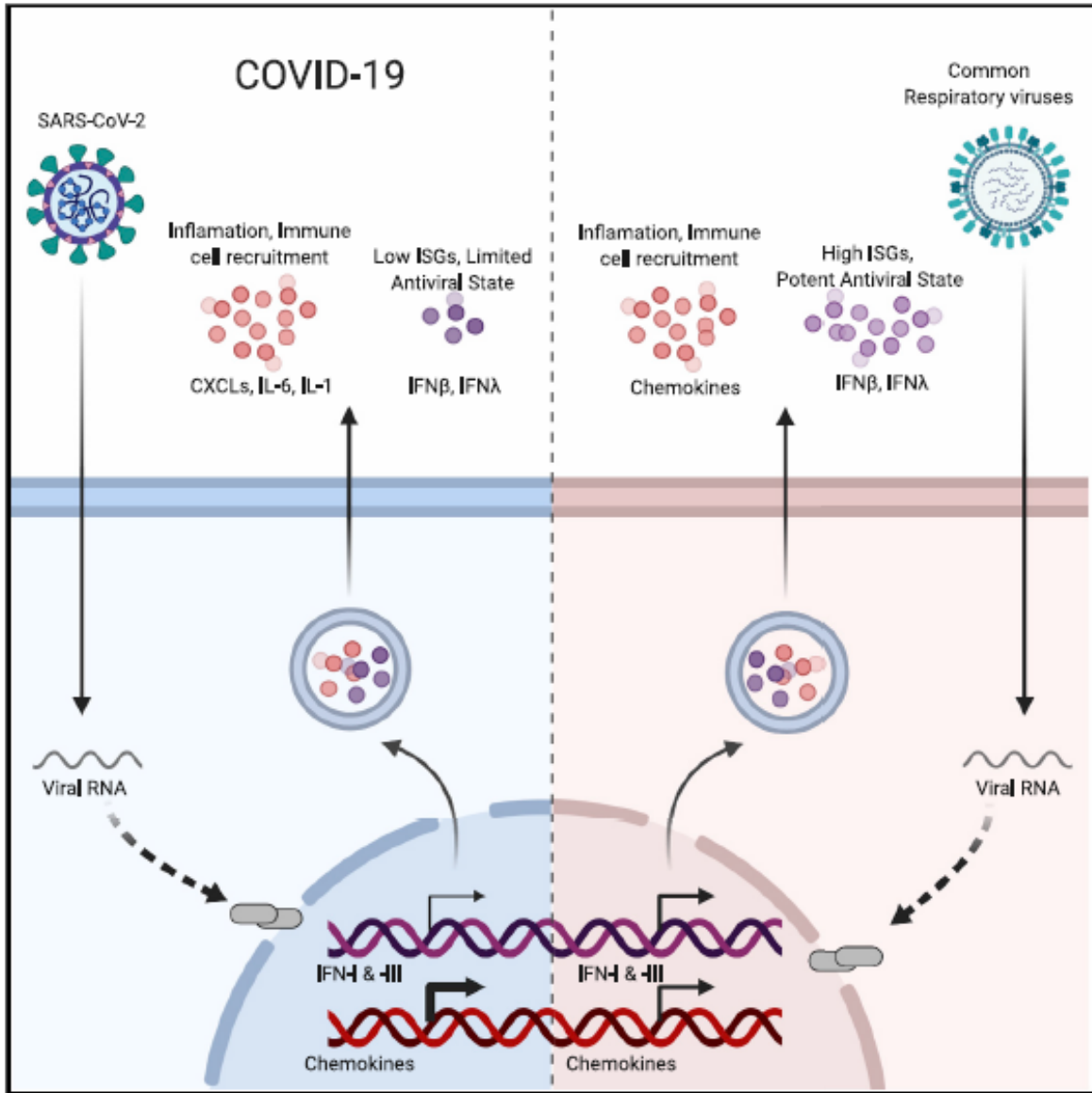


Figure 7. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. [120] Open Access Publication.



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.” [93,95,102,105,106,116,119,121-126]
- 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. [45-54,129,130,149,150]
- 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. [95,100] 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) [151,152]. 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 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.[55,153] 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 COVID19 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 use of the MATH+ protocol in 2 hospitals in the USA has reduced the hospital mortality from COVID-19 to approximately 6% (the average hospital mortality for COVID-19 across the world is reported to be 21%).

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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).



References

1. Jehi L, Ji X, Milinovich A et al. Individualizing risk prediction for positive COVID-19 testing. Results from 11,672 patients. *Chest* 2020.
2. Maggini S, Beveridge S, suter M. A combination of high-dose vitamin C plus zinc for the common cold. *Journal of International Medical Research* 2012; 40:28-42.
3. Colunga Biancatelli RM, Berrill M, Catravas JD et al. Quercetin and Vitamin C: experimental therapy for the prevention and treatment of SARS-CoV-2 via synergistic action. *Front Immunol* 2020.
4. Kyung Kim T, Lim HR, Byun JS. Vitamin C supplementaion reduces the odds of developing a common cold in Republic of Korea Army recruits: a randomised controlled trial. *BMJ Mil Health* 2020.
5. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. *Expert Rev Anti Infect Ther* 2020; 18:99-101.
6. Khaerunnisa S. Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compuns by molecular docking study. *medRxiv* 2020.
7. Chen L, Li J, Luo C et al. Binding interaction of quercetin-3-B-galactoside and its synthetic derivatives with SARS-CoV 3CL: structure-activity relationship reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry Letters* 2006; 14:8295-306.
8. Yi L, Li Z, Yuan K et al. Small molecules blocking the entry of severe respiratory syndrome coronavirus into host cells. *J Virol* 2020; 78:11334-39.
9. te Velthuis AJ, van den Worm SH, Sims AC et al. Zn²⁺ inhibits Coronavirus and Arterivirus RNA polymerase activity In Vitro and Zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010; 6:e1001176.
10. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. *Nutrients* 2017; 9.
11. Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *J Royal Soc Med Open* 2017; 8:1-7.
12. Singh M, Das RR. Zinc for the common cold. *Cochrane Database of Syst Rev* 2013; 6:CD001364.
13. Hoeger J, Simon TP, Beeker T et al. Persistent low serum zinc is associated with recurrent sepsis in critically ill patients - A pilot study. *PLoS ONE* 2017; 12:e0176069.
14. Colunga Biancatelli RM, Berrill M, Mohammed YH et al. Melatonin for the treatment of sepsis: the scientific rationale. *J Thorac Dis* 2020; 12 (Suppl 1):S54-S65.
15. Reiter RJ, Abreu-Gonzalez P, Marik PE et al. Therapeutic algorithm for use of melatonin in patients with COVID-19. *Front Med* 2020; 7:226.
16. Reiter RJ, Sharma R, Ma Q et al. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Medicine in Drug Discovery* 2020; 6:100044.
17. Zhang R, Wang X, Ni L et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* 2020; 250:117583.
18. Grant WB, Lahore H, McDonnell SL et al. Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020; 12:988.
19. Lau FH, Majumder R, Torabi R et al. Vitamin D insufficiency is prevalent in severe COVID-19. *medRxiv* 2020.
20. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? *Medicine in Drug Discovery* 2020.
21. Rhodes JM, Subramanian S, Laird E et al. Editorial: Low population mortality from COVID-19 in countries south of 35 degrees North - supports vitamin D as a factor determining severity. *Alimentary Pharmacology & Therapeutics* 2020; (in press).

22. Dancer RC, Parekh D, Lax S et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax* 2015; 70:617-24.
23. LLie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* 2020.
24. Daneshkhah A, Eshein A, Subramanian H. The role of vitamin D in suppressing cytokine storm of COVID-19 patients and associated mortality. *medRxiv* 2020.
25. Bergman P, Lindh AU, Bjorkhem-Bergman L et al. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. *PloS ONE* 2013; 8:e65835.
26. Freedberg DE, Conigliaro J, Sobieszczyk ME et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *medRxiv* 2020.
27. Caly L, Druce JD, Catton MG et al. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020.
28. Patel AN, Desai SS, Grainger DW et al. Usefulness of ivermectin in COVID-19 illness. *medRxiv* 2020.
29. Rajter JC, Sherman MS, Fatteh N et al. ICON (Ivermectin in COvid Ninteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19. *medRxiv* 2020.
30. Scheim DE. Ivermectin for COVID-19 treatment: clinical response at quasi-threshold doses via hypothesized alleviation of CD147-mediated vascular occlusion. *medRxiv* 2020.
31. Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. *Preprints* 2020.
32. Jouffroy R, Jost D, Prunet B. Prehospital pulse oximetry: a red flag for early detection of silent hypoxemia in COVID-19 patients. *Crit Care* 2020; 24:313.
33. Risch HA. Early outpatient treatment of symptomatic, high-risk Covid-19 patients that should be ramped-up immediately as key to the pandemic crisis. *medRxiv* 2020.
34. Borba MG, Val FF, Sampaio S. Effect of High vs Low Doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A randomized clinical trial. *JAMA Network Open* 2020.
35. Boulware DR, Pullen MF, Bangdiwala AS et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020.
36. Mitja O, Corbacho-Monne M, Ubals M et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: A randomized-controlled trial. *Clin Infect Dis* 2020.
37. Mitja O, Ubals M, Corbach-Monne M et al. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. *medRxiv* 2020.
38. Cavalcanti AB, Zampieri FG, Rosa RG et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* 2020.
39. Skipper CP, Pastick KA, Engen NW. Hydroxychloroquine in nonhospitalized adults with early COVID-19. *Ann Intern Med* 2020.
40. Shittu MO, Afolami OI. Improving the efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 may require zinc additives - A better synergy for future COVID-19 clinical trials. *Le Infezioni in Medicina* 2020; 2:192-97.
41. Carlucci PM, Ahuja T, Petrilli C et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. *medRxiv* 2020.
42. MacGowan A, Hamilton F, Bayliss M et al. Hydroxychloroquine serum concentrations in non-critical care patients infected with SARS-CoV-2. *medRxiv* 2020.

43. Tett SE, Cutler DJ, Day RO et al. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989; 27:771-79.
44. Nicol MR, Joshi A, Rizk ML et al. Pharmacokinetic and pharmacological properties of chloroquine and hydroxychloroquine in the context of COVID-19 infection. *medRxiv* 2020.
45. Bikdeli B, Madhavan MV, Jimenez et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol* 2020.
46. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020.
47. Klok FA, Kruip MJ, van der Meer NJ et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research* 2020.
48. Zhai Z, Li C, Chen Y et al. Prevention and treatment of venous thromboembolism associated with Coronavirus Disease 2019 Infection: A consensus statement before guidelines. *Thromb Haemost* 2020.
49. Paranjpe I, Fuster V, Lala A et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020.
50. Iba T, Levy JH, Levi M et al. Coagulopathy of coronavirus disease 2019. *Crit Care Med* 2020.
51. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. *Intensive Care Med* 2020; 46:1603-6.
52. Helms J, Tacquard C, Severac F et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; 46:1089-98.
53. Varatharajah N, Rajah S. Microthrombotic complications of COVID-19 are likely due to embolism of circulating endothelial derived ultralarge Von Willebrand Factor (eULVWF) decorated-platelet strings. *Federal Practitioner* 2020.
54. Du L, Kao RY, Zhou Y et al. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochemical & Biophysical Research Communications* 2007; 359:174-79.
55. Villar J, Confalonieri M, Pastores SM et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome (ARDS) caused by COVID-19. *Crit Care Expl* 2020; 2:e0111.
56. Fadel R, Morrison AR, Vahia A et al. Early course corticosteroids in hospitalized patients with COVID-19. *medRxiv* 2020.
57. Chroboczek T, Lacoste M, Wackenheim C et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. *medRxiv* 2020.
58. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020.
59. Cruz AF, Ruiz-Antoran B, Gomez AM et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. *medRxiv* 2020.
60. Liu J, Zheng X, Huang Y et al. Successful use of methylprednisolone for treating severe COVID-19. *J Allergy Clin Immunol* 2020.
61. Meduri GU, Bridges L, Shih MC et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016; 42:829-40.
62. Wang Y, Zhang D, Du G et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicenter trial. *Lancet* 2020.
63. Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the treatment of Covid-19-Preliminary report. *N Engl J Med* 2020.

64. Marik PE, Khangoora V, Rivera R et al. Hydrocortisone, Vitamin C and Thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; 151:1229-38.
65. Barabutis N, Khangoora V, Marik PE et al. Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest* 2017; 152:954-62.
66. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients* 2018; 10:1762.
67. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Therapeut* 2018; 189:63-70.
68. Cheng RZ. Can early and high-dose vitamin C prevent and treat coronavirus disease 2019 (COVID-19). *Medicine in Drug Discovery* 2020.
69. Wang Y, Lin H, Lin BW et al. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care* 2019; 9:58.
70. Fowler AA, Truwit JD, Hite D et al. Vitamin C Infusion for Treatment In Sepsis-Induced Acute Lung Injury- CITRIS-ALI: A Randomized, Placebo Controlled Clinical Trial. *JAMA* 2018; 322:1261-70.
71. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. *PharmaNutrition* 2020; 12:100190.
72. Iglesias J, Vassallo AV, Patel V et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. *Chest* 2020; 158:164-73.
73. Tomasa-Irriguible TM, Martinez-Vega S, Mor-Marco E et al. Low molecular weight heparins in COVID-19 patients: beware of augmented renal clearance! *Crit Care* 2020; 24:325.
74. Menezes RR, Godin AM, Rodrigues FF et al. Thiamine and riboflavin inhibit production of cytokines and increase the anti-inflammatory activity of a corticosteroid in a chronic model of inflammation induced by complete Freund's adjuvant. *Pharmacological Reports* 2020; 69:1036-43.
75. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! *J Thorac Dis* 2016; 8:1062-66.
76. Moskowitz A, Donnino MW. Thiamine (vitamin B1) in septic shock: a targeted therapy. *J Thorac Dis* 2020; 12 (suppl 1):S78-S83.
77. Woolum JA, Abner EL, Kelly A et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med* 2018; 46:1747-52.
78. Marik PE. Thiamine: An essential component of the metabolic resuscitation protocol. *Crit Care Med* 2018; 46:1869-70.
79. Lee CY, Jan WC, Tsai PS et al. Magnesium sulfate mitigates acute lung injury in endotoxemia rats. *J Trauma* 2011; 70:1177-85.
80. Salem M, Kasinski N, Munoz R et al. Progressive magnesium deficiency increases mortality from endotoxin challenge: Protective effects of acute magnesium replacement therapy [abstract]. *Crit Care Med* 1995; A260.
81. Jiang P. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? A systematic review and meta-analysis. *Shock* 2019; 47:288-95.
82. Calfee CS, Delucchi KL, Sinha P et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Resp Med* 2018; 6:691-98.
83. Zhang XJ, Qin JJ, Cheng X et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metabolism* 2020.

84. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA et al. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 2020; 24:429.
85. Hung IF, To KK, Chan JF et al. Efficacy of Clarithromycin-Naproxen-Oseltamivir combination in the treatment of patients hospitalized for influenza A (H3N2) infection. An open-label randomized, Controlled, Phase IIb/II trial. *Chest* 2017; 151:1069-80.
86. Xu Q, Wang T, Quin X et al. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19; a case series. *Crit Care* 2020; 24:250.
87. Elharrar X, Trigui Y, Dois AM et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020.
88. Keith P, Day M, Perkins L et al. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit Care* 2020.
89. Keith P, Wells AH, Hodges J et al. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: A single center retrospective review. *Crit Care* 2020.
90. Busund R, Koukline V, Utrobin U et al. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. *Intensive Care Med* 2002; 28:1434-39.
91. Poor HD, Ventetuolo CE, Tolbert T et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *medRxiv* 2020.
92. Wang J, Najizadeh N, Moore EE et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost* 2020.
93. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. *J Microbiol Immunol Infect* 2020.
94. Favalli EG, Biggioggero M, Maioli G et al. Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis* 2020.
95. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395:1033-34.
96. Zeng QL, Yu ZJ, Gou JJ et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *Clin Infect Dis* 2020.
97. Li L, Zhang W, Hu Y et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. A randomized clinical trial. *JAMA* 2020.
98. Fleming AB, Raabe V. Current studies of convalescent plasma therapy for COVID-19 may underestimate risk of antibody-dependent enhancement [letter]. *J Clin Virol* 2020; 127:104388.
99. Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-10 patients. *PNAS* 2020.
100. Jacobs JJ. Neutralizing antibodies mediate virus-immune pathology of COVID-19. *Med Hypotheses* 2020; 143:109884.
101. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. *ChinaXiv* 2020.
102. Zhang C, Wu Z, Li JW et al. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020.
103. Brouwer WP, Duran S, Kuijper M et al. Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. *Crit Care* 2019; 23:317.

104. Henry MB, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care* 2020; 58:27-28.
105. Giamarellos-Bourboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host & Microbe* 2020.
106. McGonagle D, Sharif K. The role of cytokines including interleukin-6 in COVID-19 induces pneumonia and macrophage activation syndrome-like disease. *Autoimmunity Reviews* 2020.
107. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Medicine* 2017; 15:172.
108. van de Veerdonk FL, Netea MG. Blocking IL-1 to prevent respiratory failure in COVID-19. *Crit Care* 2020; 24:445.
109. Cavalli G, De Luca G, Campochiaro C et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020.
110. Tan C, Huang Y, Shi F et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol* 2020.
111. Howell AP, Parrett JL, Malcom DR. Impact of high-dose intravenous vitamin C for treatment of sepsis on point-of-care blood glucose readings. *J Diabetes Sci Technol* 2019.
112. Stephenson E, Hooper MH, Marik PE. Vitamin C and Point of Care glucose measurements: A retrospective, Observational study [Abstract]. *Chest* 2018; 154 (suppl.):255a.
113. Zhao J, Yang Y, Huang H et al. Relationship between ABO blood group and the COVID-19 susceptibility. *medRxiv* 2020.
114. Banerjee A, Pasea L, Harris S et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020; 395:1715-25.
115. Goren A, Vamo-Galvan S, Wambier CG et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain- A potential clue to the role of androgens in COVID-19 severity. *J Cosmetic Dermatol* 2020.
116. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020.
117. Guan W, Ni Z, Hu Y et al. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med* 2020.
118. von der Thusen J, van der Eerden M. Histopathology and genetic susceptibility in COVID-19 pneumonia. *Eur J Clin Invest* 2020.
119. Zhou Y, Fu B, Zheng X et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Immunology* 2020.
120. Blanco-Melo D, Nilsson-Payant BE, Liu WC et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020.
121. Zhou F, Yu T, Du R et al. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020.
122. Giamarellos-Bourboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *medRxiv* 2020.
123. Qin C, Zhou L, Hu Z et al. Dysregulation of the immune response in patients with COVID-19 in Wuhan, China. *Lancet Infect Dis* 2020.
124. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. *J Infection* 2020.
125. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020.

126. Tay MZ, Poh CM, Renia L et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews* 2020; 20:363-74.
127. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med* 2020; 46:1105-8.
128. Teuwen LA, Geldhof V, Pasut A et al. COVID-19: the vasculature unleashed. *Nature Reviews* 2020.
129. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020.
130. Ackermann M, Verleden SE, Kuehnel M et al. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. *N Engl J Med* 2020; 383:120-128.
131. Gattinoni L, Chiumello D, Caironi P et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensive Care Med* 2020; 46:1099-102.
132. Chiumello D, Cressoni M, Gattinoni L. Covid-19 does not lead to a "typical" Acute Respiratory Distress syndrome. *Lancet* 2020.
133. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020; 24:154.
134. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005; 31:776-84.
135. Carsana L, Sonzogni A, Nasr A et al. Pulmonary post-mortem findings in a large series of COVID-19 cases from Northern Italy. *medRxiv* 2020.
136. Copin MC, Parmentier E, Duburcq T et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection [letter]. *Intensive Care Med* 2020.
137. Menter T, Haslbauer JD, Nienhold R et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *medRxiv* 2020.
138. Xu Z, Shi L, Wang Y et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Resp Med* 2020.
139. May JM, Qu ZC. Ascorbic acid prevents oxidant-induced increases in endothelial permeability. *Biofactors* 2011; 37:46-50.
140. Utoguchi N, Ikeda K, Saeki K et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. *Journal of Cellular Physiology* 1995; 163:393-99.
141. Han M, Pendem S, Teh SL et al. Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. *Free Radic Biol Med* 2010; 48:128-35.
142. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci* 2004; 1024:138-46.
143. Shodell M, Siegal FP. Corticosteroids depress INF-alpha-producing plasmacytoid dendritic cells in human blood. *J Allergy Clin Immunol* 2001; 108:446-48.
144. Thomas BJ, Porritt RA, Hertzog PJ et al. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Scientific Reports* 2014; 4:7176.
145. Singanayagam A, Glanville N, Girkin JL et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nature Communications* 2018; 9:2229.
146. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. *Lancet* 1983;995-97.
147. Draghici S, Nguyen TM, Sonna LA et al. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Nature Reviews* 2020.
148. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM et al. Zinc ionophore activity of Quercetin and Epigallocatechin-gallate: From Hepa 1-6 cells to a liposome model. *J Agric Food Chem* 2014; 62:8085-93.

149. Tang N, Bai H, Chen X et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 with coagulopathy. medRxiv 2020.
150. Sardu C, Gambardella J, Morelli MB et al. Is COVID-19 an endothelial disease? Clinical and basic evidence. medRxiv 2020.
151. World Health Organization: Coronavirus Disease 2019 (COVID-19): Situation Report -54 (14th March 2020). <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200314-sitrep-54-covid-19.pdf> . 2020. Accessed 7-9-2020.
152. Clinical management of COVID-19. Interim guidance. 27th May 2020. <https://www.who.int/publications/i/item/clinical-management-of-covid-19> WHO/2019-nCoV/clinical/2020.5 . 2020. World Health Organization. Accessed 7-10-2020.
153. Yam LY, Lau AC, Lai FY et al. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. J Infection 2007; 54:28-39.