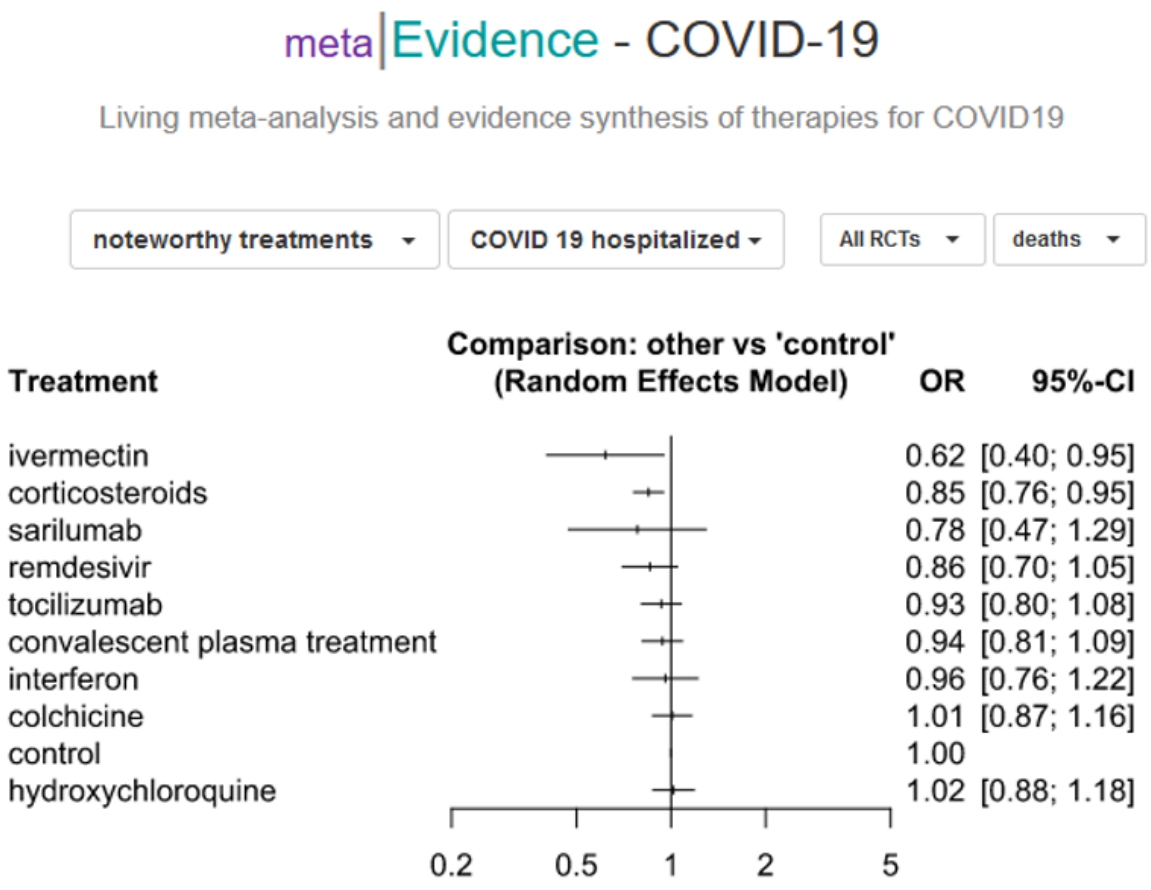
- Not recommended: Hydroxychloroquine, azithromycin, doxycycline, or quinolone antibiotics. [172,173]
- Not recommended: Colchicine. Recruitment to the colchicine arm of the RECOVERY trial has been closed as no mortality benefit was noted with colchicine (Mortality 20% colchicine, 19% standard of care). In addition, potentially serious drug-drug interactions exist with the use of colchicine and CYP 3A4 and p-glycoprotein inhibitors (ivermectin, macrolide antibiotics, cyclosporin, etc) as well as with the use of statins. [252]

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.

Figure 8. Network meta-analysis of various interventions on hospital mortality.



5. MATH + PROTOCOL (for patients admitted to the ICU) [343,344]

5.1 Core Components

1. ***Methylprednisolone*** 80 mg loading dose followed by 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 6 hourly, then titrate down as appropriate. [293-305] Pulse methylprednisolone 500-1000 mg/day for 3 days (followed by taper) may be required.[303] We suggest that all patients admitted to the ICU have a chest CT scan on admission to allow risk stratification based on the extent of the disease; those with extensive disease should be initiated on high dose corticosteroids (see section below on severe COVID). As depicted in Table 2, methylprednisolone is the corticosteroid of choice. Observational and randomized studies have clearly demonstrated the superiority of methylprednisolone over low dose dexamethasone.[345,346] These clinical findings are supported by a genomic study.[184] Methylprednisolone should be weaned slowly over two weeks once oxygen is discontinued to prevent relapse/recurrence (20mg twice daily once of oxygen, then 20 mg/day for 5 days, then 10 mg/day for 5 days). While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/countries where it is not available the following (in order of preference) may be substituted for methylprednisolone (dose adjusted according to methylprednisolone dosages), 2) prednisolone, 3) prednisone, 4) hydrocortisone, and 5) LASTLY dexamethasone.
2. ***Ascorbic acid (Vitamin C***) 50 mg/kg (or 3000 mg) IV q 6 hourly for at least 7 days and/or until transferred out of ICU.[98,107,108,347-357]. *Mega-dose vitamin C* should be considered in severely ill patients, those with progressive respiratory failure and as salvage therapy: 25 g vitamin C in 200-500 cc saline over 4-6 hours every 12 hourly for 3-5 days, then 3g IV q 6 hourly for total of 7-10 days of treatment [358] (also see https://www.youtube.com/watch?v=Au-mp6RZjCQ). Mega-dose Vitamin C appears safe in patients with ARF and ESRD. In patients with CRF a dose of 12.5 g q 12 hourly may be an adequate compromise.[359] In the study by Lankadeva et al, mega-dose vitamin C increased renal cortical blood flow and renal cortical pO2; oxalate crystals were not detected.[358] 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, should IV Vitamin C not be available, it would be acceptable to administer PO vitamin C at a dose of 1g every 4–6 hours.
3. ***Anticoagulation***: The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a marginally increased mortality in ICU patients treated with full anti-coagulation (35.3% vs. 32.6%).[306] Critically ill COVID-19 patients frequently have impaired renal and it is likely that in the absence of Xa monitoring patients were over-anticoagulated. However, full anti-coagulation should be continued on floor patients transitioned to the ICU who have normal renal function. In all other patients we would suggest intermediate dose enoxaparin i.e 60 mg/day (enhanced thromboprophylaxis) or 0.5 mg/kg q 12 hourly.[360] Full anticoagulation (enoxaparin or heparin) may be required in patients with increasing D-dimer or with thrombotic complications. Due to augmented renal clearance some patients may have reduced anti-Xa activity despite standard dosages of LMWH.[236] We therefore recommend monitoring anti-Xa activity aiming for an anti-Xa activity of 0.5 – 0.9 IU/ml. Heparin is suggested with CrCl < 15 ml/min. It should also be appreciated that vitamin C is a prerequisite for the synthesis of collagen and vitamin C deficiency is classically associated with vascular bleeding.[107,108] This is relevant to COVID-19, as vitamin C levels are undetectable in severely ill COVID-19 patients and this may partly explain the increased risks of anticoagulation in ICU patients (not treated with vitamin C). [361-363] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [364]

Note: A falling SaO2 and the requirement for supplemental oxygen should be a trigger to start anti-inflammatory treatment.

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

5.2 Additional Treatment Components

4. Highly recommended: Ivermectin 0.6 – 1.0 mg/kg day orally for 5 days or until recovered [19,62-64,142,145-152,288-290,365-371]. A higher dose (1.0 mg/kg) is suggested in patients with severe disease and/or those with delayed initiation of therapy. Note that ivermectin has potent antiviral and anti-inflammatory effects. As noted above clinical outcomes are superior with multiday as opposed to single day dosing. Furthermore, as indicated above, higher dosages and a longer treatment course are suggested with the Delta variant.
5. Nitazoxanide (NTZ) 600 mg BID for 7 days.[292] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
6. Melatonin 10 mg at night (the optimal dose is unknown).[32-34]
7. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [372-377] Thiamine may play a role in dampening the cytokine storm. [373,378]
8. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe pro-thrombotic state and increasing the inflammatory response.[186,187,311,312] As the risk of significant bleeding is increased in patients receiving both ASA and heparin, ASA should therefore not be used in patients at high risk of bleeding. In addition (as noted below) patients should receive famotidine concurrently.
9. The anti-serotonin agent, cyproheptadine. Platelet activation results in the release of serotonin, which may contribute to the immune and vascular dysfunction associated with COVID-19. [215-219] Therefore, the serotonin receptor blocker cyproheptadine 4–8 mg PO q 6 hours should be considered.
10. Anti-androgen therapy (both men and women). Spironolactone 100 mg BID for 10 days. Second line: Dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. Finasteride 10 mg is an alternative (dutasteride cannot be crushed).[200] [379] **AVOID IN PREGNANCY**. [198,203] Bicalutamide 150mg daily is also an option.

5.3 Second line treatments

11. B complex vitamins.
12. Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40 mg daily is an alternative.
13. Active forms of Vitamin D (Calcifediol 25-OH Vitamin D or Calcitriol 1,25-OH Vitamin D). [307] Calcifediol 0.5 mg day 1, followed by 0.2 mg weekly until discharged from hospital (this is high dose therapy based on the Spanish study). Calcitriol 0.5 mcg (ug) day 1 then 0.25 mcg daily for 7 days. Should calcifediol/calcitriol not be available, supplement with vitamin D3 (cholecalciferol) 20,000–60,000 IU single oral dose, followed by 20,000 IU D3 weekly until discharged from hospital. In the acute setting calcifediol/calcitriol appears to be more effective than vitamin D3. [309] Vitamin D3 takes many days to be converted to 25-OH vitamin D; [310] this may explain the lack of benefit of vitamin D3 in patients hospitalized with severe COVID-19. [87]
14. 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.

15. Atorvastatin 40- 80 mg/day (reduce dose to 40 mg if taken with ivermectin due to possible drug-drug interaction. Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[238-242] *Due to numerous drug-drug interactions simvastatin should be avoided.*
16. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [140] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [380-382]

5.4 Optional Treatments and those of uncertain benefit

17. *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [37-43].
18. *Optional:* Maraviroc 300 mg BID for 10 days (see discussion above).
19. *Optional:* JAK inhibitors ruxolitinib or baricitinib.
20. *Unclear benefit. Losartan 50- 100 mg q day (reduce to 25 -50 mg with impaired renal function) or telmisartan 40-80 mg BID (reduce to 40 mg q day /BID with impaired renal function). [246,383,384]*
21. *Unclear benefit.* CCR5 antagonists, including Maraviroc. [234] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19.[231,385] Blocking the CCR5 receptor (CCR5R) repolarizes macrophages/monocytes and decreases the production of proinflammatory cytokines (see section on repolarizing macrophages/monocytes).
22. *Not recommended:* The best information to date suggests that prophylactic azithromycin as well as doxycycline and quinolone antibiotics are of little benefit in patients with COVID-19.[285,386,387] Patients with COVID-19 are at an increased risk of developing bacterial superinfections and prophylactic antibiotics may increase the risk of infection with multi-resistant organisms.
23. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
24. *Not recommended.* Convalescent serum [388-393] nor monoclonal antibodies. [394] However, convalescent serum/ monoclonal antibodies may have a role in patients with hematologic malignancies.[395]
25. *Not recommended.* Colchicine (see above).
26. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [396-400] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [342] Tocilizumab may have of benefit in patients receiving an inadequate dose of corticosteroids.[401] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.
27. Broad-spectrum antibiotics added if complicating bacterial pneumonia is suspected based on procalcitonin levels and respiratory culture (no bronchoscopy). Due to the paradox of hyper-inflammation and immune suppression (a major decrease of HLA-DR on CD14 monocytes, T cell dysfunction and decreased CD4 and CD8 counts) secondary bacterial and fungal infections (Candida and Aspergillus species) and viral reactivation is not uncommon. [402-404] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [405] Recommended first-line therapy for CAPA is either voriconazole or isavuconazole (beware drug-drug interactions). While low CD4 counts are typical of severe COVID-19 infection, PJP infections have not been reported; therefore PJP prophylaxis is not required.
28. 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.
29. 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.

30. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible.*** Intubation is indicated in patients who have failed non-invasive ventilation and in those patients with excessive work of breathing. A subgroup of patients with COVID-19 deteriorates very rapidly. Intubation and mechanical ventilation may be required in these patients.

   a. Accept "permissive hypoxemia" (keep O2 Saturation > 84%); follow venous lactate and Central Venous O_2 saturations ($ScvO_2$) in patents with low arterial O_2 saturations
   b. N/C 1–6 L/min
   c. High Flow Nasal canula (HFNC) up to 60–80 L/min
   d. Trial of inhaled Flolan (epoprostenol)
   e. Attempt proning (cooperative repositioning-proning) [406-409]
   f. Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
   g. Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cm H_2O.
   h. Moderate sedation to prevent self-extubation
   i. Trial of inhaled Flolan (epoprostenol)
   j. 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.[410] 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.

Figure 9. "Typical" progression of Chest CT findings.

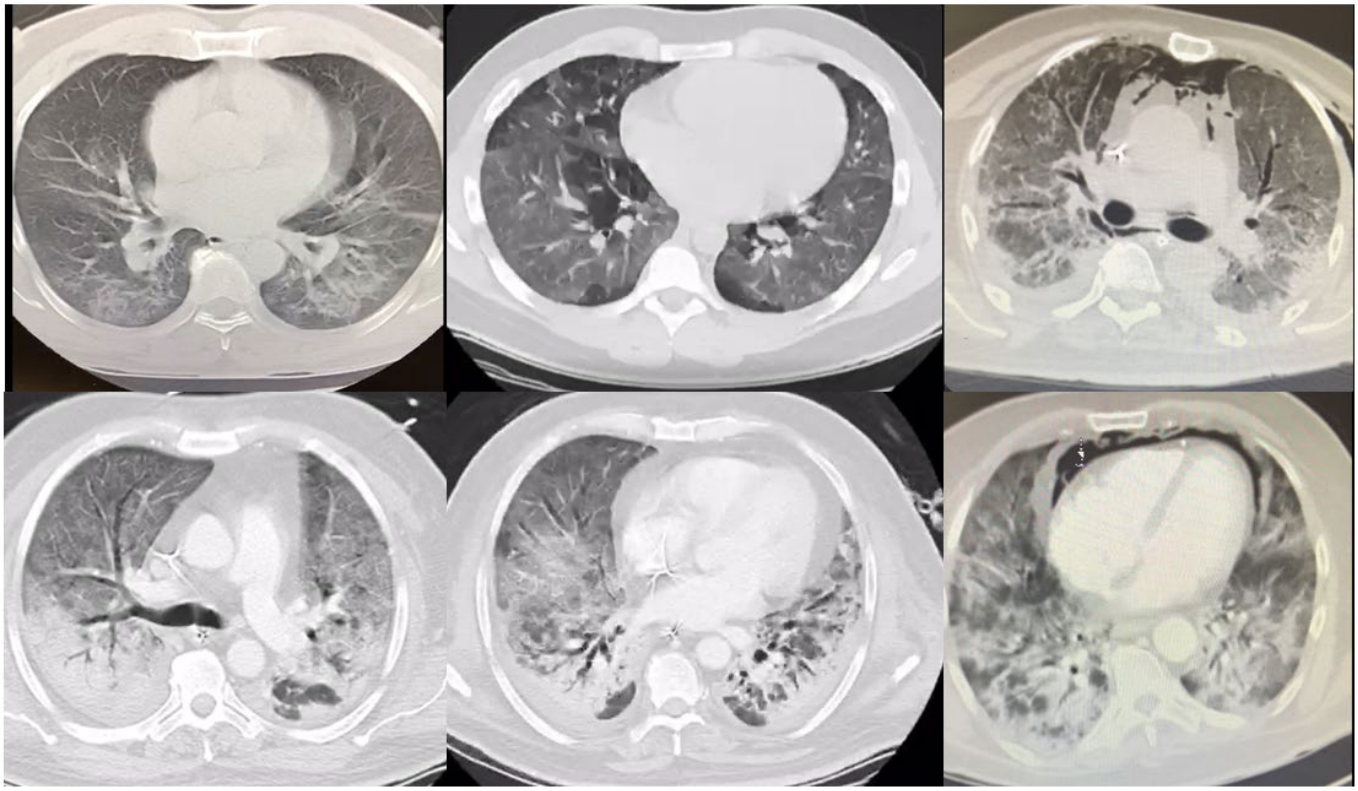


Table 2: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone- Number Need to Treat (NNT)

PUBLISHED RCT's/OCT's OF CORTICOSTEROID THERAPY IN COVID-19		ABSOLUTE DIFFERENCE IN MORTALITY	NUMBER NEEDED TO TREAT TO SAVE ONE LIFE
METHYLPREDNISONE – HOSPITAL PATIENTS (Edalatifard et al, Italy) 250mg methylprednisone daily x 3 days		5.9% vs. 42.9%	2.7
METHYLPREDNISONE – ICU PATIENTS (Confalonieri et al, Italy) 80mg methylprednisone daily x 8 days		7.2% vs. 23.3%	6.2
METHYLPREDNISONE- ARDS PATIENTS (OCT - Wu C et al- China) 1-2 mg/kg/day for 3-5 days		46.0% vs. 61.8%	6.3
METHLPREDNISONE – HOSPITAL PATIENTS, (OCT - Fadel et al, USA) 0.5-1.0mg/kg/day x 3 days		13.6% vs. 26.3%	7.8
METHYLPREDNISONE - Pts on oxygen – (Fernandez-Cruz at al, Spain) 1mg/kg/day		13.9% vs. 23.9%	10.0
METHYLPREDNISONE VS. DEXAMETHASONE (Ranjbar et al, Iran) 2mg/kg/day MP vs. 6mg/day Dexamethasone		18.6% vs 37.5%	5.3
METHYLPREDNISONE VS. DEXAMETHASONE (OCT - Ko et al, USC) >= 1mg/kg/day MP for min. 3 days vs. 6mg/day Dex for min. 7 days	OVERALL	16.4% vs. 26.5%	10
	PTS ON MV	31% vs. 54%	4.3
HYDROCORTISONE -CAPE-COVID – ICU Patients (Dequin et al France) 200mg/day with taper over 14 days – stopped early		14.7% vs 27.4%	7.9
HYDROCORTISONE –REMAP-CAP – ICU Patients (Angus et al) 200 - 400 mg/day x 7 days – stopped early		28% vs 33% (NS)	20.0
DEXAMETHASONE – CODEX – ICU Patients (Tomazini et al) 20 mg x 5 days, 10 mg x 5 days		56.3% vs 61.5%	19.2
DEXAMATHASONE – RECOVERY (Hornsby et al) 6mg/day x 10 days	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4

6. An Approach to the patient with SEVERE Life threatening COVID-19 Organizing Pneumonia

The first task of the clinician is to determine the reversibility of the pulmonary disease…. This is a critical assessment. Aggressive anti-inflammatory treatment is futile in patients with advanced fibrotic lung disease…. The horse has already bolted and allowing the patient a "peaceful death" is the most compassionate and humane approach. The reversibility of the pulmonary disease is dependent on a number of factors superseded by a good deal of clinical judgement; these include:

a) The length of time that has elapsed since the onset of symptoms. Early aggressive treatment is critical to prevent disease progression. With each day the disease becomes more difficult to reverse. The 'traditional' approach of supportive care alone is simply unacceptable.
b) The level of inflammatory biomarkers particularly the CRP. In general the CRP tracks the level of pulmonary inflammation.[411] A high CRP is indicative of a hyper-inflammatory state and potentially reversible pulmonary inflammation.
c) It is likely that advanced age is a moderating factor making the pulmonary disease less reversible.
d) A chest CT is extremely helpful in determining the reversibility of disease. BEWARE this is not ARDS but organizing pneumonia.[412] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively (see Figure 9).[411,413-419] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19.[420,421] The changes in the CT follow a stereotypic progressive pattern:
    I. Peripheral, patchy, predominantly basal ground glass opacification (GGO). GGO is defined an increase in density of lung with visualization of bronchial and vascular structures through it
    II. Progressive widespread bilateral GGO
    I. Crazy paving (CGO with interlobular and intralobular septal thickening)
    II. Air space consolidation (air bronchograms)
    III. Dense airspace consolidation
    IV. Coalescent consolidation
    V. Segmental/subsegmental pulmonary vessel dilatation
    VI. Bronchial wall thickening
    VII. Linear opacities
    VIII. Traction bronchiectasis
    IX. Cavitation
    X. Fibrotic changes with bullae and reticulation

GGO pattern is significantly more prevalent in early-phase disease compared with late-phase disease while crazy-paving and consolidation patterns are significantly more common in late-phase.[411] Therefore widespread GGO suggests reversibility while widespread consolidation with other features of more advanced disease suggest irreversible lung disease. However, when in doubt (borderline cases) a time limited therapeutic trial of the aggressive full "Monty" approach may be warranted.

7. The FULL "MONTY" for SEVERE COVID Pulmonary disease

I. Methylprednisolone 250-500 mg q 12 hourly for at least 3 days then titrate guided by clinical status and CRP.
II. Ivermectin 1.0 mg/kg for 5 days
III. Melatonin 10 mg PO at night
IV. Enoxaparin 60 mg daily; critically ill patients usually have some degree of renal impairment and will require a renally adjusted lower dose. Patients with very high D-dimer and or thrombotic complications may require full anticoagulant doses of Lovenox. It may be prudent to monitor Xa levels aiming for 0.4-0.8 IU/ml (a somewhat lower anti-Xa).
V. Vitamin C 3 g 6 hourly to 25g q 12 hourly
VI. Cyproheptadine 4–8 mg PO q 6 hourly
VII. Fluvoxamine 50- 100 mg BID or fluoxetine 20-40mg daily
VIII. Spironolactone 100 mg BID
IX. Atorvastatin 80 mg/day (reduce dose to 40mg if taken with ivermectin due to possible drug-drug interaction)
X. Thiamine 200 mg q 12 hourly
XI. Finasteride 10 mg daily or dutasteride 2mg day 1 then 1mg daily or bicalutamide 150mg daily
XII. Omega-3 fatty acids 4g/day
XIII. Famotidine 40 mg BID
XIV. Consider plasma exchange on admission to the ICU.

While it is unclear which of the above medications included in the "Severe Covid-19" cocktail contributes to improved outcomes, all of these drugs have been shown to be safe and independently to improve the outcome of patients with COVID-19. Ultimately it is irrelevant as to the contribution of each element as long as the patient improves and survives his/her ICU stay. We are in the midst of a pandemic caused by a virus causing devastating lung disease, and there is no place for "ivory tower medicine".

8. Salvage Treatments

- High dose bolus corticosteroids; 500–1000 mg/day methylprednisolone for 3 days then taper. [301,303]
- Plasma exchange [422-428]. 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".
- Mega-dose vitamin C should be considered in severely ill patients and as salvage therapy: 25g vitamin C in 200-500 cc saline over 4-6 hours, 12 hourly for 3-5 days, then 3g IV q 6 hourly for total of 7-10 days of treatment.[358,359] (also see https://www.youtube.com/watch?v=Au-mp6RZjCQ)
- In patients with a large dead-space ventilation i.e. high $PaCO_2$ despite adequate minute ventilation consider "Half-dose rTPA" to improve pulmonary microvascular blood flow; 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation.[429,430]
- Etoposide IV once per week at 50 mg/m2 until improved. [431,432] Severe-COVID pneumonia/organizing pneumonia is in essence caused by the "pulmonary macrophage activation syndrome". [433,434] Similar to the treatment of macrophage activation syndrome and HLH, etoposide may reduce macrophage numbers and improve outcome.[435-437] Etoposide is a chemotherapeutic agent and the risk/benefits should be considered in consultation with a hematologist. Furthermore, the changes in the hematological profile should be closely monitored.
- Combination inhaled nitric oxide (or epoprostenol) and intravenous almitrine (10 – 16 ug/kg/min). The combination of inhaled nitric oxide, a selective pulmonary vasodilator, and almitrine, a specific pulmonary vasoconstrictor, may improve the severe V/Q mismatch in patients with severe COVID-19 "pneumonia". [438-441]
- ECMO [442-444]. Unlike "typical ARDS", COVID-19 patients may not progress into a resolution phase. Rather, patients with COVID-19 with unresolved inflammation may progress to a severe fibro-proliferative phase and ventilator dependency. ECMO in these patients would likely serve little purpose. ECMO however may improve survival in patients with severe single organ failure (lung) if initiated within 7 days of intubation. [445]
- Lung transplantation. [446]

9. Salvage treatments of unproven/no benefit.

- Convalescent serum/monoclonal antibodies: Four RCT's failed to demonstrate a clinical benefit with the use of convalescent serum. [388-390,392,393] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[447] It is noteworthy that the only RCT demonstrating efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever. [211] Furthermore, giving antibodies directed against SARS-CoV-2 appears pointless when the virus is already DEAD (pulmonary phase). In addition, IgG is a large protein which penetrates tissues poorly, and is unlikely to achieve submucosal concentrations required for mucosal immunity.[448] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [449]
- In patients hospitalized with severe COVID-19, Canakinumab, an anti-interleukin-1 β antibody failed to improve any outcome measure. [450]

- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [451-454] 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/D with cytokine absorbing/filtering filters [455,456] This treatment strategy appears to have an extremely limited role.

10. Treatment of Macrophage Activation Syndrome (MAS)

- Severe-COVID pneumonia/organizing pneumonia is in essence caused by the "pulmonary macrophage activation syndrome" and the distinction between severe COVID and MAS is unclear (see below). [433,434]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multisystem organ failure.[435]
- "*High dose corticosteroids*." Methylprednisolone 500-1000 mg daily for three days and then wean according to Ferritin, CRP, AST/ALT. Ferritin should decrease by at least 15% before weaning corticosteroids.
- Similar to the treatment of macrophage activation syndrome and HLH, etoposide may reduce macrophage numbers and improve outcome (see above).[435-437] The combination of high dose corticosteroids and "low-dose" etoposide is an effective treatment for MAS.
- Consider plasma exchange.

11. Approach to the DELTA/P1 Variant

- Both the Delta and P1 variants are highly virulent strains of SARS-COv-2. These variants replicate to achieve very high concentrations in the nasopharynx; hence they are much more transmissible and the time from exposure to symptom onset and to the pulmonary phase is much shorter. It is not uncommon for patients to be symptomatic for as little as 3 days prior to ICU admission.
- Early (day 1) outpatient treatment (MASK +) is critical to prevent progression to the more lethal pulmonary phase.
- ICU patients frequently present with very high levels of inflammatory markers (CRP, Ferritin, D-Dimer)
- The 'Full Monty" should be started on the first ICU Day.
- In those patients with very high inflammatory markers plasma exchange should be considered on admission.

12. Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[457] A PCT is essential to rule out coexisting bacterial pneumonia.[458]
- As indicated above (corticosteroid section), a chest CT scan on admission to the ICU is very useful for risk stratification and for the initial corticosteroid dosing strategy. The Ichikado Score is a quantitative method to assess the extent of lung involvement on the CT scan.[420,459] Follow-up CXR, CT scan (if indicated) and chest ultrasound as clinically indicated.
- 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. [460]