

An overview of the MATH+, I-MASK+ and I-RECOVER Protocols

A Guide to the Management of COVID-19

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This is our recommended approach to COVID-19 based on the best (and most recent) literature. This is a highly dynamic topic; therefore, we will be updating the guideline as new information emerges. Please check on the FLCCC Alliance website for updated versions of this protocol. www.flccc.net



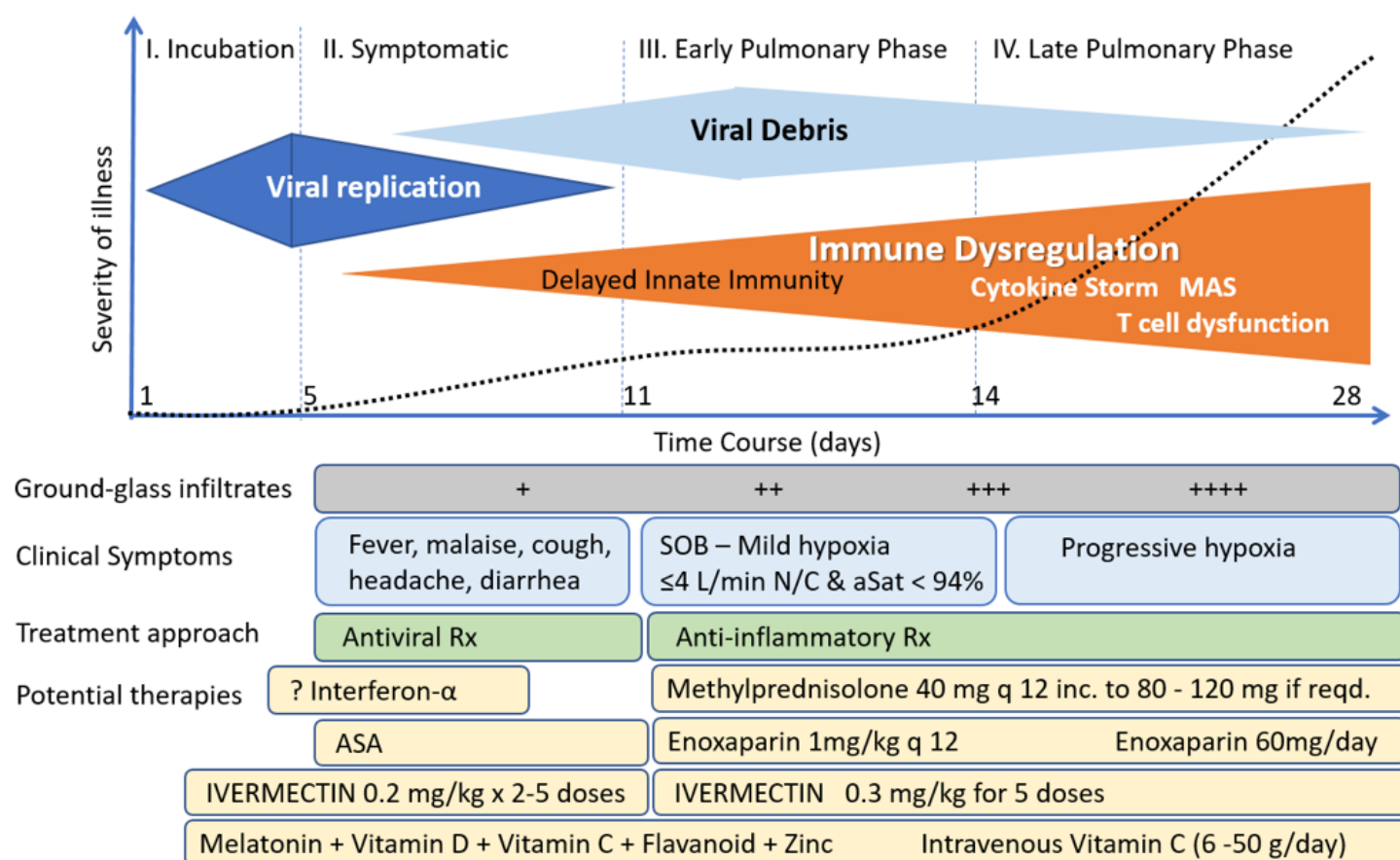
Intravenous **M**ethylprednisolone
High Dose Intravenous **A**scorbic Acid (Vitamin C)
Thiamine (Vitamin B1)
Low Molecular Weight **H**eparin
+
IVERMECTIN – Statin – Zinc – Vitamin D – Famotidine – Melatonin



Disclaimer: The information in this document is provided as guidance to physicians World-Wide on the prevention and treatment of COVID-19. Our guidance should only be used by medical professionals in formulating their approach to COVID-19. Patients should always consult with their physician before starting any medical treatment.

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



THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL-

Not too early Not too late.

Table 1. Pharmacological therapy for COVID by stage of illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/ Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	Unclear benefit	No benefit	?Trend to harm
Remdesivir	n/a	No Benefit	?? Reduced time to recovery No mortality benefit
Lopinavir-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ? Benefit	No benefit	Harm
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	No Benefit
Monoclonal Abs	n/a	Unclear benefit	Harm
Colchicine	n/a	Unclear benefit	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
LMWH	n/a	n/a	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT

*based on randomized controlled trials (see supporting information below)

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

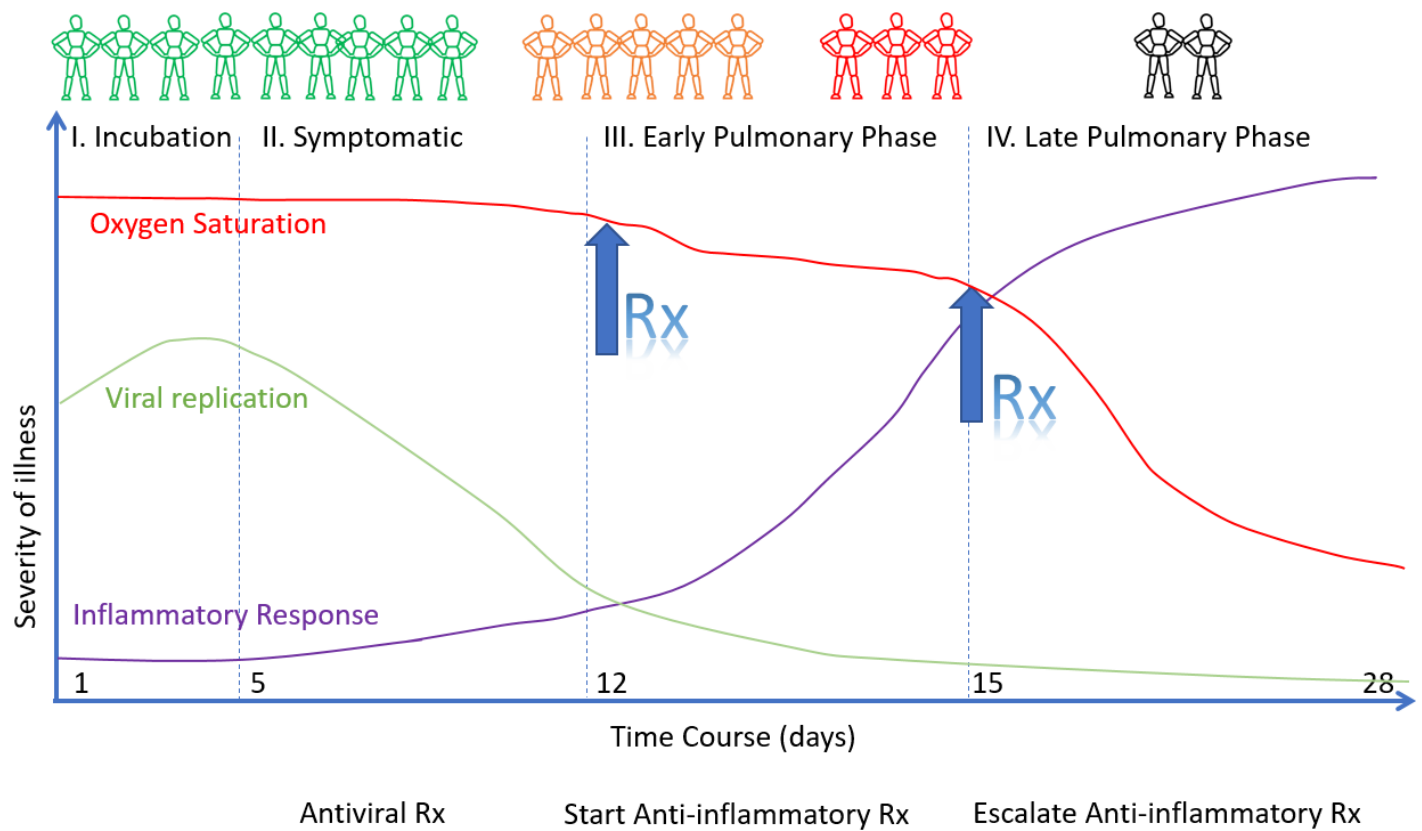


Figure 3. Time course of laboratory tests for COVID-19

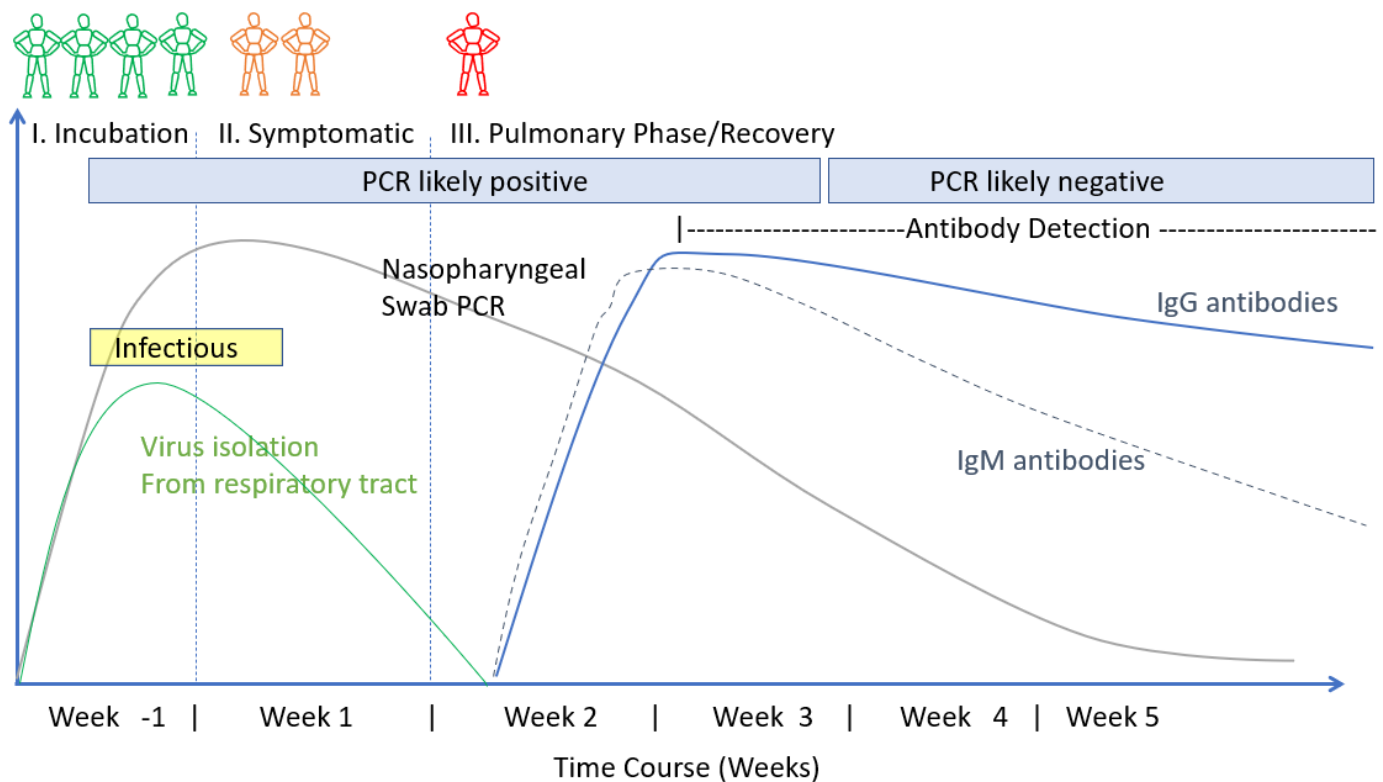
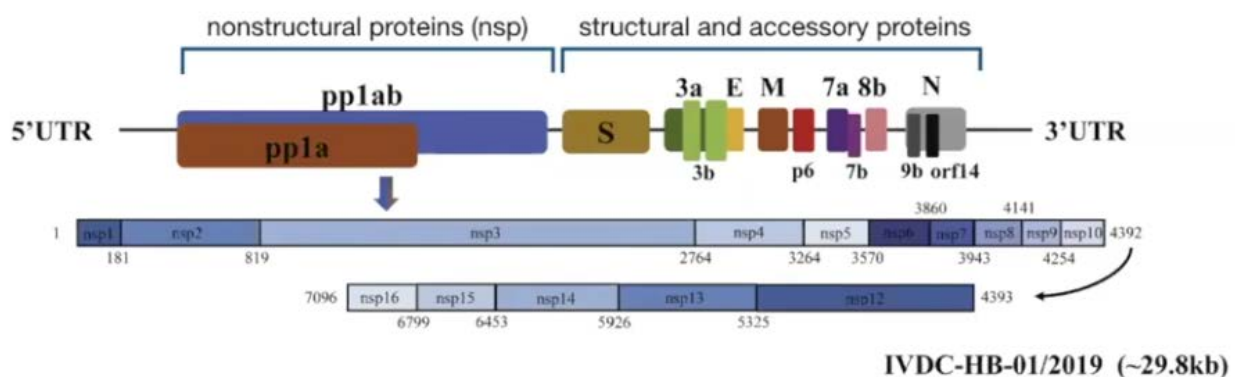


Figure 4. SARS-Co-V-2 RNA genome



While there is no cure or “Magic-bullet” for COVID-19, recently, a number of therapeutic agents have shown great promise for both the prevention and treatment of this disease including Ivermectin, Vitamin D, quercetin, melatonin, Vitamin C, fluvoxamine and corticosteroids. It is likely that no single drug will be effective in treating this complex disease and that multiple drugs with different mechanisms of action used in specific phases of the disease will be required. Furthermore, a growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [1-3]

As the pandemic has played out over the last year over three million patients have died world-wide and the pandemic shows no signs of abating. Most countries across the globe have limited resources to manage this humanitarian crisis. We developed the **MATH+ protocol** to provide guidance for the treatment of the pulmonary phase of this disease with the goal of reducing the hospital mortality from this devastating disease. However, it soon became obvious that our emphasis needed to shift to the prevention and early (home) treatment of this catastrophic disease to prevent patients progressing to the pulmonary phase and requiring hospitalization (see Figure 5). Hence, we developed the **I-MASK+ protocol**. While we strongly believe that such an approach can mitigate the development and progression of this disease, limit deaths, and allow the economy to re-open, “Health-Care authorities” across the globe have been silent in this regard, including the WHO, CDC, NIH, etc (see NIH Guidance, Figure 6a and 6b). While vaccination is part of the solution, it will take many months if not years to vaccinate 70-85% of the world’s population of 7.8 billion people required for “herd immunity” (it is questionable whether this goal will ever be achieved). We believe that the I-MASK+ protocol provides a bridge to universal vaccination. Furthermore we have developed the **I-MASS protocol** for a MASS Distribution campaign to lessen the impact of COVID-19 in resource-poor countries. Mutant strains of SARS-CoV-2 have recently appeared, these stains have demonstrated increased transmissibility.[4,5] Many of these mutations involve the spike protein (against which almost all of the vaccines have targeted), raising the real possibility that the vaccines may become less effective against the mutating strains of SARS-CoV-2.[5-7] And, finally the Post-COVID syndrome or “long-hauler syndrome” has emerged as a common and disabling disorder its pathophysiology of which is poorly understood. We offer the **I-RECOVER** protocol to help treat this disabling disorder.

Figure 5. Treatment Phases of COVID-19

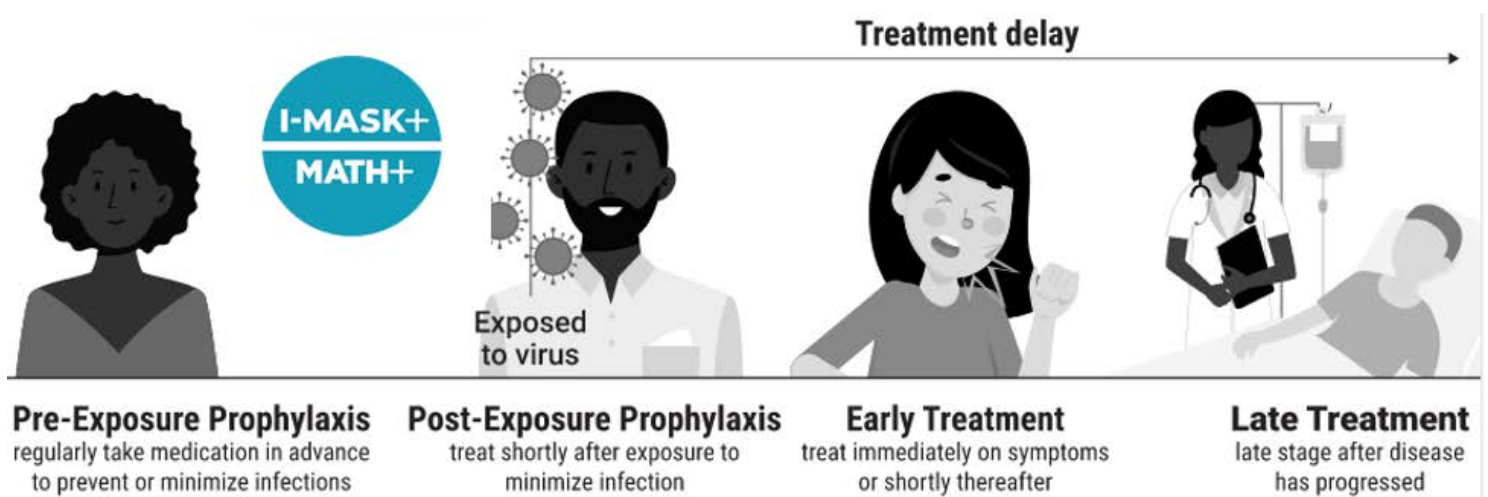


Figure 6a. NIH Recommendations for the Treatment of COVID-19 across the stages of the disease.

NIH	COVID-19 Treatment Guidelines
DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
<p>Not Hospitalized or Hospitalized but Does Not Require Supplemental Oxygen</p>	<p>No specific antiviral or immunomodulatory therapy recommended</p> <p>The Panel recommends against the use of dexamethasone (AI)</p> <p>See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.^a</p>
<p>Hospitalized and Requires Supplemental Oxygen</p> <p>(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</p>	<p>Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first (AI)^{b,c,d}</p> <p>or</p> <p>Remdesivir (dose and duration as above) plus dexamethasone^e 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first (BIII)^f</p> <p>If remdesivir cannot be used, dexamethasone^e may be used instead (BIII)</p>
<p>Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation</p>	<p>Dexamethasone^d plus remdesivir at the doses and durations discussed above (AIII)^f</p> <p>or</p> <p>Dexamethasone^{d,e} at the dose and duration discussed above (AI)</p>
<p>Hospitalized and Requires Invasive Mechanical Ventilation or ECMO</p>	<p>Dexamethasone^{d,e} at the dose and duration discussed above (AI)</p> <p>or</p> <p>Dexamethasone^e plus remdesivir for patients who have recently been intubated at the doses and durations discussed above (CIII)^f</p>

Figure 6b. NIH Recommendations for the prevention and prophylaxis of COVID-19.



COVID-19 Treatment Guidelines

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (**AIII**).
- The Panel **recommends against** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial (**AIII**).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Pre and Postexposure Prophylaxis (The I-MASK+ protocol)

The components of the I-MASK Prophylaxis and Early Treatment protocol are illustrated in Figures 7 and 9. Recent data suggests that ivermectin, melatonin as well as the combination of quercetin (or mixed flavonoids) and vitamin C may play an important role in both pre-exposure and postexposure prophylaxis. [2,8] The evidence supporting the use of Ivermectin for the prophylaxis of COVID-19 is provided by the comprehensive review by Kory et al and the meta-analysis below (Figure 8). [9] It is important to emphasize that ALL of the medications included in our prophylactic regimen are inexpensive, safe, and widely available. The I-MASK + protocol MUST be part of an overall strategy which includes common sense public health measures, i.e., masks, social distancing, and avoidance of large groups of people.[10]

Figure 7. The I-MASK prophylactic and Early Treatment Protocol.

I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

Pa

PREVENTION PROTOCOL

Ivermectin¹ (take with or after meals)	Prevention for high risk individuals 0.2 mg/kg per dose — one dose today, repeat after 48 hours, then one dose weekly*
	Post COVID-19 exposure prevention² 0.2 mg/kg per dose — one dose today, repeat after 48 hours*
Vitamin D3	1,000–3,000 IU/day
Vitamin C	500–1,000 mg twice a day
Quercetin	250 mg/day
Zinc	30–40 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)

EARLY OUTPATIENT PROTOCOL³

Ivermectin¹ (take with or after meals)	0.2–0.4 mg/kg per dose — one dose daily, minimum of 2 days, continue for 5 days or until recovered* Use upper dose range if: 1) in regions with more aggressive variants; 2) treatment started on or after day 5 of symptoms or in pulmonary phase; or 3) multiple comorbidities/risk factors.
Fluvoxamine	50 mg twice daily for 10–14 days. Add to ivermectin if: 1) minimal response after 2 days of ivermectin; 2) in regions with more aggressive variants; 3) treatment started on or after day 5 of symptoms or in pulmonary phase; or 4) numerous comorbidities/risk factors. Avoid if patient already on an SSRI.
Nasopharyngeal Sanitation	Steamed essential oil Inhalation 3 times a day (i.e. vapo-rub) and/or chlorhexidine/benzylamine mouthwash gargles and Betadine nasal spray 2–3 times a day
Vitamin D3	4,000 IU/day
Vitamin C	500–1,000 mg twice a day
Quercetin	250 mg twice a day
Zinc	100 mg/day
Melatonin	10 mg before bedtime (causes drowsiness)
Aspirin	325 mg/day (unless contraindicated)
Pulse Oximeter	Monitoring of oxygen saturation is recommended

Behavioral Prevention



WEAR MASKS

Must wear cloth, surgical, or N95 mask (without valve) in all indoor spaces with non-household persons.

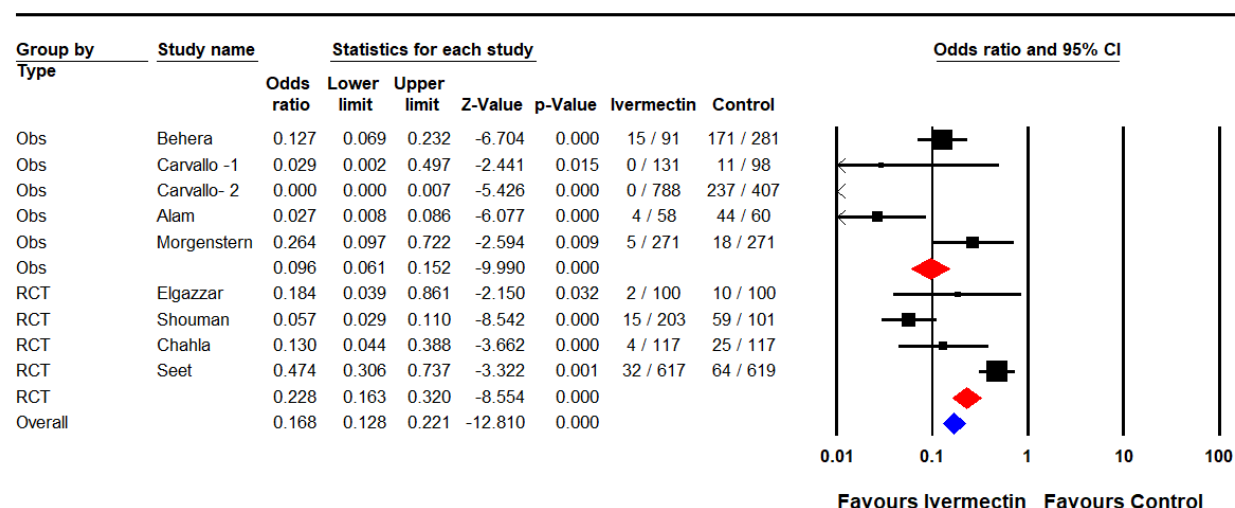
Must wear a N95 mask (without valve) during prolonged exposure to non-household persons in any confined, poorly ventilated area.



KEEP DISTANCE

Until the end of the Covid-19 crisis, we recommend keeping a minimum distance of approx. 2 m/6 feet in public from people who are not from your own household.

Figure 8. Ivermectin for Pre-and postexposure prophylaxis.



Meta Analysis

Components of the I-MASK Prophylactic Protocol

- Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561). 0.2 mg/kg immediately then repeat 2nd dose in 48 hours. Ivermectin is best taken with a meal or just following a meal (greater absorption). [11] Oropharyngeal sanitation also suggested (see section on home treatment below).
- Ivermectin for pre-exposure prophylaxis (in HCW) and for prophylaxis in high-risk individuals (> 60 years with co-morbidities, morbid obesity, long term care facilities, etc). 0.2 mg/kg per dose - start treatment with one dose, 2nd dose 48 hours later, then 1 dose every 7 days (i.e. weekly). [12-18] (also see ClinTrials.gov NCT04425850). We believe that bi-weekly dosing is likely the most practical, cost effective and safest prophylactic regimen. See dosing Table below and Figures 8 and 9. NB. Ivermectin has a number of potentially serious drug-drug interactions; please check for potential drug interactions at [Ivermectin Drug Interactions - Drugs.com](https://www.drugs.com/interactions-check.php?drug=ivermectin). (also see below) . The most important drug-drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs, and certain anti-fungal drugs. While ivermectin has a remarkable safety record, [19] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [20,21] While hepatitis is commonly quoted as a side effect, we are aware of a single case report of reversible hepatitis.[22] The safety of ivermectin in pregnancy has not been determined. [23] Ivermectin may increase the risk of congenital malformations particularly when used in the first trimester. [23] US Food and Drug Administration (FDA) has classified ivermectin as pregnancy category C—i.e, “Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”. In pregnant patients with symptomatic COVID-19 infections the risk and benefits of ivermectin should be discussed with the patient, and informed consent obtained from the patient should the drug be prescribed. Additionally, women should be counselled that low concentrations of ivermectin are present in breast milk; the implications of this finding are unclear. [24]

- Vitamin D3 1000–3000 IU/day (25-75 mcg). An alternative strategy is 40 000 IU weekly. Note RDA (Recommended Daily Allowance) is 800–1000 IU/day. The safe upper-dose daily limit is likely < 4000 IU/day. Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. [13,25-47] Vitamin D supplementation may therefore prove to be an effective and cheap intervention to lessen the impact of this disease, particularly in vulnerable populations, i.e., the elderly, those of color, obese and those living > 45° latitude. [30-45] It is likely that the greatest benefit from vitamin D supplementation will occur in vitamin D insufficient individuals who take vitamin D prophylactically; once vitamin D insufficient individuals develop COVID-19 the benefits will likely be significantly less. [48] This concept is supported by a recent study which demonstrated that residents of a long-term care facility who took vitamin D supplementation had a much lower risk of dying from COVID-19. [46] It should be noted that Former CDC Chief Dr. Tom Frieden has stated "*Coronavirus infection risk may be reduced by Vitamin D*". <https://preventepidemics.org/covid19/press/former-cdc-chief-dr-tom-frieden-coronavirus-infection-risk-may-be-reduced-by-vitamin-d/>
- Vitamin C 500 – 1000 mg BID (twice daily) and Quercetin 250 mg daily. [49-61] Due to the possible drug interaction between quercetin and ivermectin (see below) these drugs should not be taken simultaneously (i.e. should be staggered morning and night). Vitamin C has important anti-inflammatory, antioxidant, and immune enhancing properties, including increased synthesis of type I interferons.[52,62,63] Quercetin has direct viricidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [50,55,60,60,64-72] Quercetin is a potent inhibitor of inflammasome activation, which believed to play a major role in the pathophysiology of the COVID-19 immune dysfunction.[72] In addition, quercetin acts as a zinc ionophore. [73] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [2] A mixed flavanoid supplement containing quercetin, green tea catechins and anthocyanins (from berries) may be preferable to a quercetin supplement alone; [74-78] this may further minimize the risk of quercetin related side-effects. It should be noted that *in vitro* studies have demonstrated that quercetin and other flavonoids interfere with thyroid hormone synthesis at multiple steps in the synthetic pathway. [79-82] The use of quercetin has rarely been associated with hypothyroidism. The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with sub-clinical thyroidism.[83] In women high consumption of soya was associated with elevated TSH concentrations.[84] The effect on thyroid function may be dose dependent, hence for chronic prophylactic use we suggest that the lowest dose be taken. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored. It should also be noted quercetin may have important drug-drug interactions; the most important drug-drug interaction is with cyclosporin and tacrolimus. [85] In patients taking these drugs it is best to avoid quercetin; if quercetin is taken cyclosporin and tacrolimus levels must be closely monitored.
- Melatonin (slow release): Begin with 0.3 mg and increase as tolerated to 6 mg at night. [1,8,86-92]. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease.[93-95] A recent large retrospective study demonstrated that the use of melatonin in intubated patients with COVID-19 significantly reduced the risk of death (HR 0.1; p=0.0000000715).[94] It is intriguing to recognize that bats, the natural reservoir of coronavirus, have exceptionally high levels of melatonin, which may protect these animals from developing symptomatic disease. [96] The slow release (extended release) formulation of melatonin is preferred as it more closely replicates the normal circadian rhythm. [86]
- Zinc 30–50 mg/day (elemental zinc). [56,58,59,97-101] Zinc is essential for innate and adaptive immunity.[99] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[98] Due to competitive binding with the same gut transporter, prolonged high dose

zinc (> 50mg day) should be avoided as this is associated with copper deficiency. [102] Commercial zinc supplements contain 7 to 80 mg of elemental zinc, and are commonly formulated as zinc oxide or salts with acetate, gluconate, and sulfate. 220 mg zinc sulfate contains 50 mg elemental zinc.

- B complex vitamins [103-107].
- Oropharyngeal hygiene with twice daily anti-viral mouth mouth/gargle (see below).
- *Optional*: Famotidine 20–40 mg/day [108-114]. Low level evidence suggests that famotidine may reduce disease severity and mortality. However, the findings of some studies are contradictory. While it was postulated that famotidine inhibits the SARS-CoV-2 papain-like protease (PLpro) as well as the main protease (3CLpro) this mechanism has been disputed. [111] Furthermore, a number of studies have demonstrated an association between the use of proton pump inhibitors (PPI's) with an increased risk of contracting COVID-19 and with worse outcomes. [115,116] This data suggest that famotidine may be the drug of choice when acid suppressive therapy is required.
- *Optional/Experimental*: Interferon-α nasal spray for health care workers [117].

Ivermectin dosing: 200 ug/kg or fixed dose of 12 mg (≤ 80 kg) or 18 mg (≥ 80 kg).[118] Depending on the manufacturer ivermectin is supplied as 3mg, 6 mg or 12 mg tablets.

50-64.9 kg - 12mg
 65-79.9 kg - 15mg
 80-94.9 kg - 18mg
 95-109.9 kg - 21mg
 ≥ 110 kg - 24mg

Figure 9. I-MASK prophylaxis protocol.

I-MASK+
 PROPHYLAXIS & EARLY OUTPATIENT
 TREATMENT PROTOCOL FOR COVID-19



PREVENTION PROTOCOL

Ivermectin¹
 (take with or after meals)

Prevention for high risk individuals
 0.2 mg/kg per dose — one dose today, repeat after 48 hours, then one dose weekly*

Post COVID-19 exposure prevention²
 0.2 mg/kg per dose — one dose today, repeat after 48 hours*



For illustration purposes, not for brand or dosage endorsement

I-MASS

Mass distribution protocol for the Prophylaxis and Early Outpatient treatment for COVID-19

The **I-MASS protocol** has been developed for MASS Distribution in resource poor countries to lessen the impact of COVID-19.

PREVENTION PROTOCOL (for adults > 18 years and > 40 kg/90 lbs.)

IVERMECTIN: 18 mg. [118] Start treatment with one dose on day 1, and then repeat weekly (every 7 days)

VITAMIN D3: 2000 IU (50 mcg) daily

Multivitamin: Take 1 daily

Digital thermometer (optional)

EARLY AT HOME TREATMENT PROTOCOL

(for adults > 18 years and > 40 kg/90 lbs.)

IVERMECTIN: 18 mg daily for 5 days

Melatonin: 6 mg at night for 5 days

Paracetamol/Acetaminophen 500 mg (8 tablets): Take one tablet for fever.

Do not take more than 4 tablets/day.

Antiviral mouth wash: Three times daily (gargle do not swallow); if available

Drug Interactions with Ivermectin

Drug Interactions. (From Medscape).

<https://reference.medscape.com/drug/stromectol-ivermectin-342657#3>

Patients taking any of these medications should discuss with their treating physicians.

DRUG INTERACTIONS WITH IVERMECTIN			
SERIOUS (4) Use Alternative	MONITOR CLOSELY (possible) (49) Especially those with (*)		
Erdafitinib Lasmiditan Quinidine Tepotinib	Amiodarone	Glecaprevir/Pibrentasvir	Phenytoin
	Atorvastatin	Indinavir	Ponatinib
	Berotrastat	Istradefylline	Quercetin (**)
	Bosutinib	Itraconazole (*)	Ranolazine
	Clarithromycin (*)	Ivacaftor	Rifampin (*)
	Clotrimazole	Ketoconazole (*)	Ritonavir (*)
	Dronedarone	Lapatinib	Sarecycline
	Elagolix	Lomitapide	Simvastatin
	Eliglustat	Lonafarnib	Sirolimus (*)
	Erythromycin base	Loratadine	St John's Wort
	Erythromycin ethylsuccinate (*)	Lovastatin	Stiripentol
	Erythromycin lactobionate (*)	Nefazodone	Tacrolimus (*)
	Erythromycin stearate (*)	Nicardipine	Tolvaptan
	Felodipine	Nifedipine	Trazodone
	Fosphenytoin	Nilotinib	Tucatinib
	Fostamatinib	Phenobarbital	Verapamil (*)
			Warfarin (*)

(**) Not clear. May increase ivermectin levels

Symptomatic patients at home (I-MASK+ EARLY Treatment Protocol)

- Ivermectin 0.2- 0.4 mg/kg – one dose daily for 5 days or until recovered. [13,15,19,25-28,119-131] . Higher doses (0.4 mg/kg) often required in a) regions with more aggressive variants, b) treatment started on or after 5 days of symptoms or c) in patients in pulmonary phase, d) extensive CT involvement or e) extensive comorbidities/risk factors (older age, obesity, diabetes). Ivermectin is best taken with a meal or just following a meal (greater absorption). See Table 1, Figure 9 and ClinTrials.gov NCT04523831. See drug-drug interactions above. It should be noted that multiday treatment has been shown to be more clinically effective than single-day dosing.
- Vitamin C 500 – 1000 mg BID and Quercetin 250 mg BID (or mixed flavanoid supplement). Due to the possible drug interaction between quercetin and ivermectin (see above) these drugs should not be taken simultaneously (i.e. should be staggered morning and night).
- Zinc 75–100 mg/day (elemental zinc)
- Melatonin 10 mg at night (the optimal dose is unknown) [92-95]
- Calcifediol 0.2 mg day 1, day 3 and day 7 then weekly. Vitamin D3 2000–4000 IU/day (50-100 mcg) is an alternative. [132] In the acute setting calcifediol appears to be more effective than vitamin D3.[133] Calcifediol is more efficiently absorbed, achieves 25-OH vitamin D levels quicker and is three times more potent than vitamin D3. [134,135] However, it is important to note that the optimal dose of vitamin D in the acute setting is unknown.[136,137] Very high doses may paradoxically block the vitamin D receptor.
- ASA 81–325 mg/day (unless contraindicated). ASA has antiinflammatory, antithrombotic, immunomodulatory and antiviral effects.[138-140] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [141-143]
- B complex vitamins
- Oropharyngeal sanitization. [144] Inhaled steam supplemented with antimicrobial essential oils (e.g VapoRub inhalations) [145] and/or antiseptic mouthwashes/throat rinses (chlorhexidine, povidone-iodine) and/or povidone-iodine (Betadine) nasal spray/antiseptic applied 2-3 times per day. [146-148] Oropharyngeal sanitization likely reduce the viral load in the upper airways and thereby reducing the risk of symptomatic disease and likely reducing disease severity.
- *Optional:* Fluvoxamine 50 – 100 mg BID. [149-153] This SSRI is recommended in those patients with more severe symptoms/more advanced disease. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that activates sigma-1 receptors decreasing cytokine production. [149,150] In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus and inhibits melatonin degradation.[154] Antidepressant medications (SSRI) deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation.[155-157] The use of antidepressants has been associated with a lower risk of intubation and death in patients hospitalized with COVID-19. [152,153]
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction) [108-114].
- *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. [58,158-161]
- *Optional:* Interferon- α/β nasal spray, inhalation or s/c injection. [117,162-165] It should be noted that Zinc potentiates the effects of interferon.[166,167]
- *Optional (In MEN ONLY):* Men who develop COVID-19 have a significantly worse outcome than women (independent of other risk factors). [168] This effect may be mediated in part by

testosterone. Testosterone increases the expression of the transmembrane protease, serine 2 (TMPRSS2) which is required for priming of the spike protein for cell fusion. [169] The anti-androgens dutasteride 0.5 mg/day [170] and proxalutamide 200 mg /day (NCT 04446429) have been demonstrated to reduce time to viral clearance, improve time to recovery and reduce hospitalization in men with COVID-19 in the outpatient setting. It should be noted that proxalutamide is not available in the USA.

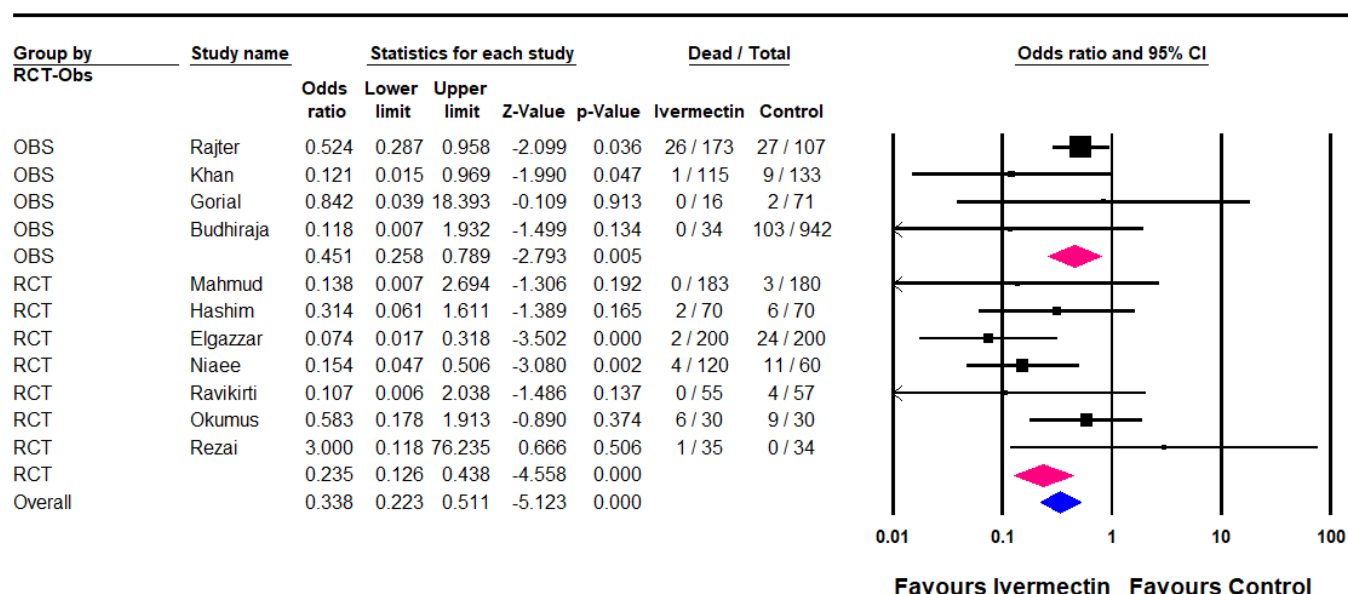
- In symptomatic patients, monitoring with home pulse oximetry is recommended (due to asymptomatic hypoxia). The limitations of home pulse oximeters should be recognized, and validated devices are preferred.[171] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[171] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [172] The following guidance is suggested: [171]
 - 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
- *Unclear benefit: Inhaled corticosteroids (budesonide).* Two recent RCTs have demonstrated more rapid symptomatic improvement in ambulatory patients with COVID-19 treated with inhaled budesonide, however, there was no difference in the rate of hospitalization.[173,174] It should be noted that both these studies were open label (no placebo in the control arm) and that the primary end-point was subjective (time to symptom resolution). Corticosteroids downregulate the expression of interferons (hosts primary antiviral defenses) and downregulated ACE-2 expression (harmful). Furthermore, two population level studies suggest that inhaled corticosteroids may increase the risk of death in patients with COVID-19. [175,176] Based on these data the role of inhaled corticosteroids in the early phase of COVID-19 is unclear.
- *Unclear benefit (best avoided).* Colchicine 0.6mg BID for 3 days then reduce to 0.6mg daily for total of 30 days. In the COLCORONA study colchicine reduced the need for hospitalization (4.5 vs 5.7%) in high risk patients. [177] Colchicine was associated with an increased risk of side effects most notably diarrhea and pulmonary embolism. It should be noted that in the RECOVERY trial colchicine failed to demonstrate a survival benefit in hospitalized patients. Due to potentially serious drug interactions with ivermectin (and other CYP 3A4 and p-glycoprotein inhibitors) as well as with statins, [178] together with its marginal benefit colchicine is best avoided.
- *Not recommended: Systemic corticosteroids.* In the early symptomatic (viral replicative phase), corticosteroids may increase viral replication and disease severity.[179]
- *Not recommended: Hydroxychloroquine (HCQ).* The use of HCQ is highly controversial.[180] The best scientific evidence from randomized controlled trials suggests that HCQ has limited/no proven benefit for post exposure prophylaxis, for the early symptomatic phase and in hospitalized patients. [181-202] 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).[191,203-205] Finally, it should be recognized that those studies which are widely promoted to support the use of HCQ are severely methodologically flawed.[206-209]
- *Not recommended: Azithromycin, doxycycline, or quinolone antibiotics.* [210,211]

Mildly Symptomatic patients (on floor/ward in hospital).

- Ivermectin 0.4 – 0.6 mg/kg daily for 5 days or until recovered. A higher dose may be required in patients with more severe disease and in those in whom treatment is delayed. [13,15,19,25-28,119-128,130]. Ivermectin is best taken with a meal or just following a meal (greater absorption). It should be noted that ivermectin has potent anti-inflammatory properties apart from its antiviral properties.[212-215] See Table 1 and Figure 10. See drug-drug interactions above.
- Methylprednisolone 80 mg bolus then 40 mg q 12 hourly (alternative: 80 mg bolus followed by 80 mg/240 ml normal saline IV infusion at 10 ml/hr); increase to 80 mg and then 125 mg 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. [216-228] We believe that the use of low-fixed dose dexamethasone is inappropriate for the treatment of the pulmonary phase of COVID-19 (see section on MATH+ below). The role of inhaled corticosteroids (budesonide) is unclear and appears to be rather limited (as reviewed above). While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/counties 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.
- Enoxaparin 1mg/kg 12 hourly (see dosage adjustments and Xa monitoring below). An interim analysis of the ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a mortality reduction with full anticoagulation (regardless of D-dimer level) in hospitalized patients with COVID-19.
- Vitamin C 500–1000 mg q 6 hourly and Quercetin 250–500 mg BID (if available)
- Zinc 75–100 mg/day
- Melatonin 10 mg at night (the optimal dose is unknown) [92]
- Calcifediol 0.2 mg day 1, day 3 and day 7 then weekly. [132] Vitamin D3 20,000–60,000 IU single oral dose is an alternative; this should be followed by 20,000 IU D3 weekly until discharged from hospital. In the acute setting calcifediol appears to be more effective than vitamin D3. [133]
- ASA 81-325 mg (if not contraindicated). Moderate-severe COVID infection results in profound platelet activation contributing to the pro-thrombotic state and increasing the inflammatory response.[142,143,229,230]
- B complex vitamins
- Famotidine 40 mg BID (20–40 mg/day in renal impairment). [108-114] Famotidine may be useful for its protective effect on gastric mucosa, its anti-viral properties and histamine blocking properties.
- Fluvoxamine 50 -100 mg BID.
- *Optional* (In MEN ONLY): The anti-androgen agents dutasteride 0.5 mg/day, proxalutamide 200 mg daily or finasteride 5 mg daily. It should be noted that proxalutamide is not available in the USA.
- *Optional*: The anti-serotonin agent, cyproheptadine 4–8 mg PO q 6 hour should be considered in patients with more severe disease. [231,232] Patients with COVID-19 have increased circulating levels of serotonin likely the result of increased platelet activation and decreased removal by the pulmonary circulation due to an extensive microcirculatory vasculopathy. [231,233-235] Increased circulating serotonin is associated with pulmonary, renal and cerebral vasoconstriction, and may partly explain the V/Q mismatch and reduced renal blood flow noted in patients with severe COVID-19 infection. [236-239] Furthermore, serotonin itself enhances platelet aggregation creating a propagating immuno-thrombotic cycle.[240] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [241]

- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. [242]
- *Optional:* Remdesivir 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [243,244] This agent has been reported to reduce time to recovery (based on an ordinal scale) in patients requiring low levels of supplemental oxygen. [244,245] The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup.[246] Considering the high cost of this agent and the lack of benefit on patient centered outcomes the role of this drug seems very limited. A recent *in vitro* study demonstrated marked synergy between Remdesivir and Ivermectin. [247] Considering the broad antiviral and anti-inflammatory effects of ivermectin, together with its remarkable safety record, this finding suggest that ivermectin should be prescribed in all patients receiving Remdesivir.
- *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. [178]
- 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 10. Metaanalysis of Ivermectin clinical studies (in hospital mortality)



Meta Analysis

MATH + PROTOCOL (for patients admitted to the ICU) [248,249]

- 1. Methylprednisolone** 80 mg loading dose then 40 mg q 12 hourly for at least 7 days and until transferred out of ICU (alternative: 80 mg bolus followed by 80 mg/240 ml normal saline IV infusion at 10 ml/hr). 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. [216-228] Pulse methylprednisolone 250–500 mg mg/day for 3 days (followed by taper) may be required.[226] 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 1, methylprednisolone is the corticosteroid of choice. Observational and randomized studies have clearly demonstrated the superiority of methylprednisolone over low dose dexamethasone.[250,251] These clinical findings are supported by a genomic study.[140] 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). The effect of corticosteroids on the profile of dysregulated immune markers is clearly illustrated in *Figure 12*. [252] While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/counties 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.[53,62,63,253-263]. *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 [264] (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.[265] 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.[264] 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:** An interim analysis of 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)%. 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).[266] 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.[62,63] 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). [267-269]

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.

Additional Treatment Components

4. **Highly recommended:** Ivermectin 0.4 – 0.6 mg/kg day orally for 5 days or until recovered [19,25-27,119,122-129,212-214,270-276]. A higher dose (0.6mg/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. See Table 1 and Figure 10. As noted above clinical outcomes are superior with multiday as opposed to single day dosing.
5. Melatonin 10 mg at night (the optimal dose is unknown).[93-95]
6. Calcifediol 0.2–0.5 mg (25-OH Vitamin D). [132] This should be followed by 0.2 mg calcifediol weekly until discharged from hospital. Should calcifediol 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 appears to be more effective than vitamin D3. [133] Vitamin D3 takes many days to be converted to 25OH vitamin D; [277] this may explain the lack of benefit of D3 in patients hospitalized with severe COVID-19. [48]
7. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [278-283] Thiamine may play a role in dampening the cytokine storm. [279,284]
8. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe prothrombotic state and increasing the inflammatory response.[142,143,229,230] 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. B complex vitamins.
11. Fluvoxamine 50 -100 mg BID.
12. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [106] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [285-287]
13. Famotidine 40 mg BID (20–40 mg/day in renal impairment). [108-114].
14. *Optional.* Atorvastatin 80 mg/day (reduce dose to 40mg if taken with ivermectin due to possible drug-drug interaction). Statins have pleiotropic 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. [288] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[289-293] Due to numerous drug-drug interactions simvastatin should be avoided.
15. *Optional:* Vascepa, Lovaza or DHA/EPA 4g day (see above). [242]
16. *Optional (In MEN ONLY):* The anti-androgen agent's dutasteride 0.5 mg/day, proxalutamide 200 mg daily or finasteride 5 mg daily. It should be noted that proxalutamide is not available in the USA.
17. *Unclear benefit.* The role of the IL-1 receptor blocker ANAKINRA is unclear. Anakinra together with corticosteroids may have a role in patients with evidence of the macrophage activation syndrome/hemophagocytotic lymphohistiocytosis. While observational studies suggest a dramatic improvement in outcome (OR 0.258 95% CI 0.162 – 0.410), [294-300] a single RCT was stopped prematurely due to futility.[301]

18. *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.[210,302,303] Patients with COVID-19 are at an increased risk of developing bacterial superinfections and prophylactic antibiotics may increase the risk of infection with multiresistant organisms.
19. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
20. *Not recommended.* Convalescent serum [304-309] nor monoclonal antibodies. [310] However, convalescent serum/ monoclonal antibodies may have a role in patients with hematologic malignancies.[311]
21. *Not recommended.* Colchicine (see above).
22. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [312-316] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising (see Figure 12). [247] Tocilizumab may have of benefit in patients receiving an inadequate dose of corticosteroids.[317] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.
23. 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, T cell dysfunction and decreased CD4 and CD8 counts) secondary bacterial and fungal infections (Candida and Aspergillus species) and viral reactivation is not uncommon. [318-320] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [321] 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.
24. 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.
25. 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.
26. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible,*** (see Figure 13)
 - a. Accept “permissive hypoxemia” (keep O₂ Saturation > 84%); follow venous lactate and Central Venous O₂ saturations (ScvO₂) in patents with low arterial O₂ 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) [322-325]
 - 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 H₂O.
 - 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.[326] 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.

Table 2: 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, Iran)		5.9% vs. 42.9%	2.7
METHYLPREDNISONE – ICU PATIENTS (Salton et al, Italy)		7.2% vs. 23.3%	6.2
METHYLPREDNISONE – HOSPITAL PATIENTS, (Fadel et al, USA)		13.6% vs. 26.3%	7.8
METHYLPREDNISONE- ARDS PATIENTS (Wu C et al- China)		46.0% vs. 61.8%	6.3
METHYLPREDNISONE - Pts on oxygen – (Fernandez-Cruz, Spain)		13.9% vs. 23.9%	10.0
CoDEX –DEXAMETHASONE - MECHANICAL VENTILATION		56.3% vs 61.5%	19.2
RECOVERY TRIAL (DEXAMATHASONE)	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4
HYDROCORTISONE -CAPE-COVID – ICU Patients (Dequin et al France)		14.7% vs 27.4%	7.9
HYDROCORTISONE –REMAP-CAP – ICU patients		28%% vs 33%	20.0

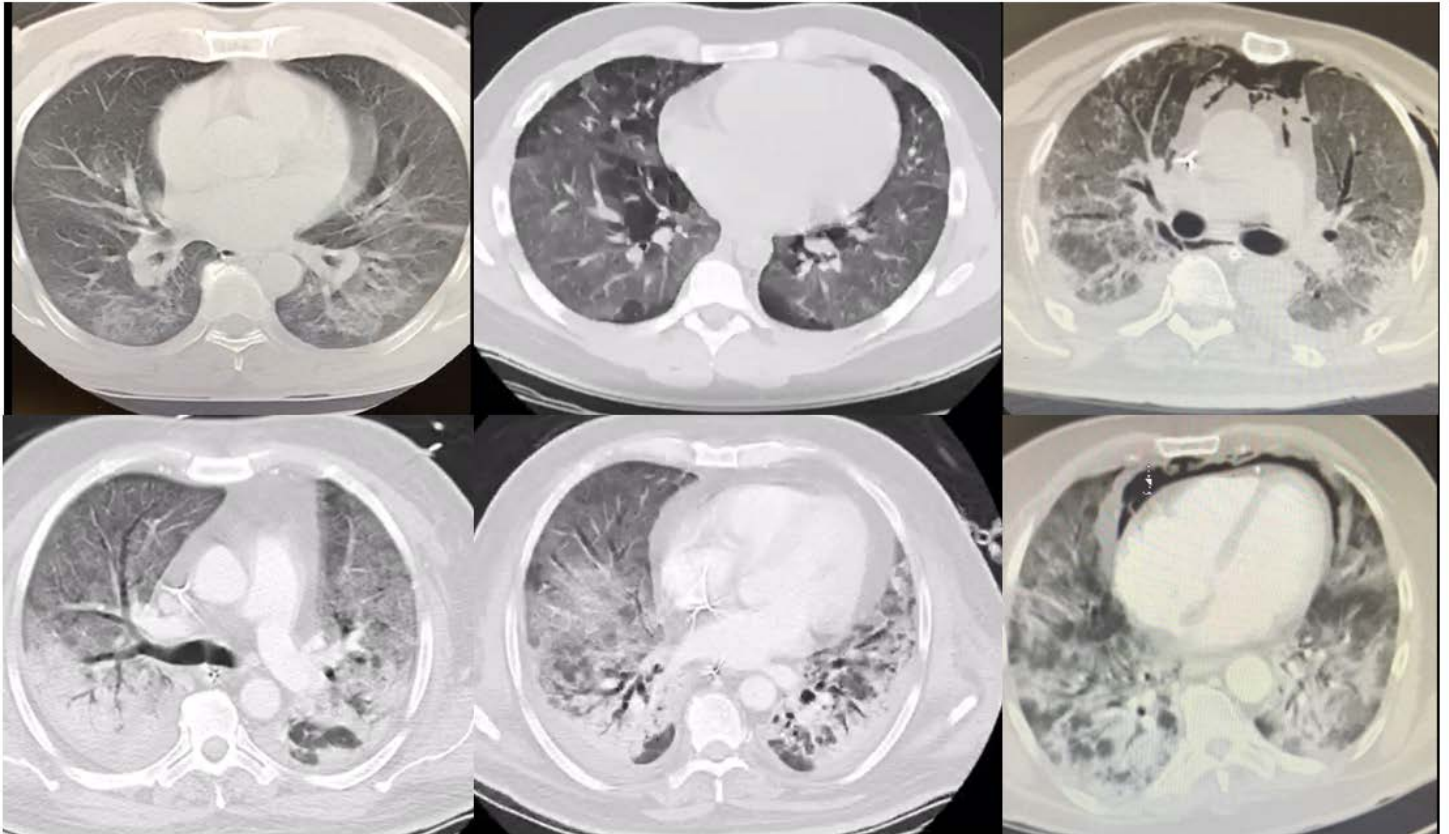
An Approach to the patient with SEVERE Life threatening COVID-19 Organizing Pneumonia

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 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.[327] A very high CRP may indicate 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.[328] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively.[327,329-335] The Ichikado is a useful quantitative score to evaluate the extent of lung involvement with COVID-19.[336,337] 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.[327] 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.

Figure 11. “Typical” progression of Chest CT findings.



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 0.4 mg/kg for 5 days
- III. Vitamin C 3 g 6 hourly to 25g q 12 hourly
- IV. Cyproheptadine 4–8 mg PO q 6 hourly
- V. Melatonin 10mg PO at night
- VI. 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 anti-coagulant doses of Lovenox. It may be prudent to monitor Xa levels aiming for 0.4-0.8 IU/ml (a somewhat lower anti-Xa).
- VII. Fluvoxamine 50- 100 mg BID
- VIII. Atorvastatin 80 mg/day (reduce dose to 40mg if taken with ivermectin due to possible drug-drug interaction)
- IX. Famotidine 40 mg BID
- X. Thiamine 200 mg q 12 hourly
- XI. MEN only: Finasteride 5 mg daily or dutasteride 0.5 mg daily

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”.

Figure 12. Comparison of circulating COVID-19 related biomarkers in response to immunomodulatory therapy.[252]

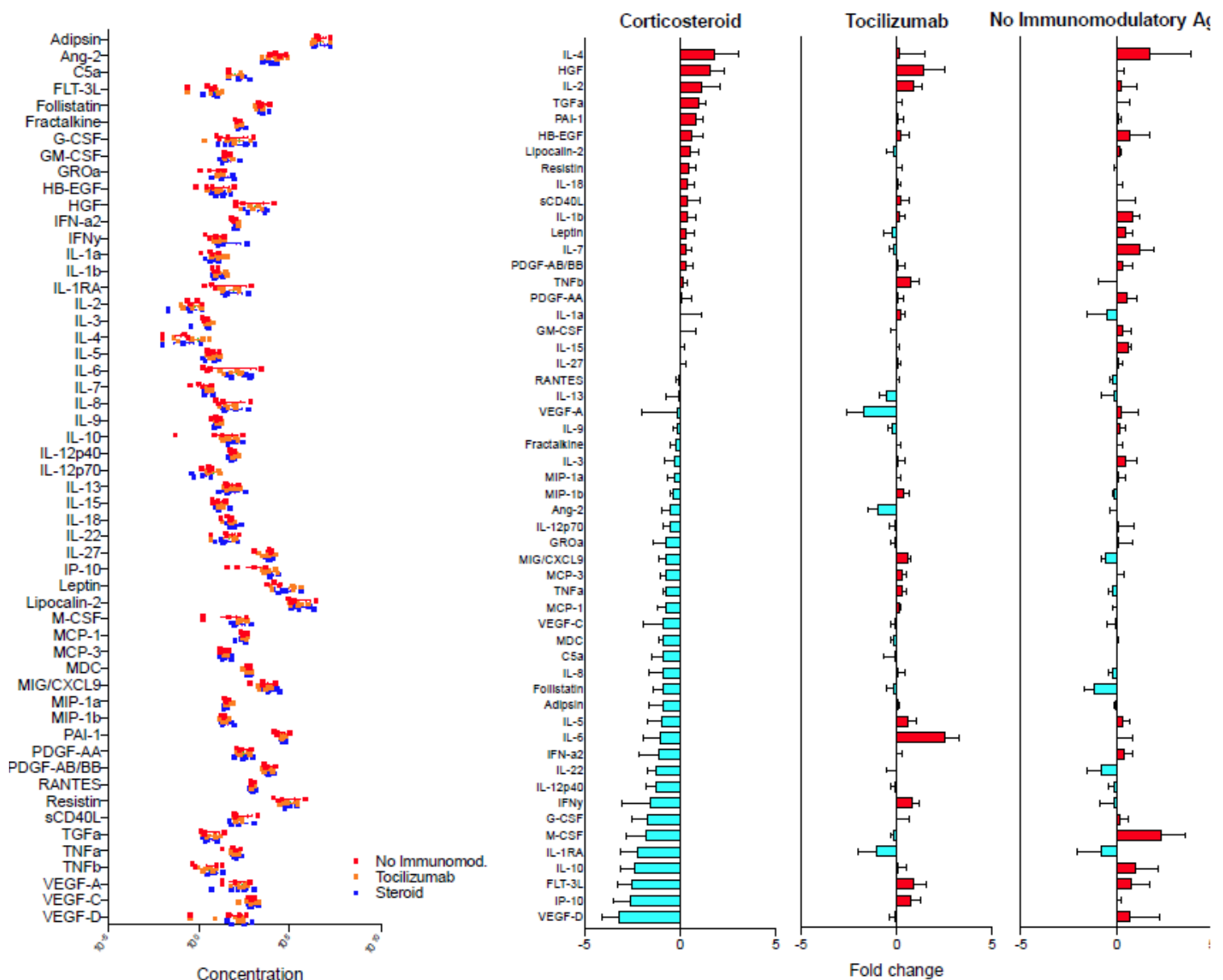
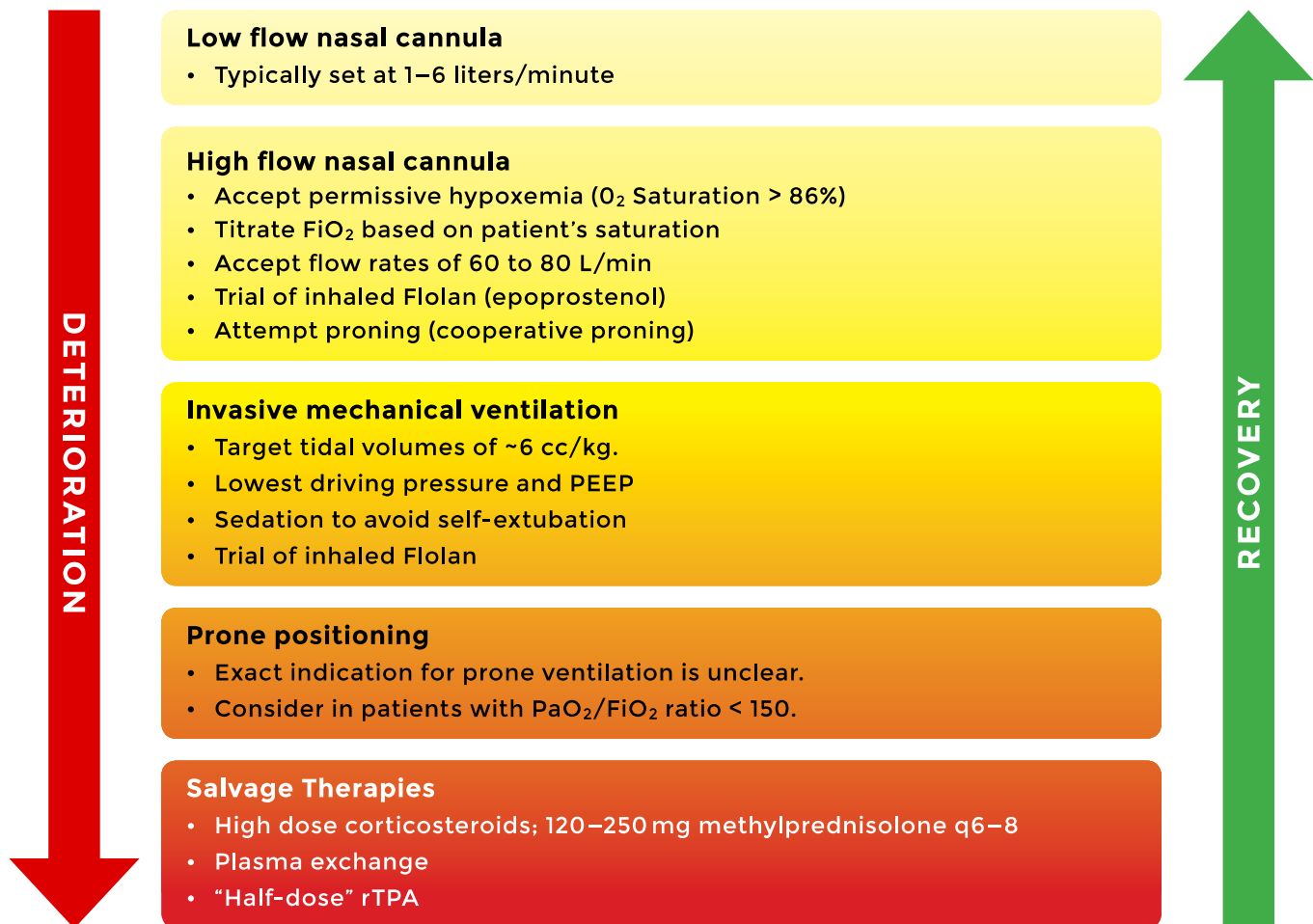


Figure 13.

General schema for respiratory support in patients with COVID-19

Try to avoid intubation if possible



Salvage Treatments

- High dose bolus corticosteroids; 500–1000 mg/day methylprednisolone for 3 days then taper. [224,226]
- Plasma exchange [338-344]. 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.[264,265] (also see <https://www.youtube.com/watch?v=Au-mp6RZjCQ>)
- 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.[345,346]
- Etoposide IV once per week at 50 mg/m² until improved. [347,348] Severe-COVID pneumonia/organizing pneumonia is in essence caused by the “pulmonary macrophage activation syndrome”. [349,350] Similar to the treatment of macrophage activation syndrome and HLH, etoposide may reduce macrophage numbers and improve outcome.[351-353] 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”. [354-357]
- ECMO [358-360]. 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. [361]
- Lung transplantation (see Figure 13). [362]

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. [304-306,308,309] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[363] 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.[364] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [365]
- Janus Kinase inhibitors downregulate cytokine expression and may have a role in this disease. [366-368] The role of the combination of Baricitinib and Remdesivir is unclear.[369]
- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [370-373] 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 [374,375] This treatment strategy appears to have an extremely limited role.

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. [349,350]
- 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.[351]
- “*High dose corticosteroids.*” Methylprednisolone 500-1000 mg daily for three days and then 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).[351-353] The combination of high dose corticosteroids and “low-dose” etoposide is an effective treatment for MAS.
- Consider plasma exchange.

Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[376] A PCT is essential to rule out coexisting bacterial pneumonia.[377]
- 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.[336,378] 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. [379]
- 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. [380,381]
- ECHO as clinically indicated; Patients may develop a severe “septic” cardiomyopathy and/or COVID-19 myocarditis. [382,383]

Post ICU management

- Enoxaparin 40–60 mg s/c daily
- Methylprednisolone 40 mg day, then wean slowly, follow CRP and oxygen requirements – wean off over two weeks once oxygen is discontinued to prevent relapse/recurrence
- Vitamin C 500 mg PO BID
- Melatonin 3–6 mg at night
- Vascepa, Lovaza or DHA/EPA 4g day (important for resolution of inflammation)

Figure 14. Lung Transplantation (graphic From Chest)

Lung Transplantation for COVID-19

Practical tips for referring providers

Who to refer?	Why?	When should you refer?	How to refer?
<p>Patients with severe, irreversible, single organ (lung) failure, who would otherwise be a candidate based on local transplant center protocols.</p> <p>Patients should be alert, able to participate in transplant discussions and decisions, and have strong rehabilitation potential.</p>	<p>Lung transplantation is a potentially lifesaving therapy for patients with:</p> <ul style="list-style-type: none"> • Irreversible, fibrotic ARDS • Severe, chronic fibrotic lung disease from COVID-19 	<ul style="list-style-type: none"> • At least 4-6 weeks after onset of severe lung injury and development of fibrotic changes • After allowing sufficient time for lung recovery • After the patient tests negative for SARS-CoV-2 	<p>Call transplant centers early with the following information:</p> <ul style="list-style-type: none"> • Patient age • Duration of illness • BMI/nutrition status • Degree and duration of mechanical support (eg, ventilation, ECMO) • Status of comorbidities • Rehab potential • Success of awakening trials • Family/social support • Insurance information

Aslam S; ISHLT. Guidance from the ISHLT regarding the SARS CoV-2 pandemic. Revised February 1, 2021.

Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Respir Med*. 2020;8(10):P944-P946.



Post Hospital Discharge management

- a. Patients have an increased risk of thromboembolic events post-discharge. [384,385] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include:[386]
 - i. Increased D dimer (> 3 times ULN)
 - ii. Increased CRP (> 2 times ULN) [387]
 - iii. Age > 60
 - iv. Prolonged immobilization
- b. Patients with unresolved pulmonary infiltrates and/or those who remain dyspneic and/or oxygen dependent should be discharged on a tapering course of corticosteroids (prednisone).
- c. Patients should continue to receive vitamin C, melatonin, omega-3 fatty acids and ? famotidine. These agents may reduce this risk of developing the post-COVID syndrome.

The post-COVID-19 syndrome (Long-haul syndrome)

The post-COVID syndrome is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain and cognitive dysfunction.[388-399] Up to 80% of patients experience prolonged illness after Covid-19. The post-COVID-19 syndrome may persist for months after the acute infection and almost half of patients report reduced quality of life. Patients may suffer prolonged neuropsychological symptoms, including multiple domains of cognition.[397,400] A puzzling feature of the long-haul syndrome is that it is not predicted by initial disease severity; post-COVID-19 frequently affects mild-to-moderate cases and younger adults that do not require respiratory support or intensive care. [399]

The post-COVID syndrome is highly heterogeneous and likely results from a variety of pathogenetic mechanisms. Ongoing respiratory symptoms (SOB, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[401] Brain MRIs 3 months post-infection demonstrated micro-structural changes in 55% of patients. [402] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [403] as well as severe cerebral vasoconstriction. [404] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 “pseudovirions” may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[405] The features of the post-COVID syndrome overlap with those of the myalgic encephalomyelitis/chronic fatigue syndrome.[399] Furthermore, the similarity between the mast cell activation syndrome and post-COVID syndrome has been observed, and many consider post-COVID to be a variant of the mast cell activation syndrome.[406] Mast cells are present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for corticotrophin releasing hormone.[407] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation.[407] The “brain-fog”, cognitive impairment and general fatigue reported in long-COVID may be due to neurovascular inflammation. Auto-reactive antibodies have been reported in patients with post-COVID syndrome and COVID-19 autoimmunity may play a role in this syndrome. [399]

It is likely that patients who received inadequate anti-inflammatory treatment (corticosteroids, fluvoxamine, ivermectin, etc) during the acute phase of COVID are much more likely to develop the post-COVID syndrome. In patients with ongoing respiratory symptoms chest imaging is suggested (preferably a chest CT scan). Those with unresolved pulmonary inflammation (organizing pneumonia) should be treated with a course of corticosteroids (prednisone) and closely followed. Similar to patients who have recovered from septic shock, [408] 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 and extended corticosteroids (titrated to the CRP) offered to these patients. It should be noted that much like omega-3 fatty acids (see below) corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4.[409] An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. Pulmonary function testing demonstrates a restrictive type pattern with decreased residual volume and DLCO.[394] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [370-373] however additional data is required before this therapy can be more generally recommended. As discussed above, the serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. [241]

I-RECOVER: The I-RECOVER Protocol for the treatment of the “Long-haul Syndrome”.

Although numerous reports describe the epidemiology and clinical features of post-COVID syndrome, [388-398] studies evaluating treatment options are glaringly sparse.[312] Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific treatment recommendations.[410] In general, while the treatment of ‘Long COVID’ should be individualized, the following treatments may have a role in the treatment of this disorder.

First-line treatment.

- Prednisone 60 mg daily then taper, based on clinical response (in patients with ongoing organizing pneumonia and those with ongoing inflammation; see above)
- Ivermectin has been reported to have a role in the treatment of post-COVID-19 syndrome. [312] A dose of 0.2mg/kg day for 5 days is suggested. A repeat course is suggested in those who respond poorly or relapse once the treatment is stopped. The anti-inflammatory properties of ivermectin may mediate this benefit.
- Omega-3 fatty acids: Vascepa, Lovaza or DHA/EPA 4 g day. Omega-3 fatty acids play an important role in the resolution of inflammation by inducing resolvins production. [160,161]
- Luteolin 100-200 mg day or quercetin 250 mg day (or mixed flavanoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells,[407,411-414] and have been demonstrated to reduce neuroinflammation. [415]
- Famotidine 20-40mg day (histamine-2 blocker for Mast Cell Activation syndrome). [406]
- Melatonin 2- 5mg at night (slow release/extended release) with attention to sleep hygiene.
- Vitamin D3 1000-3000 u/day and Vitamin C 500 mg BID (vitamin C inhibits histamine).[62]
- Functional rehabilitation with light aerobic exercise paced according to individual capacity.[399]
- Behavioral modification and psychological support may help improve survivors’ overall well-being and mental health. [399]

Second-line approach (after poor response to first-line protocol)

- Repeat first-line therapy including corticosteroids and ivermectin. Increase dose of ivermectin to 0.4mg/kg day for 5-10 days.
- Atorvastatin 40 mg daily (increase resolvins synthesis) [408]
- Fluvoxamine, especially in those with neurocognitive issues. Start at 25 mg daily, Increase slowly to 50 -100 mg day. Monitor response closely. Teens and young adults who are prescribed fluvoxamine can experience acute anxiety which needs to be monitored for and treated by the prescribing clinician to prevent rare escalation to suicidal or violent behavior
- Optional: H1 receptor blocker (for mast cell activation syndrome).
- Optional: montelukast 10mg/day (for mast cell activation syndrome)

Patients and health care providers are referred to the following Website:

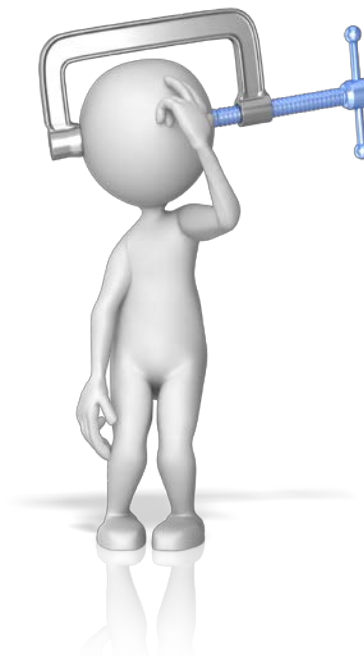
<https://covidlonghaulers.com/>

Maintaining mental health and the avoiding the misinformation pandemic

‘Misinformation on the Coronavirus might be the most contagious thing about it’

Dr. Tedros, WHO Director General

- The Panic and misinformation spread by Social Media travels faster than the pandemic itself. What you can do?
 - Avoid social media as much as possible; excess social media exposure increases the likelihood of anxiety and depression[416]
 - Read the news/information from reliable sources (if you can find one)
 - Have a designated time for checking information
 - People share false claims about COVID-19 partly because they simply fail to think sufficiently about whether or not the content is accurate when deciding what to share. [417]
 - Stay connected to positive people! Remotely!
 - Have a plan for staying in touch with family and friends
 - Identify positive influencers...limit contact with other “worriers”
 - Isolation can cause rumination/anxious thinking to escalate
 - Maintain a sense of *hope, humanity and kindness toward others*
 - Seek professional help if anxiety is overwhelming
- Recognize the things you can control
 - WEAR A MASK when in contact with others
 - Establish social distancing; stand/sit about 6 feet away from others
 - Limit attendance at large gatherings
 - Eliminate your contact with those who are ill
 - DON'T go to work or school if you are sick
 - Practice self-care
 - Good sleep, balanced diet, exercise
 - Mindfulness/Meditation/Relaxation activities



Key Concepts of the I-MASK and MATH+ Treatment Protocols

This is an extraordinarily 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). [418]
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).[419]
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, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[219,420-430] The phenotype at presentation determines the prognosis and impacts the optimal approach to treatment. It is noteworthy that obesity and increasing BMI are critical prognostic factors. This may be related to the fact that there are more ACE-2 receptors in visceral fat than in the lung. [431]
7. The pulmonary phase is characterized by immune dysregulation, [366,368,401,423,432-443] a pulmonary microvascular injury (vasculopathy),[401,443-446] with activation of clotting and a pro-coagulant state together with the characteristics of an organizing pneumonia. [328,447]
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. [401]
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.
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). [328,448,449]

12. **THIS is NOT ARDS** (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS.[450-452] The ground glass infiltrates are peripheral and patchy, [448] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with “typical ARDS”. [453] 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 an extremely dangerous approach. The hypoxia is due to a organizing pneumonia with 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 anticoagulation to limit the microvascular and macrovascular clotting and supplemental oxygen to help overcome the hypoxia.
14. Ivermectin has emerged as a highly effective drug for the prophylaxis and treatment COVID-19. Ivermectin inhibits viral replication and has potent anti-inflammatory properties. Emerging clinical data (including RCT’s) suggest that ivermectin may have an important clinical benefit across the spectrum of phases of the disease, i.e pre-exposure prophylaxis, postexposure prophylaxis, during the symptomatic phase and during the pulmonary phase. [19,25-27,119,122-128,212-214,270-276,454] In the recommended dosages, Ivermectin is remarkably safe and effective against SARS-CoV-2 (see Table 1 and Figures 8 and 10). However, as noted above there is the potential for serious drug-drug interaction.
15. 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. [455]
16. 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.
17. 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. 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.[425,449,456-458] Corticosteroids seem to be of little benefit in established AFOP. High dose methylprednisolone and Mega-dose vitamin C 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.
18. 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,[459,460] and necessitates pulse oximetry in symptomatic patients managed at home (as discussed above).
19. 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.[461] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[462,463] as well as viral replication [127,464]. Most importantly LWWH inhibits heparanase (HPSE).[465] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[465] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [466] 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. [255,260] Vitamin C protects the endothelium from oxidative injury.[62,467-469] Furthermore, vitamin C Increases the expression of interferon-alpha [52] while corticosteroids (alone) decrease expression of this important protein. [470-473] 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. [221,474] 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 particularly 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),[475] genomic data specific for SARS-CoV-2,[140] and a long track record of successful use in inflammatory lung diseases. (see Table 1)



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.” [366,368,423,432,434-442] In addition, post-mortem examination has demonstrated features of the “macrophage activation syndrome”, with hemophagocytosis and a hemophagocytic lymphohistiocytosis-like disorder.[401] These autopsy studies have shown minimal viral cytopathic effects providing further validation that it is the hosts immune response to the virus rather than the virus itself which is killing the host.[401,476-478]
- 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 von Willebrand factor.[141] Furthermore, ACE-2 receptors are present on platelets and this may contribute to the massive platelet aggregation characteristic of severe COVID-19 disease.[143,230,479] These blood clots impair blood flow. [445,446,480-492] It should be noted that the thrombotic microangiopathy appears to target predominantly the pulmonary and cerebral circulation. [401]
- 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 with a severe V/Q mismatch.

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. [365,368,401,460] 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) [493,494]. 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) Alliance (UM), identified the errors made by these organizations in their analyses of corticosteroid studies based on the findings of the SARS and H1N1 pandemics.[216,495] 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.[496] 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.[179] 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, [217,218,224,474,497-499] as well as a randomized controlled study.[226] A recent study from the COVID-19 SPANISH ICU Network strongly supports our approach. [500] These authors demonstrated that pre-ICU corticosteroids and corticosteroids administered within 48 hours of admission to the ICU reduced mortality. However, patients who received late corticosteroids (> 48 hours after ICU admission) did not demonstrate a mortality benefit and these patients had a significantly higher risk of secondary infections. Furthermore (and most importantly) early high-dose corticosteroids (> 1 mg/kg methylprednisolone eq/day) was associated with a significantly reduced mortality compared to early low-dose corticosteroids. It should be recognized that the mortality benefit with methylprednisolone was not replicated in a Brazilian RCT.[455] In this study, methylprednisolone was started late (day 13 after symptom onset) and 3 days after intubation (???), and was stopped prematurely 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.[501] This will likely be a non-issue when all patients are treated with ivermectin.

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.[249] If such early initiation of treatment could be systematically achieved, the need for mechanical ventilators and ICU beds will decrease dramatically.

Further resources:

The scientific rationale for the MATH + protocol is reviewed in this paper.[248,249] please visit our website for further information as well as for common questions (Q & A section).

<https://covid19criticalcare.com/> or www.flccc.net

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>

Long-COVID: <https://covidlonghauers.com/>

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