

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
September 28th, 2020

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.

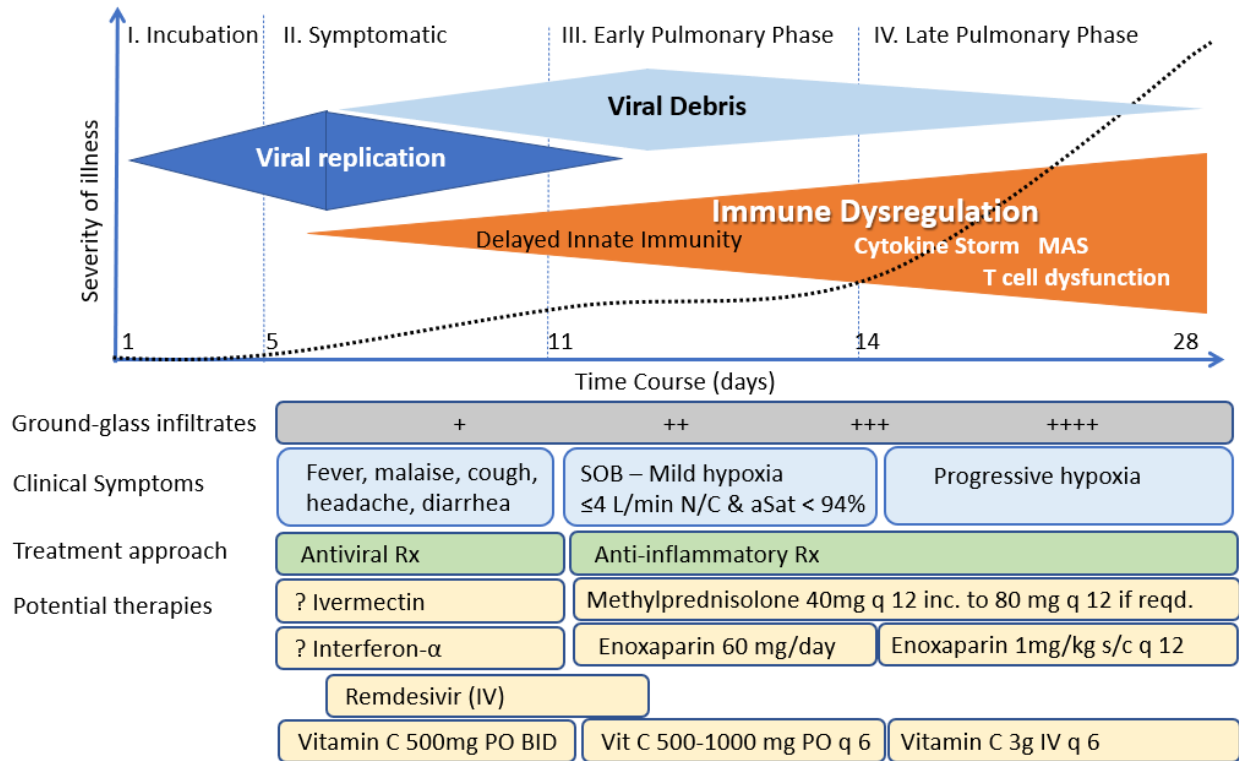
MATH+
HOSPITAL TREATMENT PROTOCOL FOR COVID-19

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

FLCCC
ALLIANCE

Front Line Covid-19
Critical Care Alliance
www.covid19criticalcare.com

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

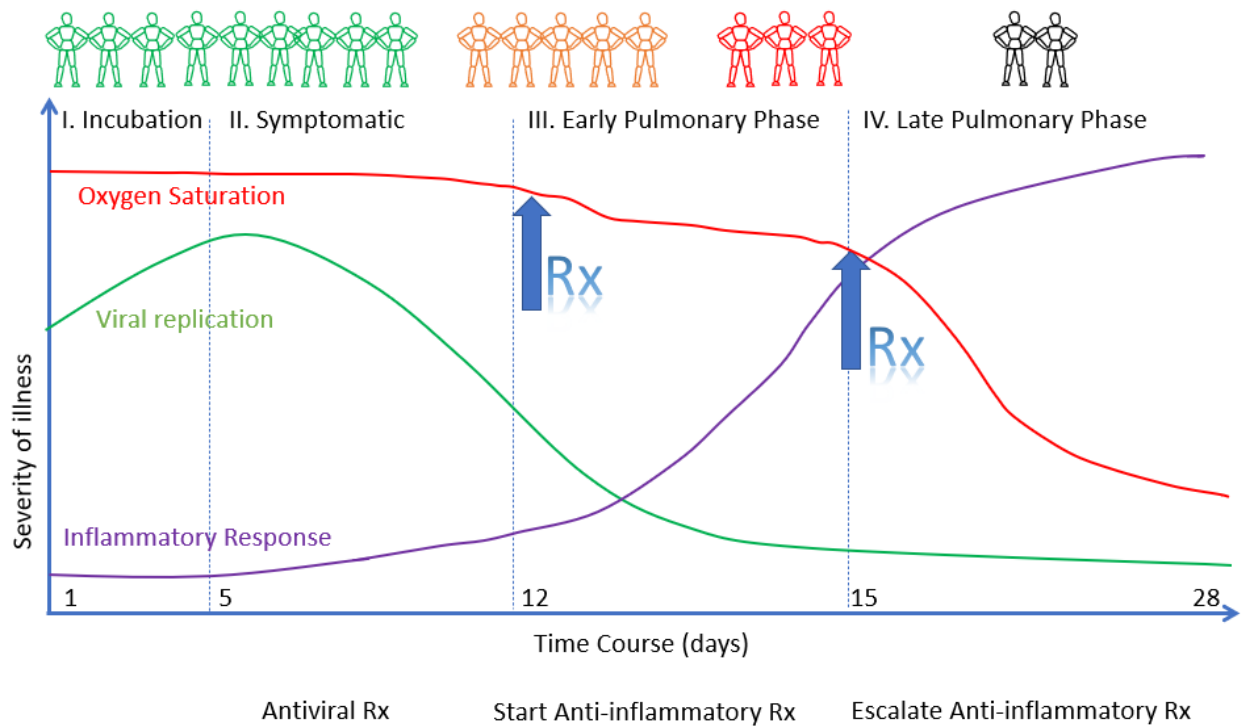


Figure 3. Time course of laboratory tests for COVID-19

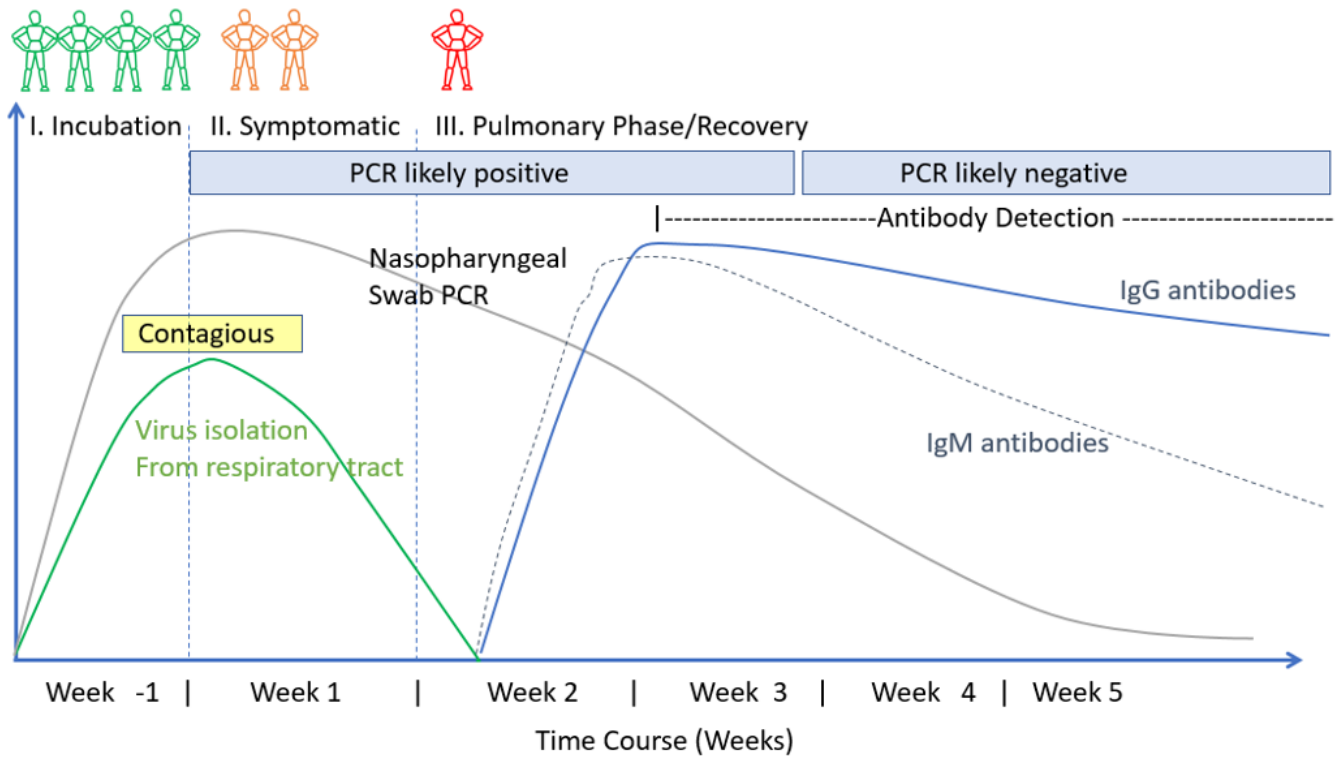
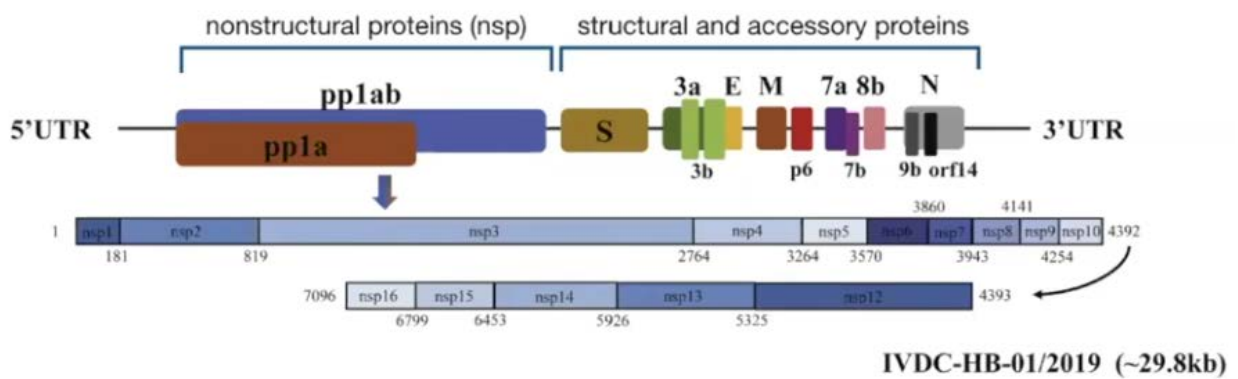


Figure 4. SARS-Co-V-2 RNA genome



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 may 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 \geq 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)		<u>5.9% vs. 42.9%</u>	<u>2.7</u>
METHYLPREDNISONE - ICU PATIENTS (Confalonieri et al, Italy)		<u>7.2% vs. 23.3%</u>	<u>6.2</u>
METHYLPREDNISONE - HOSPITAL PATIENTS, (Fadel et al, USA)		<u>13.6% vs. 26.3%</u>	<u>7.8</u>
METHYLPREDNISONE- ARDS PATIENTS (Wu C et al - China)		<u>46.0% vs.61.8%</u>	<u>6.3</u>
METHYLPREDNISONE - Pts on oxygen - (Fernandez-Cruz, Spain)		<u>13.9% vs. 23.9%</u>	<u>10.0</u>
CoDEX – DEXAMETHASONE – MECHANICAL VENTILATION		<u>56.3% vs. 61.5%</u>	<u>19.2</u>
RECOVERY TRIAL (DEXAMATHASONE)	<u>PTS ON OXYGEN</u>	<u>23.3% vs. 26.2%</u>	<u>28.6</u>
RECOVERY TRIAL (DEXAMATHASONE)	<u>PTS ON MV</u>	<u>29.3% vs. 41.4%</u>	<u>8.4</u>
HYDROCORTISONE-CAPE-COVID - ICU Patients (Dequin et al France)		<u>14.7% vs. 27.4%</u>	<u>7.9</u>
HYDROCORTISONE - REMAP-CAP - ICU patients		<u>28% vs. 33%</u>	<u>20.0</u>

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 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) [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 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 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 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.[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 IFN γ 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 IFN γ (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.

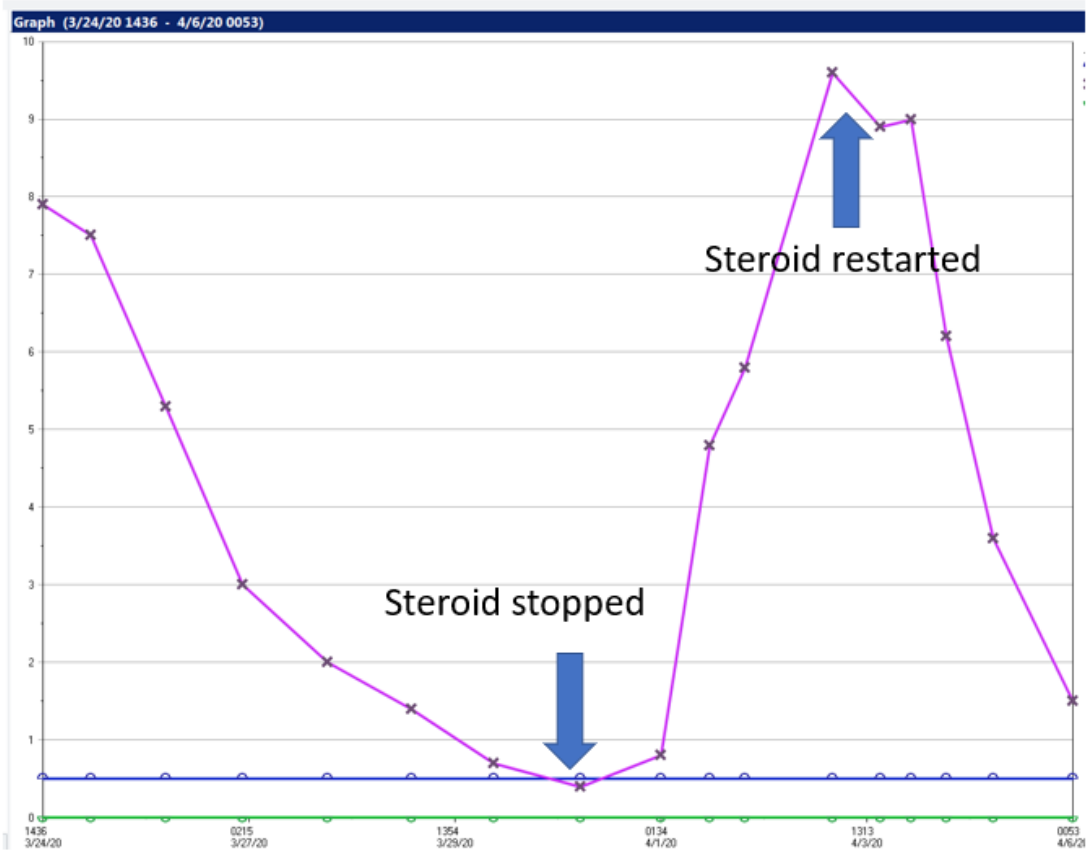


Figure 6.

General schema for respiratory support in patients with COVID-19

TRY TO AVOID INTUBATION IF POSSIBLE

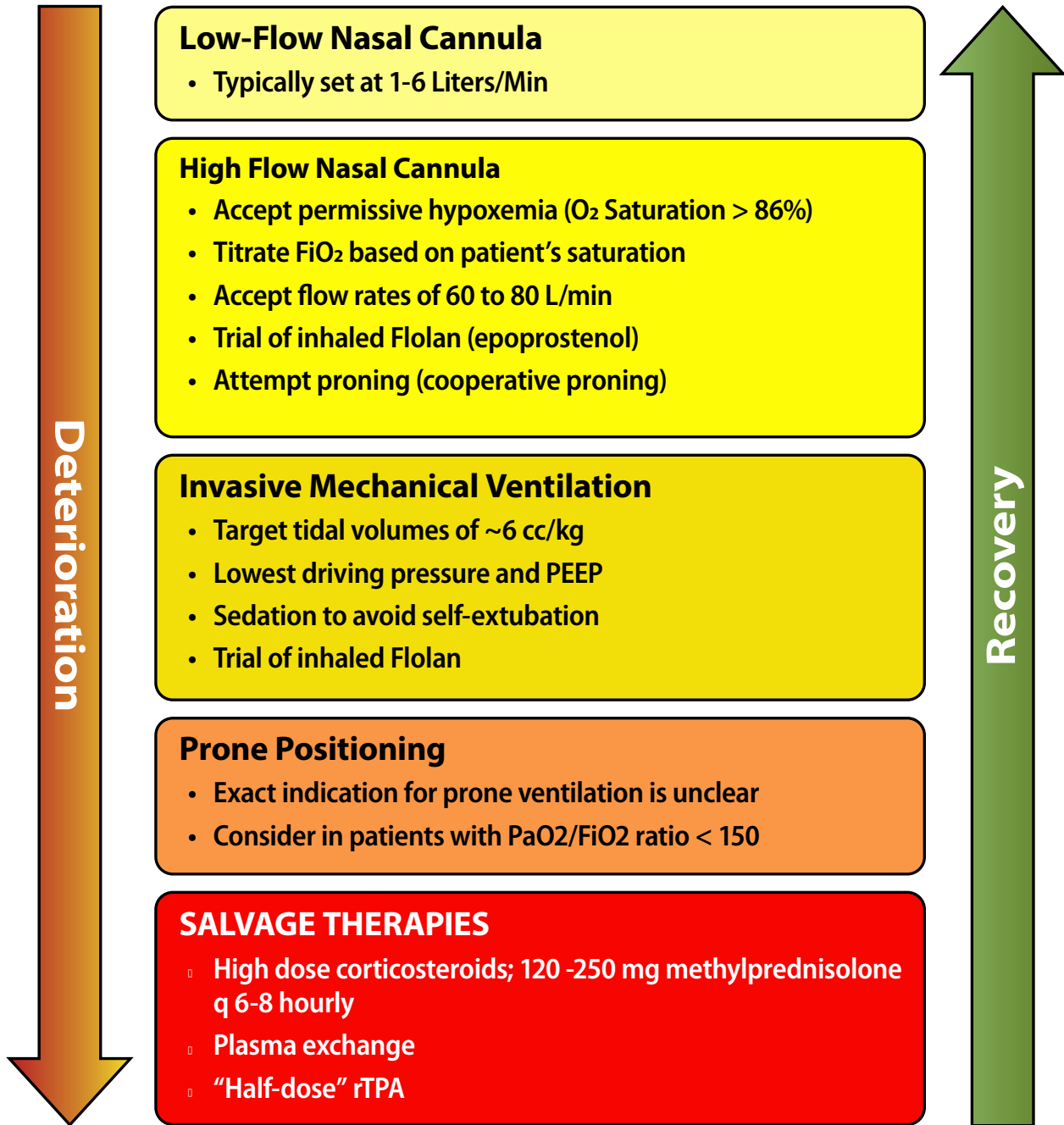
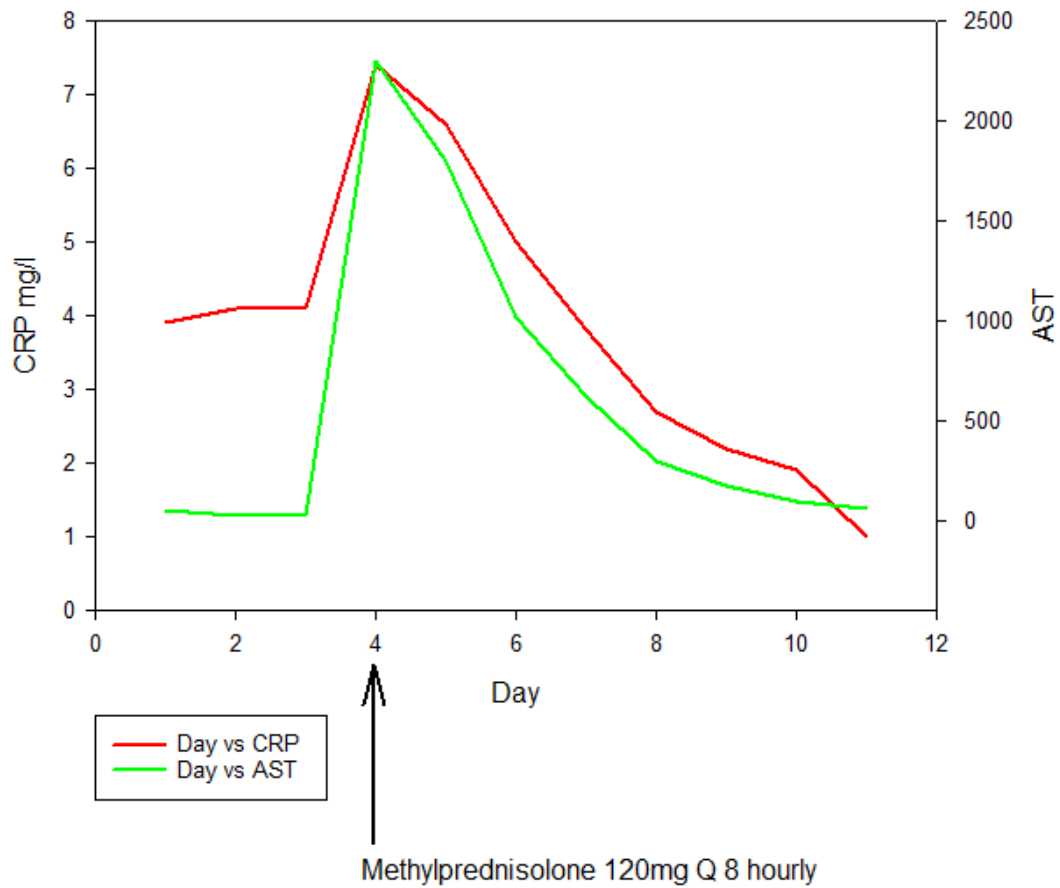


Figure 7. SARS-CoV-2 induced Macrophage Activation Syndrome (MAS) treated with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)



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) decrease 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:
- 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]
 - 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]
 - 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>



FRONT LINE COVID-19 CRITICAL CARE ALLIANCE
MATH+ HOSPITAL TREATMENT PROTOCOL FOR COVID-19

References

1. Jehi L, Ji X, Milinovich A, erzurum S, Rubin B, Gordon S. Individualizing risk prediction for positive COVID-19 testing. Results from 11,672 patients. *Chest* 2020.
2. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French Cb, Aliaono JL. Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020; 12:988.
3. Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, Cirillo JD. Vitamin D insufficiency is prevalent in severe COVID-19. *medRxiv* 2020.
4. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? *Medicine in Drug Discovery* 2020.
5. Rhodes JM, Subramanian S, Laird E, Kenny RA. 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).
6. 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.
7. 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.
8. Daneshkhah A, Eshein A, Subramanian H. The role of vitamin D in suppressing cytokine storm of COVID-19 patients and associated mortality. *medRxiv* 2020.
9. Bergman P, Lindh AU, Bjorkhem-Bergman L, Lindhagen L. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* 2013; 8:e65835.
10. Shakoor H, Feehan J, Dhaheri AS, Ali HI, Platat C, Ismail LC. Immune-boosting role of vitamins D,C,E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19. *Maturitas* 2020.
11. Calder PC. Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention & Health* 2020; 3.
12. Carpagnano GE, Lecce V, Quaranta VN, Zito A, Buonamico E. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J Endocrinol Invest* 2020.
13. srael A, Cicurel A, Feldhamer I et al. The link between vitamin D deficiency and Covid-19 in a large population. *medRxiv* 2020.
14. Radujkovic A, Hippchen T, Tiwari-Heckler S, Dreher S, Merle U. Vitamin D deficiency and outcome of COVID-19 patients. *Nutrients* 2020; 12:2757.
15. Colunga Biancatelli RM, Berrill M, Mohammed YH, Marik PE. Melatonin for the treatment of sepsis: the scientific rationale. *J Thorac Dis* 2020; 12 (Suppl 1):S54-S65.
16. Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A. Therapeutic algorithm for use of melatonin in patients with COVID-19. *Front Med* 2020; 7:226.
17. Reiter RJ, Sharma R, Ma Q, Dominquez-Rodriguez A, Marik PE, Abreu-Gonzalez P. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Medicine in Drug Discovery* 2020; 6:100044.
18. Zhang R, Wang X, Ni L, Di X, Ma B. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* 2020; 250:117583.
19. Kleszczynski K, Slominski AT, Steinbrink K, Reiter RJ. Clinical trials for use of melatonin to fight COVID-19 are urgently needed. *Nutrients* 2020; 12.
20. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited. *Aging Clin Exp Res* 2020.
21. 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.
22. Colunga Biancatelli RM, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: experimental therapy for the prevention and treatment of SARS-CoV-2 via synergistic action. *Front Immunol* 2020.
23. Kyung Kim T, Lim HR, Byun JS. Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: a randomised controlled trial. *BMJ Mil Health* 2020.
24. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. *Expert Rev Anti Infect Ther* 2020; 18:99-101.
25. Hiedra R, Lo KB, Elbashabsheh M, Gul F, Wright RM. The use of IV vitamin C for patients with COVID-19: a case series. *Exp Rev Anti Infect Ther* 2020.
26. Khaerunnisa S. Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compuns by molecular docking study. *medRxiv* 2020.

27. Chen L, Li J, Luo C, Liu H, Xu W, Chen G. 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.
28. Nain Z, Rana HK, Lio P, Islam SM, Summers MA, Moni MA. Pathogenic profiling of COVID-19 and SARS-like viruses. *Briefings in Bioinformatics* 2020.
29. Yi L, Li Z, Yuan K et al. Small molecules blocking the entry of severe respiratory syndrome coronavirus into host cells. *J Virol* 2020; 78:11334-9.
30. Abian O, Ortega-Alarcon D, Jimenez-Alesanco A, Ceballos-Laita L, Vega S. Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. *International Journal of Biological Macromolecules* 2020; 164:1693-703.
31. Pistollato F, Masias M, Agudo P, Giampieri F. Effects of phytochemicals on thyroid function and their possible role in thyroid disease. *Ann N Y Acad Sci* 2019; 1433:3-9.
32. Tonstad S, Jaceldo-Siegl K, Messina M, Haddad E. The association between soya consumption and serum thyroid-stimulating hormone in the Adventist Health Study-2. *Public Health Nutr* 2016; 19:1464-70.
33. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. 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.
34. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. *Nutrients* 2017; 9.
35. 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.
36. Singh M, Das RR. Zinc for the common cold. *Cochrane Database of Syst Rev* 2013; 6:CD001364.
37. Hoeger J, Simon TP, Beeker T, Marx G, Haase H. Persistent low serum zinc is associated with recurrent sepsis in critically ill patients - A pilot study. *PloS ONE* 2017; 12:e0176069.
38. Freedberg DE, Conigliaro J, Sobieszczyk ME, Markowitz DD. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *medRxiv* 2020.
39. Janowitz T, Baglenz E, Pattinson D, Wang TC, Conigliaro J. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. *Gut* 2020; 69:1592-7.
40. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. *Am J Gastroenterol* 2020.
41. Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang XP, White KM. COVID-19: Famotidine, Histamine, Mast Cells, and mechanisms. *Research Square* 2020.
42. Meng Z, Wang T, Chen L, Chen X, Li L. An experimental trial of recombinant human interferon alpha nasal drops to prevent COVID-19 in medical staff in an epidemic area. *medRxiv* 2020.
43. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? *Drugs* 2020.
44. Muller C, Karl N, Ziebuhr J, Pleschka S. D,L-lysine acetylsalicylate + glycine impairs coronavirus replication. *J Antivir Antiretrovir* 2020.
45. Varatharajah N. COVID-19 CLOT: What is it? Why in the lungs? Extracellular histone, "auto-activation" of prothrombin, emperipolesis, megakaryocytes, "self-association" of Von Willebrand factor and beyond. *Preprints* 2020.
46. Hammock BD, Wang W, Gilligan MM, Panigrahy D. Eicosanoids. The overlooked storm in Coronavirus Disease 2019 (COVID-19)? *Am J Pathol* 2020.
47. Das UN. Can bioactive lipids inactivate coronavirus (COVID-19)? *Arch Med Res* 2020; 51:282-6.
48. Lee CR, Zeldin DC. Resolvin infectious inflammation by targeting the host response. *N Engl J Med* 2015; 373:2183-5.
49. Serhan CN. Novel pro-resolving lipid mediators in inflammation are leads for resolution physiology. *Nature* 2014; 510:92-101.
50. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020.
51. Patel AN, Desai SS, Grainger DW, Mehra MR. Usefulness of ivermectin in COVID-19 illness. *medRxiv* 2020.
52. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. ICON (Ivermectin in COvid Ninteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19. *Lancet* 2020.
53. Gorial FI, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM. Effectiveness of Ivermectin as add-on therapy in COVID-19 management (Pilot Trial). *medRxiv* 2020.

54. Scheim DE. Ivermectin for COVID-19 treatment: clinical response at quasi-threshold doses via hypothesized alleviation of CD147-mediated vascular occlusion. medRxiv 2020.
55. Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. Preprints 2020.
56. Idelsis Esquivel-Moynelo I, Perez-Escribano J, Duncan-Roberts Y, Dania Vazquez-Blonquist D. Effect of combination of interferon alpha-2b and interferon-gamma or interferon alpha 2b alone for elimination of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv 2020.
57. Davoudi-Monfarad E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M. Efficacy and safety of interferon B-1a in treatment of severe COVID-19: A randomized clinical trial. medRxiv 2020.
58. Wang N, Zhan Y, Zhu L, Hou Z, Liu F, Song P. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host & Microbe 2020;ePub.
59. Berg K, Bolt G, Andersen H, Owen TC. Zinc potentiates the antiviral action of human IFN-alpha tenfold. J Interferon Cytokine Res 2001; 21:471-4.
60. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. J Interferon Cytokine Res 1997; 17:469-72.
61. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home: Potential pitfalls and practical guidance. Ann Thorac Med 2020.
62. 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.
63. Risch HA. Early outpatient treatment of symptomatic, High-Risk Covid-19 patients that should be ramped-up immediately as key to the pandemic crisis. Am J Epidemiol 2020.
64. 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.
65. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020.
66. Mitja O, Corbacho-Monne M, Ubals M, Tebe C, Penafiel J. Hydroxychloroquine for early treatment of adults with mild Covid-19: A randomized-controlled trial. Clin Infect Dis 2020.
67. Mitja O, Ubals M, Corbach-Monne M, Alemany A, Suner C. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. medRxiv 2020.
68. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LC, Veiga VC, Avezum A. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 2020.
69. Skipper CP, Pastick KA, Engen NW. Hydroxychloroquine in nonhospitalized adults with early COVID-19. Ann Intern Med 2020.
70. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323:2493-502.
71. Geleris J, Sun Y, Platt J, Zucker J. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020.
72. Magagnoli J, Narendran S, Pereira F. Outcomes of hydroxychloroquine usage in United states veterans hospitalized with COVID-19. medRxiv 2020.
73. Lopez A, Duclos G, Pastene B, Bezulier K, Guihaumou R, Solas C. Effects of hydroxychloroquine on Covid-19 in Intensive Care Unit Patients: Preliminary Results. Int J Antimicrob Agents 2020.
74. Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medRxiv 2020.
75. Elsayah HK, Elsokary MA, Elrazzaz MG, ElShafey MG. Hydroxychloroquine for treatment of non-severe COVID-19 patients: systematic review and meta-analysis of controlled clinical trials. medRxiv 2020.
76. Axfors C, Schmitt AM, Janiaud P, van 't Hooft J, Abd_elsalam S, Abdo EF. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials. medRxiv 2020.
77. Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. Br J Clin Pharmacol 1989; 27:771-9.

78. MacGowan A, Hamilton F, Bayliss M, Read L, Attwood M. Hydroxychloroquine serum concentrations in non-critical care patients infected with SARS-CoV-2. medRxiv 2020.
79. Nicol MR, Joshi A, Rizk ML, Sabato PE, Savic RM. Pharmacokinetic and pharmacological properties of chloroquine and hydroxychloroquine in the context of COVID-19 infection. medRxiv 2020.
80. Hoffmann M, Mosbauer K, Hoffman-Winkler H, Kaul A, Kleine-Weber H. Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. Nature 2020.
81. 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; 2:192-7.
82. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv 2020.
83. Gautret P, Lagier JC, Parola P, Hoang VT. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020.
84. Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Raoult D. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Travel Medicine and Infectious Disease 2020.
85. Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Raoult D. Clinical efficacy of chloroquine derivatives in COVID-19 infection: Comparative meta-analysis between big data and the real world. New Microbes and New Infections 2020.
86. Morgan A, Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. J Altern Complement Med 2010; 16:753-9.
87. Effect of Dexamethasone in hospitalized patients with COVID-19-Preliminary report. N Engl J Med 2020.
88. Schultze A, Walker AJ, MacKenna B, Morten CE, Bhaskaran K, Brown JP. Inhaled corticosteroids use and the risk of COVID-19 related death among 966,461 patients with COPD or asthma: An OpenSAFELY analysis. medRxiv 2020.
89. Castillo ME, Costa LM, Barrios JM et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol 2020.
90. Quesada-Gomez JJ, Bouillon R. Is calcifediol better than cholecalciferol for vitamin D supplementation? Osteoporosis International 2018; 29:1697-711.
91. Cesareo R, Falchetti A, Attanasio R, Tabacco G, Naciu AM. Hypovitaminosis D: Is it time to consider the use of calcifediol? Nutrients 2019; 11:1016.
92. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med 2019; 381:2529-40.
93. Amrein K, Martucci G, McNally JD. When not to use meta-analysis: Analysing the meta-analysis on vitamin D in critical care. Clin Nutr 2017; 36:1729-30.
94. Hsu A, Liu Y, Zayac AS, Olszewski AJ, Reagan JL. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. Thrombosis Research 2020.
95. Kwon PS, Oh H, Kwon SJ et al. Sulphated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discovery 2020; 6:50.
96. Bikdeli B, Madhavan MV, Jimenez, Chuich T, Dreyfus I. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020.
97. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020.
98. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno P. Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: A single Health System Study. J Am Coll Cardiol 2020.
99. Klok FA, Kruip MJ, van der Meer NJ, Arbous MS. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research 2020.
100. Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z. Prevention and treatment of venous thromboembolism associated with Coronavirus Disease 2019 Infection: A consensus statement before guidelines. Thromb Haemost 2020.
101. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020.
102. Iba T, Levy JH, Levi M, Connors JM. Coagulopathy of coronavirus disease 2019. Crit Care Med 2020.
103. 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.

104. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; 46:1089-98.
105. 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.
106. Du L, Kao RY, Zhou Y, He Y. Cleavage of spike protein of SARS coronavirus by protease factor Xa is associated with viral infectivity. *Biochemical & Biophysical Research Communications* 2007; 359:174-9.
107. Taccone FS, Gevenois PA, Peluso L, Pletchette Z, Lheureux O. Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically ill coronavirus disease 2019 patients. *Crit Care Med* 2020.
108. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome (ARDS) caused by COVID-19. *Crit Care Expl* 2020; 2:e0111.
109. Fadel R, Morrison AR, Vahia A et al. Early course corticosteroids in hospitalized patients with COVID-19. *medRxiv* 2020.
110. Chroboczek T, Lacoste M, Wackenheim C, Challan-Belval T, Amar B, Boisson T. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. *medRxiv* 2020.
111. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020.
112. Cruz AF, Ruiz-Antoran B, Gomez AM, Lopez AS. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. *medRxiv* 2020.
113. Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. *J Allergy Clin Immunol* 2020.
114. Meduri GU, Bridges L, Shih MC, Marik PE, Siemienluk RA, Kocak M. 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.
115. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. *JAMA* 2020.
116. Ruiz-Irastorza G, Pijoan JI, Bereciatu E, Dunder S, Dominguez J, Garcia-Escudero P. Second week methylprednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *medRxiv* 2020.
117. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. The CoDEX randomized clinical trial. *JAMA* 2020.
118. Edalatfard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S. Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020.
119. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA* 2020.
120. Dequin PF, Heming N, Meziani F, Plantefeve G, Voiriot G. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. A randomized Clinical trial. *JAMA* 2020.
121. Wang Y, Zhang D, Du G, Du R. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicenter trial. *Lancet* 2020; 395:1569-78.
122. Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the treatment of Covid-19-Preliminary report. *N Engl J Med* 2020;ePub.
123. Spinner CD, Gottlieb RL, Criner GJ, Lopez JR, Cattelan AM. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. A randomized clinical trial. *JAMA* 2020.
124. McCreary EK, Angus DC. Efficacy of remdesivir in COVID-19. *JAMA* 2020.
125. Siemieniuk RA, Bortoszko JJ, Ge L, Zeraatkar D, Izcovich A. Drug treatments for Covid-19: living systematic review and network meta-analysis. *BMJ* 2020.
126. Ranieri VM, Pettilia V, Karvonen MK, Jalkanen J, Nightingale P. Effect of intravenous interferon B-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome. A randomized clinical trial. *JAMA* 2020.
127. Marik PE, Kory P, Varon J, Iglesias J, Meduri GU. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. *Exp Rev Anti Infect Ther* 2020.

128. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C and Thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; 151:1229-38.
129. Barabutis N, Khangoora V, Marik PE, Catravas JD. Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest* 2017; 152:954-62.
130. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients* 2018; 10:1762.
131. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Therapeut* 2018; 189:63-70.
132. Cheng RZ. Can early and high-dose vitamin C prevent and treat coronavirus disease 2019 (COVID-19). *Medicine in Drug Discovery* 2020.
133. Wang Y, Lin H, Lin BW, Lin JD. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care* 2019; 9:58.
134. Fowler AA, Truitt 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.
135. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. *PharmaNutrition* 2020; 12:100190.
136. Iglesias J, Vassallo AV, Patel V, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. *Chest* 2020; 158:164-73.
137. de Melo AF, Homem-de-Mello M. High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection. *Crit Care* 2020; 24:500.
138. Zhang J, Rao X, Li Y et al. High-dose vitamin C infusion for the treatment of critically ill COVID-19. *Research Square* 2020.
139. Jonmarker S, Hollenberg J, Dahlberg M, Stackelberg O. Dosing of thromboprophylaxis and mortality in critically ill COVID-19 patients. *medRxiv* 2020.
140. Tomasa-Irriguible TM, Martinez-Vega S, Mor-Marco E, Herraiz-Ruiz A, Ragner-Pardo L. Low molecular weight heparins in COVID-19 patients: beware of augmented renal clearance! *Crit Care* 2020; 24:325.
141. Menezes RR, Godin AM, Rodrigues FF, Coura GM, Melo IS, Brito AM. 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.
142. Vatsalya V, Li F, Frimodig J, Gala KS, Srivastava S, Kong M. Therapeutic prospects for Th-17 cell immune storm syndrome and neurological symptoms in COVID-19: Thiamine efficacy and safety, In-vitro evidence and pharmacokinetic profile. *medRxiv* 2020.
143. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! *J Thorac Dis* 2016; 8:1062-6.
144. Moskowitz A, Donnino MW. Thiamine (vitamin B1) in septic shock: a targeted therapy. *J Thorac Dis* 2020; 12 (suppl 1):S78-S83.
145. Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, Morris PE, Flannery AH. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med* 2018; 46:1747-52.
146. Marik PE. Thiamine: An essential component of the metabolic resuscitation protocol. *Crit Care Med* 2018; 46:1869-70.
147. Lee CY, Jan WC, Tsai PS, Huang CJ. Magnesium sulfate mitigates acute lung injury in endotoxemia rats. *J Trauma* 2011; 70:1177-85.
148. Salem M, Kasinski N, Munoz R, Chernow B. Progressive magnesium deficiency increases mortality from endotoxin challenge: Protective effects of acute magnesium replacement therapy [abstract]. *Crit Care Med* 1995;A260.
149. 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.
150. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Resp Med* 2018; 6:691-8.

151. 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.
152. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 2020; 24:429.
153. Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Research Square* 2020.
154. Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. *Am J Cardiol* 2020.
155. Oldenburg CE, Doan T. Azithromycin for severe COVID-19. *Lancet* 2020.
156. Futado RH, Berwanger O, Fonseca HA, Correa TD, Ferraz LR, Lapa MG. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised trial. *Lancet* 2020.
157. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. *Intensive Care Med* 2020.
158. Xu Q, Wang T, Quin X, Zha L. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19; a case series. *Crit Care* 2020; 24:250.
159. Elharrar X, Trigui Y, Dois AM, Touchon F. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020.
160. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit Care* 2020.
161. Keith P, Wells AH, Hodges J, Fast SH. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: A single center experience. *Crit Care* 2020; 24:518.
162. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. *Intensive Care Med* 2002; 28:1434-9.
163. Morath C, Weigand MA, Zeier M, Speer C, Tiwari-Heckler S. Plasma exchange in critically ill COVID-19 patients. *Crit Care* 2020; 24:481.
164. Khamis F, Al-Zakwani I, Al Hashmi S, Al Dowaiki S, Al Bahrani M. Therapeutic plasma exchange in adults with severe COVID-19 infection. *Int J Infect Dis* 2020.
165. Fernandez J, Gratacos-Gines J, Olivas P, Costa M, Nieto S, Mateo D. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. *Crit Care Med* 2020.
166. Gucyetmez B, Atalan HK, Sertdemir I, Cakir U, Telci L. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. *Crit Care* 2020; 24:492.
167. Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *medRxiv* 2020.
168. Wang J, Najzadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA. Tissue plasminogen activator (tPA) treatment for COVID-19 associated respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost* 2020.
169. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. *ChinaXiv* 2020.
170. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonists Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020.
171. Rosas IO, Brau N, Waters M et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. *medRxiv* 2020.
172. Scherger S, Henao-Martinez A, Franco-Paredes C, Shapiro L. Rethinking interleukin-6 blockade for treatment of COVID-19. *Medical Hypotheses* 2020; 144:110053.
173. Zeng QL, Yu ZJ, Gou JJ, Li GM. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *Clin Infect Dis* 2020.
174. Li L, Zhang W, Hu Y, Tong X, Zeng S, Yang J. 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; 324:460-70.
175. 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.

176. Duan K, Liu B, Li C, Zhang H. Effectiveness of convalescent plasma therapy in severe COVID-10 patients. *PNAS* 2020.
177. Jacobs JJ. Neutralizing antibodies mediate virus-immune pathology of COVID-19. *Med Hypotheses* 2020; 143:109884.
178. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. *J Microbiol Immunol Infect* 2020.
179. Favalli EG, Biggoggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis* 2020.
180. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395:1033-4.
181. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. *Medical Hypotheses* 2020; 144:11005.
182. Saba A, Vaidya PJ, Chavhan VB, Achlerkar A, Leuppi J. Combined pirfenidone, azithromycin and prednisolone in post-H1N1 ARDS pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35:85-90.
183. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD. Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Resp Med* 2020; 8:750-2.
184. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Resp Med* 2020; 8:807-15.
185. Brouwer WP, Duran S, Kuijper M, Inc C. 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.
186. 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; 58:27-8.
187. Abrams D, Lorusso R, Vincent JL, Brodie D. ECMO during the COVID-19 pandemic: when is it unjustified. *Crit Care* 2020; 24:507.
188. Bryce C, Grimes Z, Pujadas E et al. Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. *medRxiv* 2020.
189. Slaats J, ten Oever J, van de Veerdonk FL, Netea MG. IL-1B/IL-6/CRP and IL-18/ferritin: Distinct inflammatory programs in infections. *PLoS Pathog* 2016; 12:e1005973.
190. Colafrancesco S, Alessandri C, Conti F, Priori R. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmunity Reviews* 2020; 19:102573.
191. Giamarellos-Bouboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host & Microbe* 2020.
192. 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.
193. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A, Dimopoulos G. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Medicine* 2017; 15:172.
194. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol* 2020.
195. 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.
196. Stephenson E, Hooper MH, Marik PE. Vitamin C and Point of Care glucose measurements: A retrospective, Observational study [Abstract]. *Chest* 2018; 154 (suppl.):255a.
197. Patel H, Calip GS, DiDomenico RJ, Schmock GT. Comparison of cardiac events associated with azithromycin vs amoxicillin. *JAMA Network Open* 2020; 3:e2016864.
198. Brosnahan SB, Bhatt A, Berger JS, Yuriditsky E, Iturrate E. COVID-19 pneumonia hospitalizations followed by re-presentation for presumed thrombotic event. *Chest* 2020.
199. Spyropoulos AC, Lipardi C, Xu J, Peluso C, Spiro TE. Modified IMPROVE VTE Risk Score and elevated D-Dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open* 2020; 4:e59-e65.
200. Kunutsor SK, Seidu S, Blom AW, Khunti K. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. *Eur J Epidemiol* 2017; 32:657-67.

201. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020.
202. Prescott HC, Girard TD. Recovery from Severe COVID-19. Leveraging the lessons of survival from sepsis. *JAMA* 2020.
203. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute Covid-19 in primary care. *BMJ* 2020.
204. Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC. Cerebral micro-structural changes in COVID-19 patients - An MRI-based 3-month follow-up study. *EClinicalMedicine* 2020.
205. Riche F. Protracted immune disorders at one year after ICU discharge in patients with septic shock. *Crit Care* 2018; 22:42.
206. Andreaskos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. *Allergy* 2020.
207. Dalli J, Chiang N, Serhan CN. Elucidation of novel 13-series resolvins that increase with atorvastatin and clear infections. *Nat Med* 2015; 21:1071-5.
208. Kurcicka L, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med* 2020; 173:262-7.
209. Cheng HY, Jian SW, Liu DP, Huang WT, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med* 2020; 180:1156-63.
210. Zhao J, Yang Y, Huang H, Li D, Gu D. Relationship between ABO blood group and the COVID-19 susceptibility. *medRxiv* 2020.
211. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A. 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.
212. Goren A, Vamo-Galvan S, Wambier CG, McCoy J. 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.
213. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020.
214. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med* 2020.
215. von der Thusen J, van der Eerden M. Histopathology and genetic susceptibility in COVID-19 pneumonia. *Eur J Clin Invest* 2020.
216. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. *Ann Intern Med* 2020.
217. Pujadas E, Chaudhry F, McBride R, Richter F, Zhao S. SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Resp Med* 2020.
218. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. *Science* 2020; 369.
219. Zhang Q, Bastard P, Liu Z, Le Pen J, Chen J, Korol C. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020.
220. Zhou Y, Fu B, Zheng X, Wang D, Zhao C. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev* 2020; 7:998-1002.
221. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020.
222. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020.
223. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *medRxiv* 2020.
224. Qin C, Zhou L, Hu Z, Zhang S. Dysregulation of the immune response in patients with COVID-19 in Wuhan, China. *Lancet Infect Dis* 2020.
225. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. *J Infection* 2020.
226. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020.
227. Tay MZ, Poh CM, Renia L, MacAry PA. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews* 2020; 20:363-74.

228. 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.
229. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nature Reviews* 2020.
230. Varga Z, Flammer AJ, Steiger P, Habrecker M, Andermatt R, Zinkernagel AS. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020.
231. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. *N Engl J Med* 2020; 383:120-8.
232. Kory P, Kanne JP. SARS-CoV-2 organizing pneumonia: "Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?". *BMJ Open Res* 2020; 7:e000724.
233. Torrealba JR, Fisher S, Kanne JP, Butt YM, Glazer C, Kershaw C. Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. *Human Pathology* 2018; 71:30-40.
234. Kanne JP, Little BP, Chung JH, Elicker BM. Essentials for radiologists on COVID-19: an Update-Radiology Scientific Expert Panel. *Radiology* 2020.
235. Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection [letter]. *Intensive Care Med* 2020.
236. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensive Care Med* 2020; 46:1099-102.
237. Chiumello D, Cressoni M, Gattinoni L. Covid-19 does not lead to a "typical" Acute Respiratory Distress syndrome. *Lancet* 2020.
238. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020; 24:154.
239. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005; 31:776-84.
240. Jeronimo CM, Farias ME, Almeida FF, Sampaio VS, Alexandre MA, Melo GC. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020.
241. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P. Pulmonary post-mortem findings in a large series of COVID-19 cases from Northern Italy. *medRxiv* 2020.
242. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H. 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.
243. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Resp Med* 2020.
244. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med* 2020.
245. Schurink B, Roos E, Radonic T, Barbe E, Bouman CS. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 2020.
246. Buijssers B, Yanginlar C, Maciej-Hulme ML, de Mast Q. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine* 2020.
247. Kim SY, Jin W, Sood A, Montgomery DW, Grant OC, Fuster MM. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. *Antiviral Res* 2020; 181:104873.
248. Clausen TM, Sandoval DR, Spliid CB et al. SARS-CoV-2 infection depends on cellular heparan sulphate and ACE2. *bioRxiv* 2020.
249. Huang X, Han S, Liu x, Wang T, Xu H. Both UFH and NAH alleviate shedding of endothelial glycocalyx and coagulopathy in LPS-induced sepsis. *Exp Thera Med* 2020; 19:913-22.
250. Buijssers B, Yanginlar C, de Nooijer A, Grondman I, Jonkman I, Rother N. Increased plasma heparanase activity in COVID-19 patients. *medRxiv* 2020.
251. May JM, Qu ZC. Ascorbic acid prevents oxidant-induced increases in endothelial permeability. *Biofactors* 2011; 37:46-50.
252. Utoguchi N, Ikeda K, Saeki K et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. *Journal of Cellular Physiology* 1995; 163:393-9.
253. Han M, Pendem S, Teh SL, Sukumaran DK, Wu F, Wilson JX. Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. *Free Radic Biol Med* 2010; 48:128-35.
254. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci* 2004; 1024:138-46.

255. Shodell M, Siegal FP. Corticosteroids depress INF-alpha-producing plasmacytoid dendritic cells in human blood. *J Allergy Clin Immunol* 2001; 108:446-8.
256. Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Scientific Reports* 2014; 4:7176.
257. Singanayagam A, Glanville N, Girkin JL, Ching YM, Marcellini A. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nature Communications* 2018; 9:2229.
258. Salton F, Confalonieri P, Santus P et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. *medRxiv* 2020.
259. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. *Lancet* 1983;995-7.
260. 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.
261. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, Ortiz M, O'Sullivan CK. 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.
262. Rhodes J, Dunstan F, Laird E, Subramanian S, Kenny RA. COVID-19 mortality increases with northerly latitude after adjustment for age suggesting a link with ultraviolet and vitamin D. *BMJ Nutrition, Prevention & Health* 2020.
263. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 with coagulopathy. *medRxiv* 2020.
264. Sardu C, Gambardella J, Morelli MB, Wang X. Is COVID-19 an endothelial disease? Clinical and basic evidence. *medRxiv* 2020.
265. 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.
266. 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.
267. Yam LY, Lau AC, Lai FY, Shung E, Chan J. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. *J Infection* 2007; 54:28-39.
268. Saune PM, Bryce-Alberti M, Portmann-Baracco AS, Accinelli RA. Methylprednisolone pulse therapy: An alternative management of severe COVID-19. *Respiratory Medicine Case Reports* 2020; 31:101221.
269. Fernandez-Cruz A, Ruiz-Antoran B, Gomez AM et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. *medRxiv* 2020.
270. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv* 2020.
271. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone. A potential strategy to avoid steroid-related *Strongyloides* hyperinfection. *JAMA* 2020; 324:623-4.