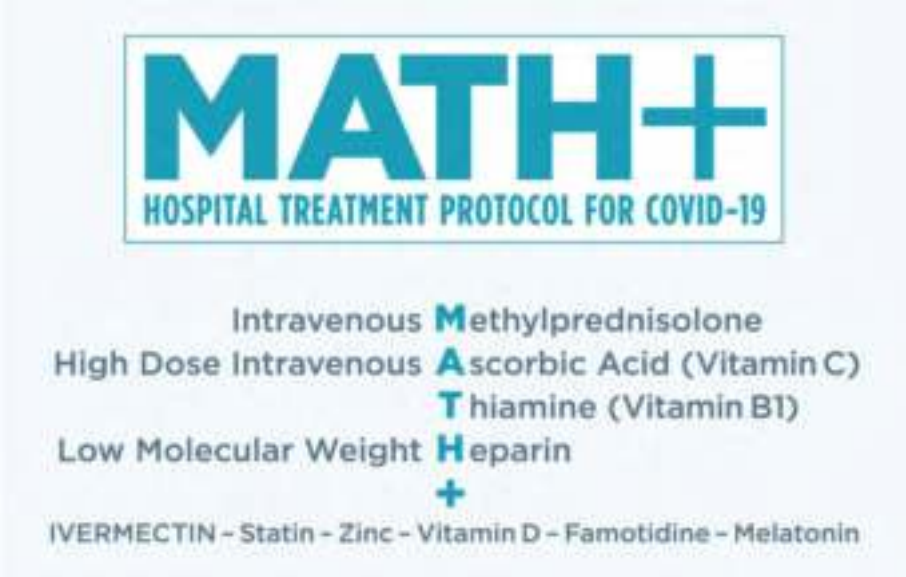
An overview of the MATH+, I-MASK+ and I-RECOVER Protocols

A Guide to the Management of COVID-19

(updated as of 01 January 2022)

Developed and updated by Paul Marik, MD, FCP (SA), FRCP (C), FCCP, FCCM for the COVID-19 Critical Care Alliance (FLCCC Alliance).

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



Disclaimer: The information in this document is provided as guidance to physicians worldwide 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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1. Introduction

1.1. THE VACCUM OF TRUTH

"The first step is to give up the illusion that the primary purpose of modern medical research is to improve Americans' health most effectively and efficiently. In our opinion, the primary purpose of commercially funded clinical research is to maximize financial return on investment, not health."

—John Abramson, M.D., Harvard Medical School

We are living through a period of time characterized by a ***Vacuum of Truth***, with misinformation, disinformation, blatant lies, censorship, and nefarious intentions being the order of the day. It is difficult to dissect out the actual truth and discern whom to trust. Furthermore, it is no longer controversial to acknowledge that drug makers rigorously control medical publishing and that *The Lancet*, *NEJM*, and *JAMA* are utterly corrupted instruments of Big Pharma. *The Lancet* editor, Richard Horton, confirms, "Journals have devolved into information laundering operations for the pharmaceutical industry."

Dr. Marcia Angell, who served as an *NEJM* editor for 20 years, says journals are "primarily a marketing machine." [1] Pharma, she says, has co-opted "every institution that might stand in its way. Complex scientific and moral problems are not resolved through censorship of dissenting opinions, deleting content from the Internet, or defaming scientists and authors who present information challenging to those in power. Censorship leads instead to greater distrust of both government institutions and large corporations. [2]

1.2 The use of "Off Label Drugs"

Once the FDA approves a prescription medication, federal laws allow any U.S. physician to prescribe the duly approved drug for any reason. [3] Thirty percent of all prescriptions written by American doctors, exercising their medical judgment, are for off-label uses. The Attorney General of Nevada as well as many other states have asserted the right of physicians to prescribe "off-label" drugs such as ivermectin and hydroxychloroquine for the treatment of COVID-19. The office of Nebraska Attorney General Doug Peterson released a legal opinion on October 15 2021 saying it didn't see data to justify legal action against health care professionals who prescribe ivermectin or hydroxychloroquine.

1.3. Overview of the treatment of COVID-19

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, fluvoxamine, spironolactone, corticosteroids, curcumin (turmeric), *Nigella sativa* and antiandrogen therapy. It is critical to recognize that infection with SARS-CoV-2 progresses through a number of stages/phases and that treatment is highly stage-specific (see Figures 1-4 and Table 1). 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. A growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [4-6] Furthermore, an understanding of the structure of SARS-CoV-2 (see Figure 5) as well as the pathophysiology/pathogenesis of COVID-19 is critical in treating the disease. [7] Finally, the relentless malpractice of deliberately withholding effective early COVID treatments, and of forcing the use of toxic remdesivir in hospitalized patients, may have unnecessarily killed up to 500,000 Americans (see Figures 6a-c). [2]

As the pandemic has played out over the last year, over four million patients have died worldwide, 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+ and the Test and Treat protocols.** 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, so-called "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". 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, demonstrating increased transmissibility.[8,9] [10] Many of these mutations involve the spike protein (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.[9,11,12] And, finally the Post-COVID syndrome or "long-hauler syndrome" has emerged as a common and disabling disorder, and its pathophysiology is poorly understood. We offer the **I-RECOVER** protocol to help treat this disabling disorder. Recently, the post-vaccination syndrome has emerged as a problematic entity; we believe that the **I-RECOVER** protocol has utility in treating this syndrome.

Figure 1. Treatment phases of COVID-19

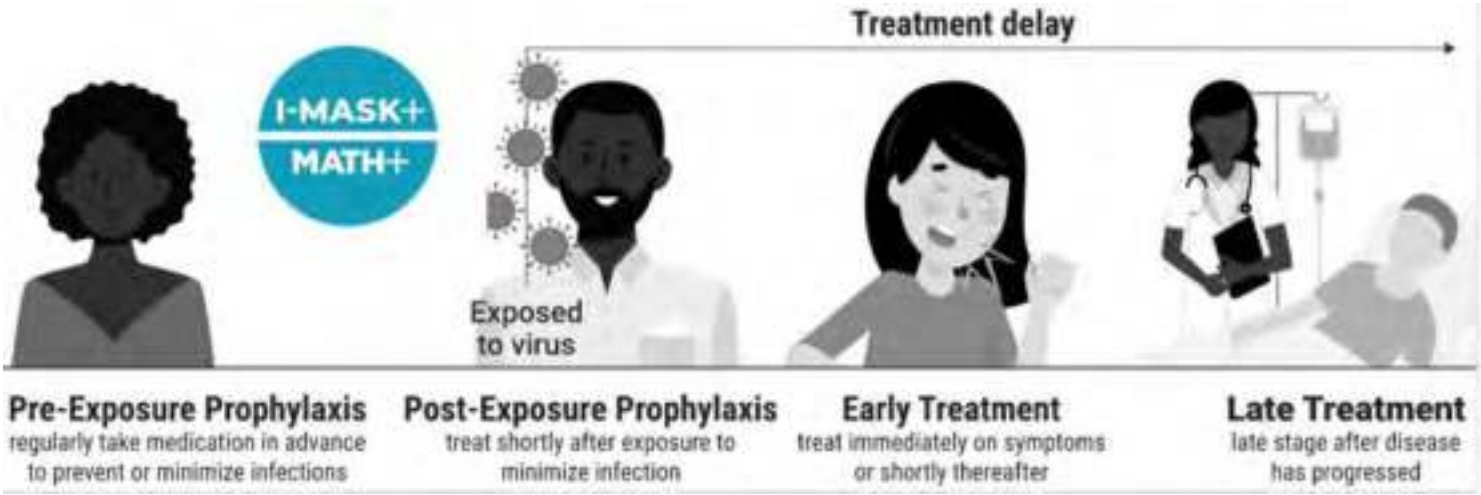
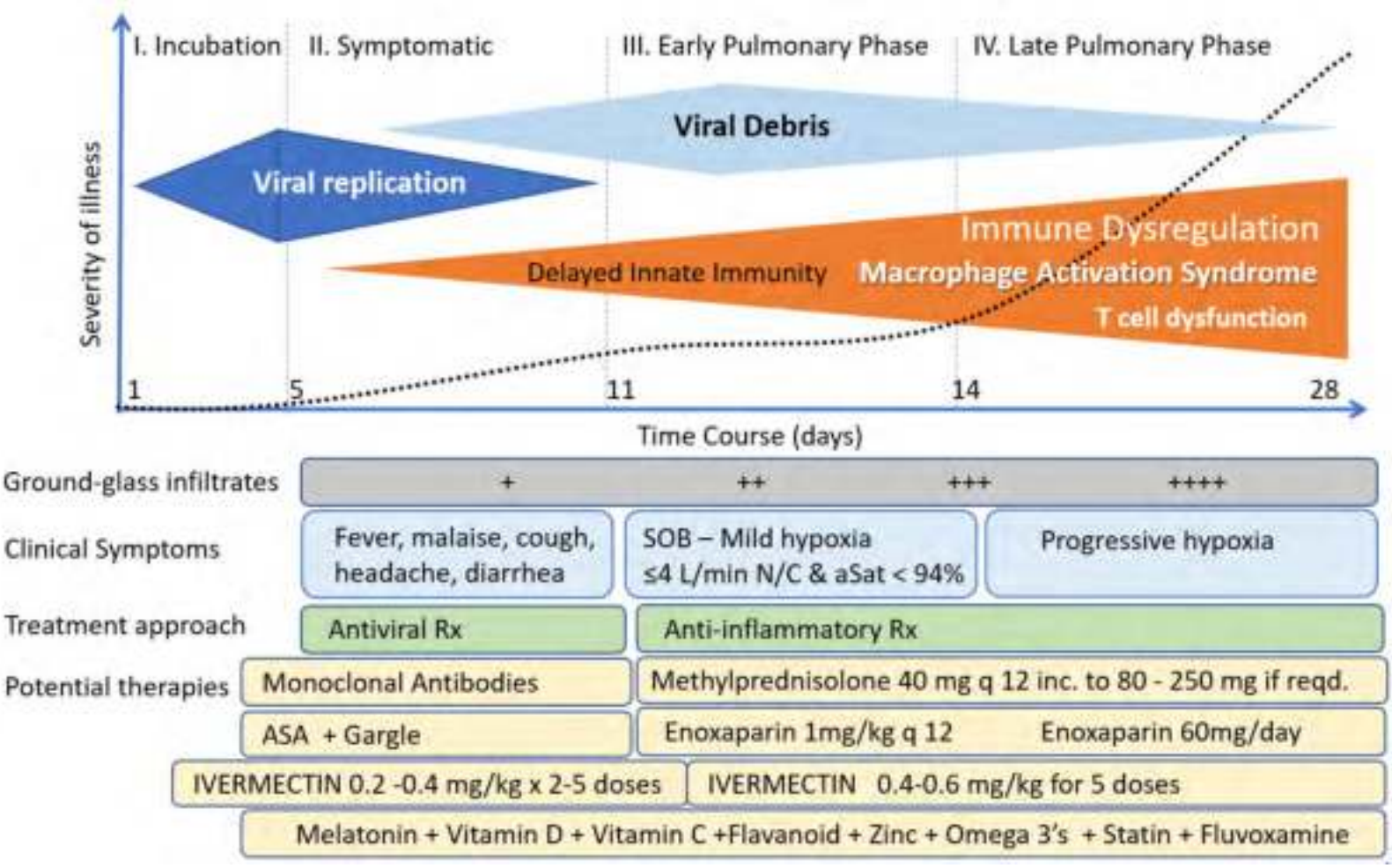


Figure 2. The course of COVID-19 and general approach to treatment

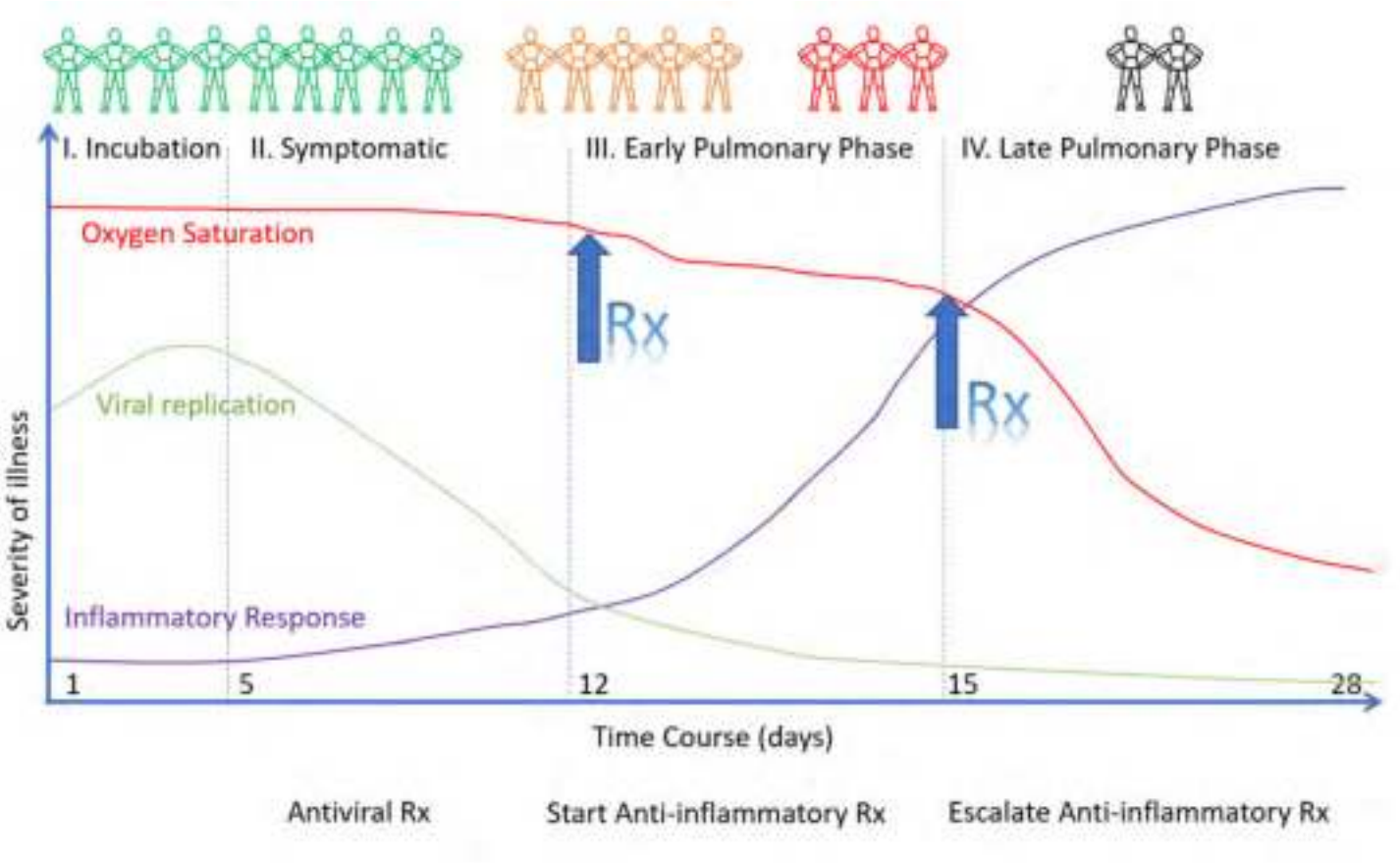


THIS IS A STEROID-RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL.

Not too early. Not too late.

Figure 3. Timing of the initiation of anti-inflammatory therapy



Note: Viral Replication in Figures 2 and 3 are typical for the original Wuhan SARS-CoV-2 virus (alpha strain). SARS-CoV-2 delta and gamma (P1) variants may present prolonged duration of viral replication. Furthermore, the time course from incubation to symptom onset and to the pulmonary phase may be shortened. The time course of Omicron is unclear at this time.

Figure 4. Time course of laboratory tests for COVID-19

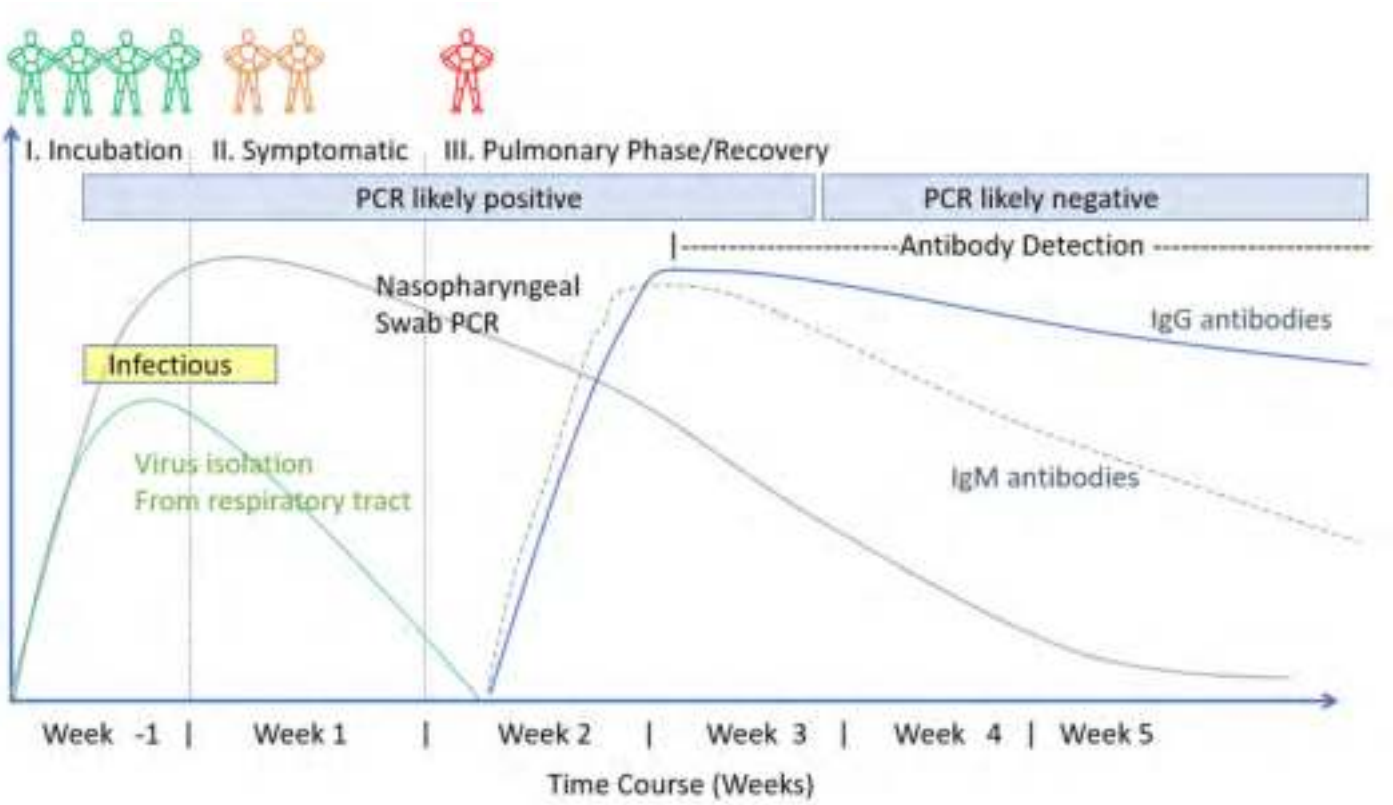


Figure 5. SARS-Co-V-2 structure and RNA genome

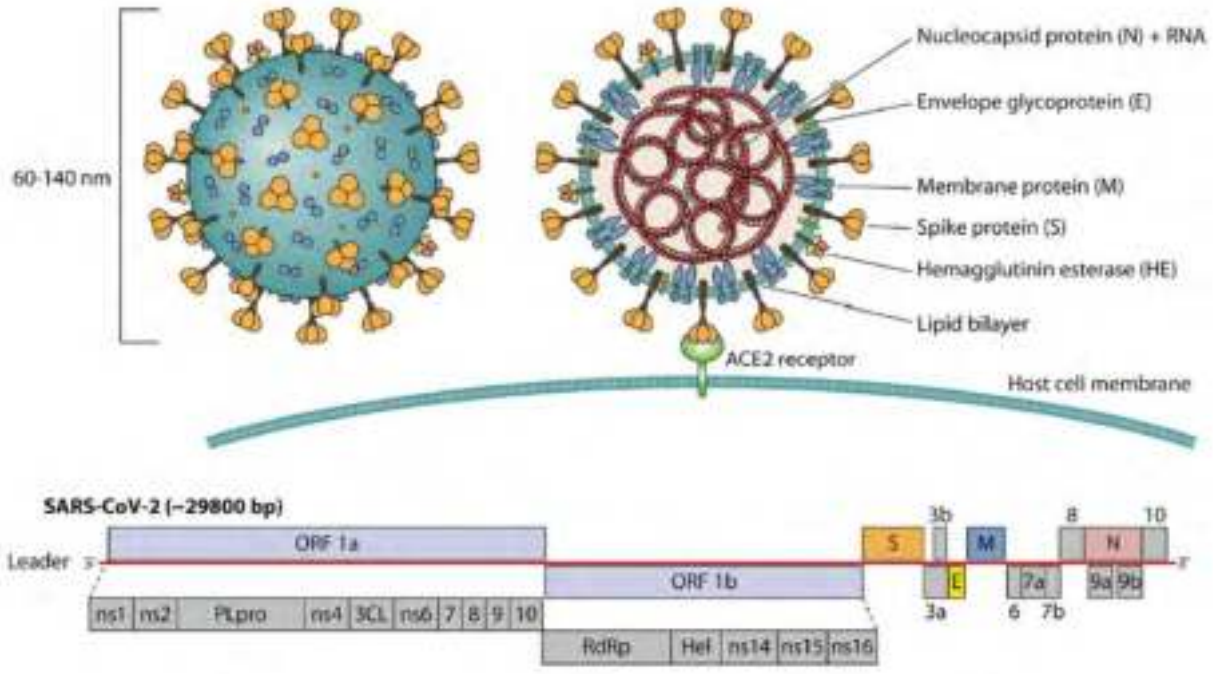


Table 1. Pharmacological therapy for COVID by stage of illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Anti-androgen Rx	Benefit	BENEFIT	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Corticosteroids	n/a	Trend to harm	BENEFIT
LMWH	n/a	n/a	BENEFIT
Monoclonal Abs	BENEFIT	BENEFIT (early)	HARM
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Remdesivir	n/a	? Benefit	HARM
Lopivinar-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	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

* Based on randomized controlled trials (see supporting information below)
** Due to extensive fraudulent activity around the design and conduct of RCTs, the benefit of HCQ is supported largely by numerous consistently positive observational trials.

Figure 6a. NIH recommendations for the treatment of COVID-19 across the stages of the disease. (Last Updated: October 19, 2021)

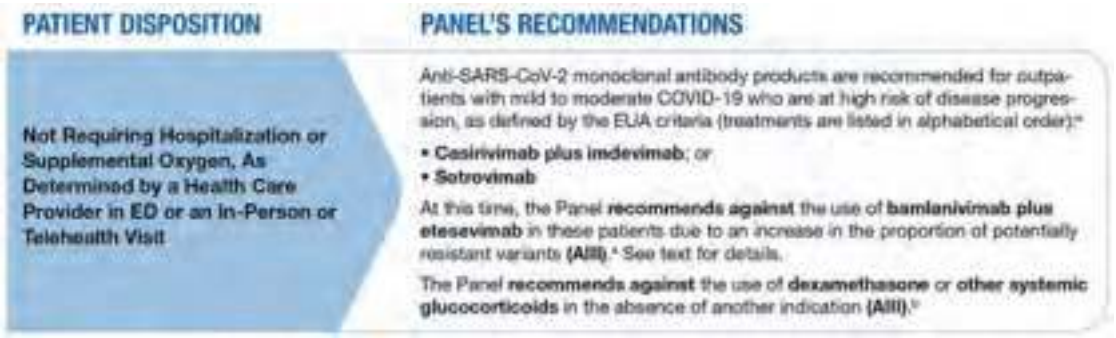


Figure 6b. Therapeutic management of hospitalized adults with COVID-19 based on disease severity. (Last Updated: December 16, 2021)

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., baricitinib[e] or tocilizumab[e]) **(CIIa)**.
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the 2 options above.[d,f]
Hospitalized and Requires MV or ECMO	• **Dexamethasone (AI)**[g] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, IV **sarilumab** can be used **(BIIa)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] Corticosteroids prescribed for an underlying condition should be continued.
[b] If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).
[c] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large placebo-controlled trial showed that remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.
[d] Drugs are listed alphabetically. There are no studies directly comparing baricitinib and tocilizumab, and there is insufficient evidence to recommend 1 drug or 1 class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
[e] If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
[f] The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
[g] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of **remdesivir** monotherapy in these patients **(AIIa)**.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Figure 6c. NIH recommendations for prevention of SARS-CoV-2 infection. (Last Updated: December 16, 2021)

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
- The Panel recommends using 1 of the following anti-SARS-CoV-2 monoclonal antibodies (listed alphabetically) as post-exposure prophylaxis (PEP) for people who are at high risk of progressing to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history outlined in the text below:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion **(BIII)**; *or*
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous injections **(AI)** or an IV infusion **(BIII)**.
- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 PEP **(AI)**.
- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**.
- The Panel **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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

The components of the I-MASK+ Prophylaxis and Early Treatment protocol are illustrated in Figures 7a-c. Recent data suggests that ivermectin, melatonin as well as the combination of quercetin (or mixed flavonoids) and Vitamin C as well as oropharyngeal sanitation may play an important role in both pre-exposure and postexposure prophylaxis. [5,13] The evidence supporting the use of ivermectin for the prophylaxis of COVID-19 is provided by the comprehensive review by Kory et al. [14] 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 that includes common sense public health measures, i.e., masks (only for prolonged exposure in confined, poorly ventilated environments), short term quarantine of infected patients, and high risk individuals (advanced aged and comorbidities) avoiding large public and family gatherings. [15] Standard surgical and cloth masks likely only reduce risk of transmission for finite periods in confined environments. For prolonged protection in such settings, N95 type masks would be required.

2.1 Core Components of the I-MASK Prophylactic Protocol

- Ivermectin for post-exposure prophylaxis (see ClinTrials.gov NCT04422561). 0.4 mg/kg immediately then repeat 2nd dose in 48 hours. Ivermectin is best taken with a meal or just following a meal (greater absorption). [16] Oropharyngeal sanitation also suggested (see section on home treatment below).
- Ivermectin for pre-exposure prophylaxis (in healthcare workers) 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, take 2nd dose 48 hours later, then 1 dose every 7 days (i.e. weekly). [17-22] For those at high risk of contracting COVID-19, we now recommend twice weekly dosing. See Dosing Table below. Ivermectin has a number of potentially serious drug-drug interactions); please check for potential drug interactions at Ivermectin Drug Interactions - Drugs.com (also see Table 4 below). The most important drug-drug interactions occur with *cyclosporin, tacrolimus, anti-retroviral drugs*, and certain antifungal drugs. While ivermectin has a remarkable safety record, [23] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [24,25] While hepatitis is commonly quoted as a side effect, we are aware of one published case report of reversible hepatitis. [26] The safety of ivermectin in pregnancy has not been determined. [27] Ivermectin may increase the risk of congenital malformations particularly when used in the first trimester. [27] 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 fetus 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. [28]
- Melatonin (slow release/extended release): Begin with 0.3 mg and increase as tolerated to 6 mg at night. [4,13,29-35]. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease. [36-38] Multiple studies have demonstrated the benefit of melatonin at various stages of the disease. [39-41] 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). [37] 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. [42] Similarly, children have high levels of circulating melatonin approximating those of bats, while elderly people – particularly those over the age of 60 – have very low melatonin levels; this may partly explain the increased

vulnerability of the elderly to COVID-19. The slow release (extended release) formulations of melatonin are preferred as they more closely replicate the normal circadian rhythm. [29] There is marked inter-individual variation in the metabolism of melatonin (first pass metabolism), hence the dose must be individualized. [29] High serum levels are associated with hyper-REM sleep and bad dreams. Rapid release melatonin (usual over-the-counter formulation) results in early high peaks that do not replicate the normal circadian pattern; hence it is important to take the slow release/extended-release formulation.

- Oropharyngeal hygiene with twice daily antiviral mouthwash/gargle (see Figure 7 and below).
- Monoclonal antibodies for post-exposure prophylaxis. A single subcutaneous injection of REG-COV2 (a combination of the monoclonal antibodies casirivimab and imdevimab) has been demonstrated to reduce the risk of symptomatic COVID-19 infection in close contacts by 92.6% (7.8% to 1.5%). [43] Monoclonal antibodies are recommended in high-risk individuals, namely, > 65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunosuppressed, coronary heart disease, etc. See infusioncenter.org and call 1-877-332-6585 In USA for eligibility and location.
- *Optional:* Famotidine 20–40 mg/day [44-50]. 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. [47] Furthermore, a number of studies have demonstrated an association between the use of proton pump inhibitors (PPIs) with an increased risk of contracting COVID-19 and with worse outcomes. [51,52] This data suggest that famotidine may be the drug of choice when acid suppressive therapy is required.
- *Optional:* Hydroxychloroquine (HCQ) 200 mg BID for 5 days together with ZINC (75-100mg elemental zinc) post COVID-19 exposure. [53-56]

Disclaimer: The safety of ivermectin in pregnancy has not been established. Particularly the use in the 1st trimester should be discussed with your doctor beforehand.

Ivermectin dosing table: 200 ug/kg (0.2 mg/kg) or fixed dose of 12 mg (≤ 80kg) or 18 mg (≥ 80kg). [57] Depending on the manufacturer ivermectin is supplied as 3mg, 6 mg or 12 mg tablets.

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

2.2 Nutritional Supplements (in order of priority, not all required)

- Curcumin (Turmeric). Curcumin has antiviral activity against a number of viruses including SARS-CoV-2. In addition, this spice has anti-inflammatory, antioxidant and immune modulating properties. [58-62] Emerging data suggests that curcumin improves the clinical outcome of patients with COVID-19. [63,64]
- *Nigella Sativa* (black cumin) and honey. Both honey and Nigella Sativa have anti-viral, anti-microbial, anti-inflammatory, and immune-modulatory effects with proven safety profiles. [65-72] It should be noted that thymoquinone (the active ingredient of *Nigella Sativa*) decreases the absorption of cyclosporine and phenytoin. [73] Patients taking these drugs should therefore avoid taking *Nigella Sativa*. Furthermore, two cases of serotonin syndrome have been reported in patients taking *Nigella Sativa* who underwent general anaesthesia (probable interaction with fentanyl. [74]

- Vitamin D3 3000- 5000 IU/day (75-125 mcg) (this is the default dosing when the baseline vitamin D level is not available). 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 quoted as < 5000 IU/day. It is however **EXTREMELY IMPORTANT** to stress that the optimal regimen for Vitamin D supplementation for both the prophylaxis and treatment of COVID-19 should be based on the baseline vitamin D level (see Tables 2 & 3. The OPTIMAL target vitamin D level is > 50 ng/ml; at this level the risk of acquiring COVID-19 approximates ZERO. [75] It may take many months/years to achieve optimal levels in a patient with a vitamin D level of < 12 ng/ml taking 5000 IU /day. Vitamin D has numerous immunological properties that play a vital role in limiting the acquisition and severity of COVID-19.[76] Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. [77-103] 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^{o} latitude. [83-98,101] In addition, vitamin D supplementation may be important in pregnant patients.[104] 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. [105] This concept is supported by a recent study that demonstrated that residents of a long-term care facility who took vitamin D supplementation had a much lower risk of dying from COVID-19. [99]
- Probiotics. There appears to be a bi-directional relationship between the microbiome esp. Bifidobacterium and COVID-19. Low levels of Bifidobacterium may predispose to COVID-19 and increase its severity. [106-109] COVID-19 depletes the microbiome of Bifidobacterium, which may then increase the severity and duration of COVID-19 symptoms. Kefir (a fermented milk drink) is high in Bifidobacterium and other probiotics that have demonstrated health benefits. [110,111] Kefir, probiotic yogurt and/or the addition of Bifidobacterium Probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) may normalize the microbiome, which may reduce the risk and severity of COVID-19.
- Vitamin C 500 – 1000 mg BID (twice daily) and Quercetin 250 mg daily. [112-124] 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. [115,125,126] Quercetin has direct virucidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [113,118,123,123,127-135] Quercetin is a potent inhibitor of inflammasome activation, which is believed to play a major role in the pathophysiology of the COVID-19 immune dysfunction. [135] In addition, quercetin acts as a zinc ionophore. [136] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [5] A mixed flavonoid supplement containing quercetin, green tea catechins and anthrocyanins (from berries) may be preferable to a quercetin supplement alone; [137-141] 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. [142-145] 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 subclinical thyroidism. [146] In women, high consumption of soya was associated with elevated TSH concentrations. [147] 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. [148] In patients taking these drugs it is best to avoid quercetin; if quercetin is taken cyclosporin and tacrolimus levels must be closely monitored.

- Zinc 30–40 mg/day (elemental zinc). [119,121,122,149-153] Zinc is essential for innate and adaptive immunity. [151] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus. [150] 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. [154] 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 zin*c* sulfate contains 50 mg elemental zinc.
- B complex vitamins [155-159].

2.3 Prevention Protocol in Children and Adolescents

- Multivitamin with age-appropriate dosages of Vitamin C, D and B complex
- Oropharyngeal sanitization with mouth gargle twice daily (very important)
- Curcumin
- *Nigella sativa* and honey
- Kefir, probiotic yogurt and/or Bifidobacterium probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic).
- Children's Zinc lozenges/chewable 3-5mg/day

Table 2. Guidance on upfront loading dose regimens to replenish Vitamin D stores in the body

Serum vitamin D (ng/mL)	Frequency of administration (per week)	Duration of therapy (weeks)	Total dose for correction * (IU millions)
≤ 5	100,000 IU, one dose; 50,000 twice a week	14	1.3 to 1.5
6–10	50,000 twice a week	12	1.0 to 1.2
11–15	50,000 twice a week	10	0.8 to 1.0
16–20	50,000 twice a week	8	0.6 to 0.8
21–25	50,000 once a week	10	0.4 to 0.5
26–30	50,000 once a week	6	0.2 to 0.3
Maintenance regimens	50,000 IU, or	Monthly	Maintenance
	1,000 to 2,000 IU	Daily	Maintenance
	4,000 or 5,000	Daily	High risk persons

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Table 3. Rapid and effective Vitamin D supplementation in patients with COVID-19 infection

COVID-19 VITAMIN D (CHOLECALCIFEROL) SUPPLEMENTATION										
	Patient Definition	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	TOTAL PERIOD	TOTAL DOSE
INPATIENT	Serum 25OHD level < 12 ng/mL	100.000 IU	10.000 IU	10.000 IU	10.000 IU	10.000 IU	10.000 IU	10.000 IU	14 Days	320.000 IU
	Serum 25OHD level 20–12 ng/mL	100.000 IU	5.000 IU	5.000 IU	5.000 IU	5.000 IU	5.000 IU	5.000 IU	14 Days	260.000 IU
	Serum 25OHD level 20–30 ng/mL	100.000 IU	2.000 IU	2.000 IU	2.000 IU	2.000 IU	2.000 IU	2.000 IU	14 Days	224.000 IU
ICU PATIENT	Serum 25OHD level < 12 ng/mL	100.000 IU	100.000 IU	100.000 IU	100.000 IU	100.000 IU			5 Days	500.000 IU
	Serum 25OHD level 20–12 ng/mL	100.000 IU	100.000 IU	100.000 IU	100.000 IU				4 Days	400.000 IU
	Serum 25OHD level 20–30 ng/mL	100.000 IU	100.000 IU	50.000 IU					3 Days	250.000 IU

Reproduced with permission from Gonen et al. [161]

Table 4. Drug interactions with ivermectin (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	Amiodarone	Glecaprevir/Pibrentasvir	Phenytoin
Lasmiditan	Atorvastatin	Indinavir	Ponatinib
Quinidine	Berotralstat	Istradefylline	Quercetin (**)
Tepotinib	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

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

3.1 First Line Treatments (in order of priority, not all required)

- Ivermectin 0.3- 0.6 mg/kg – one dose daily for 5 days or until recovered. [19,23,77-80,162-177]. Higher doses (0.6 mg/kg) are often required: a) in regions with more aggressive variants, b) if 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). **A dose of 0.3-0.4 mg/kg may be appropriate for the Omicron variant.** Ivermectin is best taken with a meal or just following a meal (greater absorption). See drug-drug interactions above. It should be noted that multiday treatment has been shown to be more clinically effective than single-day dosing.
- Nitazoxanide (NTZ) 600 mg BID for 5 days was shown to reduce disease progression, hospitalization and death when used early in outpatients with mild to moderate disease. [178] The combination of NTZ and ivermectin has been shown to reduce viral clearance and symptom progression in outpatients with COVID-19. [179,180] NTZ is an oral antiparasitic drug having activity against many protozoa and helminths and – similar to ivermectin – has been shown to have antiviral and immune-modulatory effects. [181,182] Like ivermectin, NTZ has broad spectrum antiviral activity that includes SARS-CoV-2. [182-185] Furthermore, as NTZ and ivermectin have differing modes of action, it is likely that these two drugs have synergistic antiviral and anti-inflammatory effects.[180,183,186] NTZ should therefore be 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.
- Oropharyngeal sanitization (see figure 7b and c). [187] Inhaled steam supplemented with antimicrobial essential oils (e.g VapoRub™ inhalations) has been demonstrated to have virucidal activity. [188] Antiseptic-antimicrobial mouthwashes (chlorhexidine, povidone-iodine, cetylpyridinium chloride and the combination of eucalyptus, menthol and thymol [Listerine™]) have been shown to inhibit SARS-CoV-2 replication and to reduce viral load in research studies. [189-196] A mouthwash containing cetylpyridinium chloride (CPC) has broad antimicrobial properties and has been shown to be effective in controlling gingivitis and gingival plaque. [196-198] An *in-vitro* study demonstrated that CPC was highly viricidal against a human coronavirus. [199] In a primary prophylaxis study, a povidone-iodine throat spray administered three times daily proved to be highly effective in reducing the risk of laboratory confirmed SARS-CoV-2 infection. In patients with symptomatic disease treated at home with a 1% povidone iodine mouthwash/gargle, together with nasal and eye drops, resulted in a dramatic reduction in morbidity, hospitalization and death. [200] A nasal spray with 1% povidone-iodine (for example Immune Mist™) administered 2-3 times per day is recommended in post-exposure prophylaxis and in symptomatic patients (early phase of COVID-19 infection). [191] Due to low level systemic absorption, povidone-iodine nasal spray should not be used for longer than 5-7 days in pregnant women. While the use of an iodine-containing mouthwash over a six-month period was demonstrated to increase serum iodine levels, thyroid function tests remained unchanged. [201] Oropharyngeal sanitization will likely reduce the viral load in the upper airways, thereby reducing the risk of symptomatic disease and likely reducing disease severity. This may be particularly important with the Delta variant, which replicates to achieve viral high loads in the nasopharynx/oropharynx.
- ASA 325 mg/day (unless contraindicated). ASA has anti-inflammatory, antithrombotic, immunomodulatory, and antiviral effects. [202-204] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [205-207]

- Melatonin 10 mg at night. [35-41] The slow release/extended-release preparation is preferred as it minimizes the risk of bad dreams.
- Curcumin (turmeric). Curcumin has antiviral activity against SARS-CoV-2. In addition, this spice has anti-inflammatory and immune modulating properties. [58-62]
- *Nigella Sativa* (black cumin) and honey. A randomized placebo-controlled study demonstrated that the combination of honey and *Nigella sativa* (HNS) hastened recovery, decreased viral shedding and reduced mortality in patients with both moderate and severe COVID-19 infection. [67]
- Kefir and/or Bifidobacterium Probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome.
- Vitamin D 3000 - 5000 IU daily (125 mcg) if baseline Vitamin D level is unknown. The optimal dose of Vitamin D in the acute setting is controversial. [208,209] However, the dosing schedule as outlined in Table 3 is suggested. [161]
- Vitamin C 500 – 1000 mg BID and Quercetin 250 mg BID (or mixed flavonoid 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).
- Hydroxychloroquine (HCQ) 200 mg BID for 5-10 days. [53-56] HCQ may be taken in place of ivermectin or together with ivermectin. While ivermectin should be avoided in pregnancy, the FDA considers HCQ safe in pregnancy. Some 200 peer-reviewed studies (C19Study.com) by government and independent researchers deem HCQ safe and effective against Coronavirus, especially when taken prophylactically or when taken in the initial stages of illness along with zinc and azithromycin. Unfortunately, most of the RCTs that have been conducted to date used toxic doses of HCQ and/or were given very late in the disease and were clearly designed by the "captured" agencies to fail. [2] Instead of using the standard treatment dose of 400 mg/day, the 17 WHO studies administered a borderline lethal *daily* dose starting with 2,400 mg on Day 1 and using 800 mg/day thereafter. Brazilian prosecutors have accused the authors of one study with committing homicide by purposefully poisoning and murdering the elderly subjects of their study. [210]
- 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. [211] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous. [211] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [212] The following guidance is suggested: [211]
    - Use the index or middle finger
    - 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

3.2 Second Line Treatments

- B complex vitamins
- Anti-androgen therapy. Androgens augment SARS-CoV-2 infectivity by promoting the expression of transmembrane protease (TMPRSS2) that primes the spike viral entry protein. [213] In addition androgens are pro-inflammatory. [214] Spironolactone is the anti-androgen of choice (in both men and women). Spironolactone has pleiotropic effects in COVID-19 including anti-androgen, anti-inflammatory, anti-fibrotic and restores the RAAS (angiotensin 1-7). [215-218]

The optimal anti-androgenic dose of spironolactone appears to be 100 mg BID. Proxalutamide is the most potent antiandrogen; this agent has been demonstrated to have remarkable efficacy in patients with COVID. [219] The 5-alpha reductase inhibitors dutasteride or finasteride are second line anti-androgen agents (in both men and women). These drugs block the conversion of testosterone to the biologically more active hormone dihydrotestosterone. Finasteride has a very short half-life of 6 hours, compared to 5 weeks for dutasteride. [220,221] Both spironolactone and dutasteride decrease expression of TMPRSS2. [222] Multiple clinical studies support the notion that androgens exacerbate COVID-19 and that anti-androgen therapy improves clinical outcomes. The anti-androgens dutasteride, proxalutamide and spironolactone have been demonstrated to reduce time to viral clearance, improved time to recovery and reduced hospitalization (outpatients) as well as reduced mortality (hospitalized patients) in both men and women. [219,223-228] Dutasteride has been used in women with alopecia and reported to be safe. [229,230] However, this agent **MUST** be avoided in pregnant women. We therefore recommend dutasteride 2 mg day 1, followed by 1.0 mg for 10 days.

- Fluvoxamine 50 – 100 mg BID. [231-238] This selective serotonin reuptake inhibitor (SSRI) is recommended in those patients with more severe symptoms/more advanced disease. Fluvoxamine is a SSRI that activates sigma-1 receptors decreasing cytokine production. [231,232] In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus and inhibits melatonin degradation.[239,240] Antidepressant medications (SSRI) deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation. [241-243] The use of antidepressants has be associated with a lower risk of intubation and death in patients hospitalized with COVID-19. [234,235,244,245] Fluoxetine (Prozac; 20-40mg daily), has activity against the sigma-1 receptor and is an alternative should fluvoxamine not be available. [246]
- Monoclonal antibodies for early outpatient treatment (within 7 days of symptom onset). In the REG-COV2 outpatient study, 4057 patients with at least one risk factor for severe COVID were randomized to a single intravenous infusion of REG-COV2 (a combination of the monoclonal antibodies casirivimab and imdevimab) or placebo. [247] In this study the median duration of symptoms prior to enrollment was 3 days. The composite endpoint of hospitalization and death was reduced by 71% (4.6 % to 1.3%). While not reported in the publication, the mortality rate was not significantly different between groups!!! [247] The duration of symptoms was 4 days shorter in the REG-COV2 group. Monoclonal antibodies appear to reduce the risk of hospitalization in patients with mild to moderate disease if administered within 4 days of symptoms.[248,249] The timely administration of monoclonal antibodies are recommended in high-risk individuals, namely, > 65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunosuppressed, coronary heart disease, etc. See infusioncenter.org and call 1-877-332-6585 In USA for eligibility and location. Sotrovimab is a monoclonal antibody that neutralizes SARS-CoV-2 by targeting an evolutionarily conserved epitope that lies outside the rapidly evolving receptor binding motif. [250] *In vitro*, data suggests that Sotrovimab retained activity against variants of interest and concern (VOC), including the alpha, beta, gamma, delta, and lambda variants. With the rapid emergence of VOC Sotrovimab may be the preferred monoclonal antibody.

3.3 Optional treatments and those of uncertain benefit

- *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. Omega-3 fatty acids reprogram macrophages/monocytes from a M1 phenotype to a M2 phenotype.[251-253] As discussed later

this is critical in the management of COVID-19. In addition, omega-3 fatty acids may have antiviral properties. [121,254-257]

- *Optional:* Maraviroc 300 mg BID for 10 days. Maraviroc is a C-C-chemokine 5 receptor blocker (CCR5). Genomic and proteomic data have demonstrated that the CCR5 axis plays a major role in the pathophysiology of coronavirus infection, largely by recruiting activated monocytes to the lung. [258-260] Preliminary data demonstrated that disruption of the CCR5 axis with monoclonal antibodies was associated with an improved outcomes in patients with COVID-19. [261-263] Maraviroc is a CCR5 blocker that has been extensively used in patients with HIV, with a good safety record. [264-266] Clinical data suggests that maraviroc may be useful as an adjunctive agent in both acute COVID-19 infection and in the long-haul syndrome. However, at this time there is limited published data on the utility of this drug. Due to the very low risk of hepatotoxicity monitoring LFT's are recommended. Price and availability may however be an issue.
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction*) [44-50].*
- *Optional*: Interferon-α/β nasal spray, inhalation or s/c injection. [267-271] It should be noted that Zinc potentiates the effects of interferon. [272,273]
- *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). [296-298] SARS -CoV-2 binds the ACE-2 receptor with internalization of the receptor and decreased ACE-2 activity. This results in increased circulating levels of angiotensin II with decreased levels of the vasodilator angiotensin 1-7. Increased angiotensin II levels have been demonstrated to be linearly associated with viral load and lung injury.[299] The role of ARBs in patients with COVID-19 is controversial as clinical studies have produced conflicting results. [274,275] However, it should be noted that ARBs may act synergistically with statins. [302] ARBs are *contraindicated in pregnancy.*
- *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, with no difference in the rate of hospitalization. [276,277] 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 downregulate ACE-2 expression (harmful). Furthermore, two population level studies suggest that inhaled corticosteroids may increase the risk of death in patients with COVID-19. [278,279] In a more recent RCT, the inhaled corticosteroid Ciclesonide failed to achieve the primary efficacy end point of reduced time to alleviation of all COVID-19 related symptoms. [280] 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 a total of 30 days. In the COLCORONA study, colchicine reduced the need for hospitalization (4.5 vs 5.7%) in high risk patients. [281] 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, [282] 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. [283]
- *Not recommended:* Prophylactic azithromycin, as well as doxycycline, or quinolone antibiotics are of little benefit in patients with COVID-19. [284-286]

7a. i-MASK Early treatment protocol

EARLY TREATMENT PROTOCOL[5] (for Delta variant)

1. First line agents (use any or all medicines; listed in order of priority/importance)

ANTI-VIRALS

Ivermectin[2]
0.4–0.6 mg/kg per dose (take with or after a meal) — one dose daily, take for 5 days or until recovered. Use upper dose if: **1)** in regions with aggressive variants (e.g. Delta); **2)** treatment started on or after day 5 of symptoms or in pulmonary phase; or **3)** multiple comorbidities/risk factors.

and/or **Nitazoxanide**
500 mg 2 x daily for 5 days after meals. Combine with ivermectin (preferred) or substitute if ivermectin is not available. (Nitazoxanide is often unavailable or high-priced in the USA.)

ANTI-SEPTIC ANTI-VIRALS

Antiviral mouthwash: Gargle 3 x daily (do not swallow; must contain chlorhexidine, povidone-iodine, or cetylpyridinium chloride). **Iodine nasal spray/drops**: Use 1% povidone-iodine commercial product as per instructions 2–3 x daily. If 1%-product not available, must first dilute the more widely available 10%-solution[6] and apply 4–5 drops to each nostril every 4 hours. (No more than 5 days in pregnancy.)

ANTI-COAGULANTS / IMMUNE FORTIFYING

Aspirin	325 mg daily (unless contraindicated)
Vitamin D	Vitamin D3 5,000 IU daily.
	See dosing Table 3
Melatonin	10 mg before bedtime (causes drowsiness)

SYNERGISTIC THERAPIES

Quercetin	250 mg 2 x daily
Zinc	100 mg/day (elemental zinc)
Vitamin C	500–1,000 mg 2 x daily

NUTRITIONAL THERAPEUTICS (for 14 days)[4]

Curcumin	(turmeric)	500 mg 2 x daily
Nigella Sativa	(black cumin seed)	80 mg/kg daily
Honey		1 gram/kg daily

PULSE OXIMETER

Monitoring of oxygen saturation is recommended
(for instructions see page 3)

Figure 7b. Naso-oropharyngeal sanitization

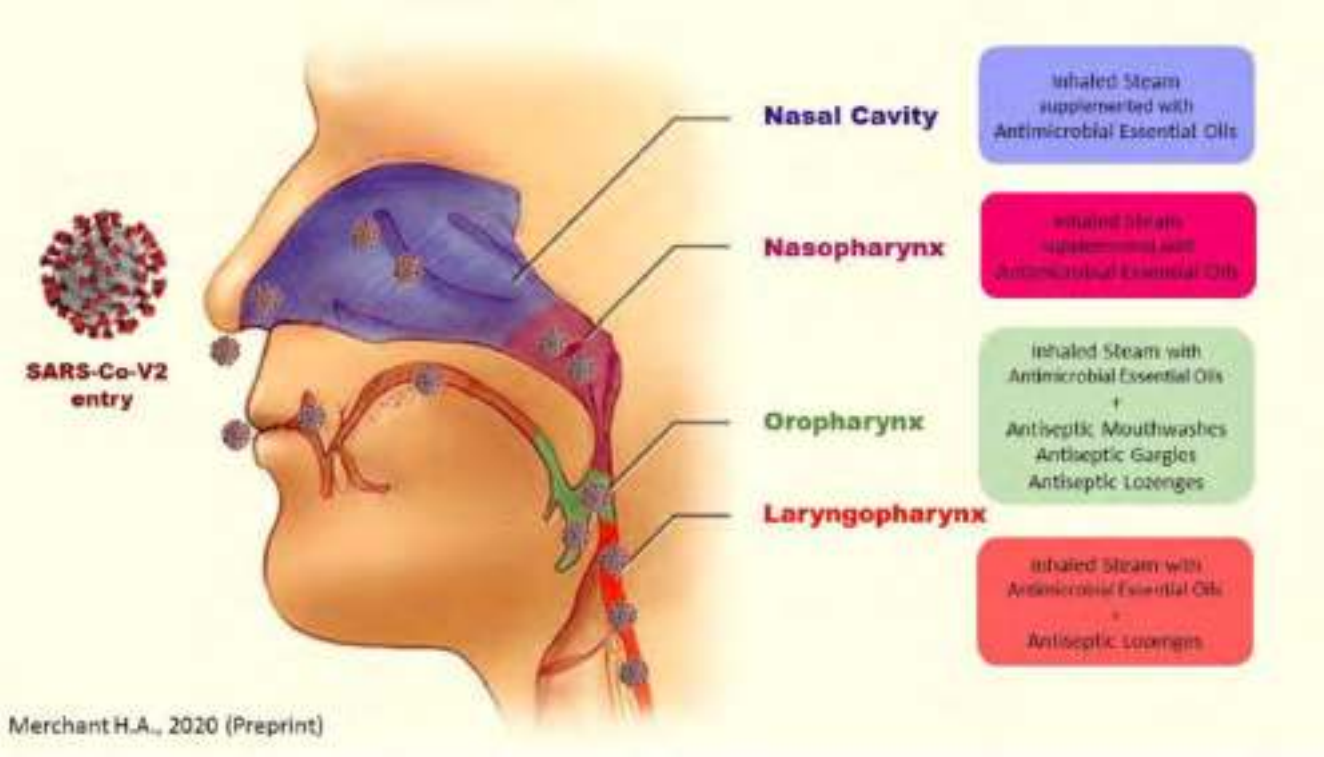


Figure 7c. Commercial products available for Naso-oropharyngeal sanitization

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

4.1 First Line Therapies (in order of priority)

- It is important to note that ivermectin, LMWH and corticosteroids form the foundation of care for the hospitalized patient. Multiple RCTs have demonstrated that these drugs reduce the mortality of patients hospitalized with COVID-19 (See independent meta-analysis Figure 8).
- 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. [19,23,77-80,162-171,173,175-177]. While ivermectin retains full efficacy against the variants (as best we know), the Delta variant results in very high viral loads and may take longer to eradicate. 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.[287-290] Preliminary data suggest that Ivermectin in a dose of 0.3-0.4 mg/kg is highly effective against the Omicron variant; however, in keeping with the general treatment principles, early treatment is preferred. See drug-drug interactions above.
- Nitazoxanide (NTZ) 600 mg BID for 7 days.[291] 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.
- Methylprednisolone 80 mg bolus followed by 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. [292-304] We believe that the use of low-fixed dose dexamethasone is inappropriate for the treatment of the pulmonary phase of COVID-19. 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). The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a significant reduction of the primary end point (composite of organ support days and hospital mortality) regardless of D-Dimer levels.[305]
- Vitamin C 500–1000 mg q 6 hourly and Quercetin 250–500 mg BID (if available)
- Zinc 75–100 mg/day (elemental zinc)
- Melatonin 10 mg at night . [35-41]
- Anti-androgen therapy (both men and women). Spironolactone 100 mg BID for 10 days. Second line anti-androgen: Dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. **AVOID IN PREGNANCY**. [219,223,224]
- Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40mg daily is an alternative.

4.2 Second Line and optional treatments

- Vitamin D. The optimal dose and vitamin D formulation for the treatment of acute disease is highly controversial. Vitamin D3 takes many days to be converted to 25-OH vitamin D; [306] this may explain the lack of benefit of vitamin D3 in patients hospitalized with severe COVID-19.[105] Vitamin D stores are best repleted in the weeks to months before patients contract

COVID-19. Nevertheless, for patients hospitalized with COVID-19 the dosing scheme as listed in table 3 is suggested.

- ASA 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. [206,207,307,308]
- B complex vitamins
- Atorvastatin 40-80 mg/day (reduce dose to 40 mg if taken with ivermectin due to possible drug-drug interaction). Statins have pleiotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. Statins reprogram macrophages/monocytes from a M1 phenotype to a M2 phenotype. [309,310] As discussed later, this is critical in the management of COVID-19. In addition, statins decrease expression of PAI-1. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [311] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19. [312-316] Due to numerous drug-drug interactions (including ivermectin) simvastatin should be avoided.
- *Optional:* Maraviroc 300 mg BID for 10 days (see above and section on Long-Covid).
- *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [44-50] Famotidine may be useful for its protective effect on gastric mucosa, its anti-viral properties and histamine blocking properties.
- *Optional:* JAK inhibitors ruxolitinib or baricitinib. JAK inhibitors target JAK1, JAK2, JAK3, and whose inhibition downregulates the JAK/STAT signaling pathway decreasing cytokine concentrations. [317] These drugs have been shown to decrease the use of mechanical ventilation and the risk of death. [318,319] In these studies low doses of corticosteroids were used. The role of JAK inhibitors with appropriate corticosteroid dosing is unclear
- *Optional:* The anti-serotonin agent, cyproheptadine 4–8 mg PO q 6 hour should be considered in patients with more severe disease. [320,321] 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. [320,322-324] 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. [325-328] Furthermore, serotonin itself enhances platelet aggregation creating a propagating immuno-thrombotic cycle.[329] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [330]
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. [331] Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed
- *Not recommended:* Remdesivir. The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup. [332] The VA study showed no mortality benefit with Remdesivir and a longer length of hospital stay. [333] Most recently, the DisCoVeRy trial reported no outcome benefit from remdesivir. [334] A meta-analysis of the six published RCTS demonstrate no mortality reduction with Remdesivir; interestingly enough, the independent studies demonstrate a trend to harm while the two studies conducted by Gilead demonstrate a mortality benefit. (See figure 9).
- Not recommended: 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. [282]

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. Ivermectin real-time meta-analysis of 71 studies (from ivmeta.com).

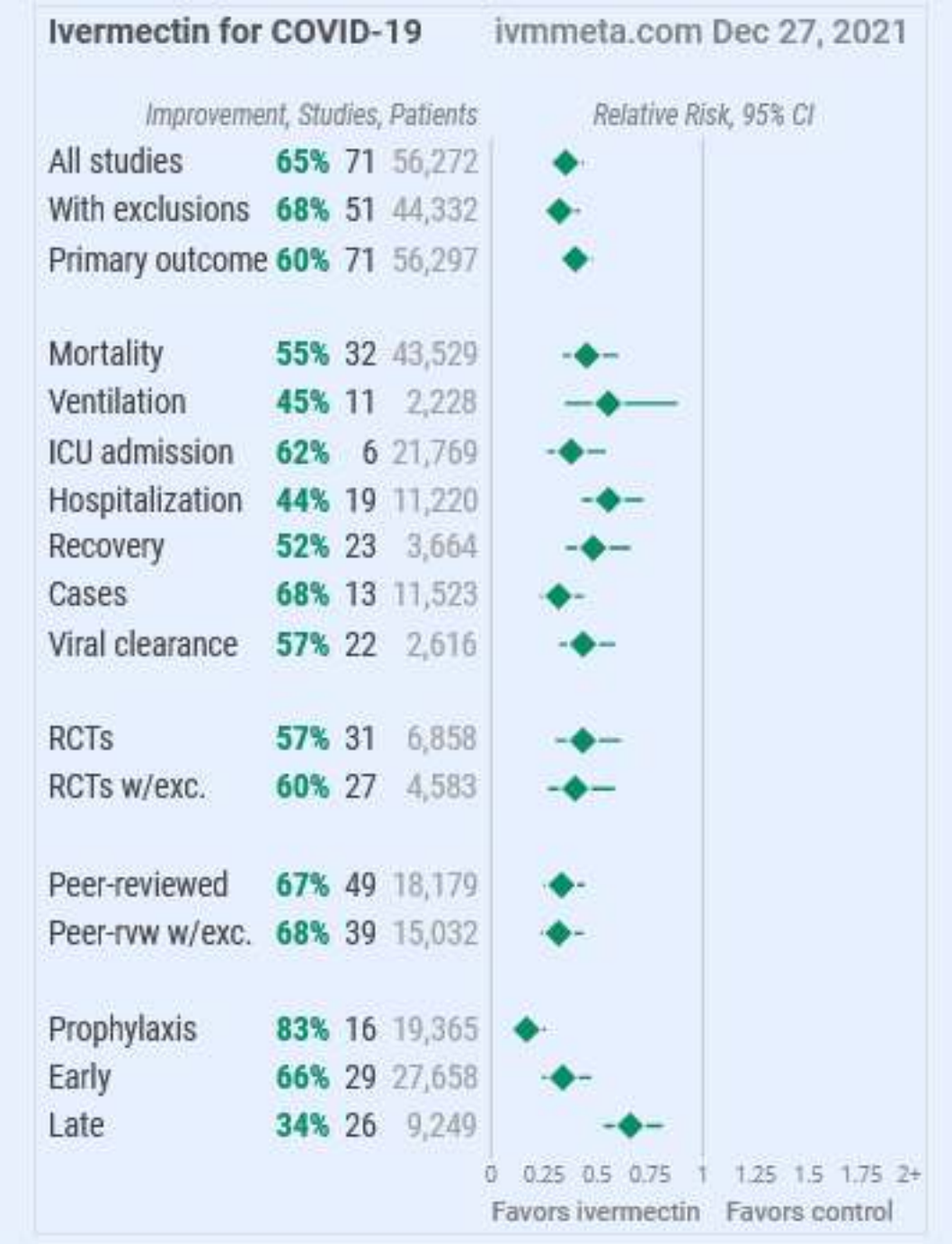
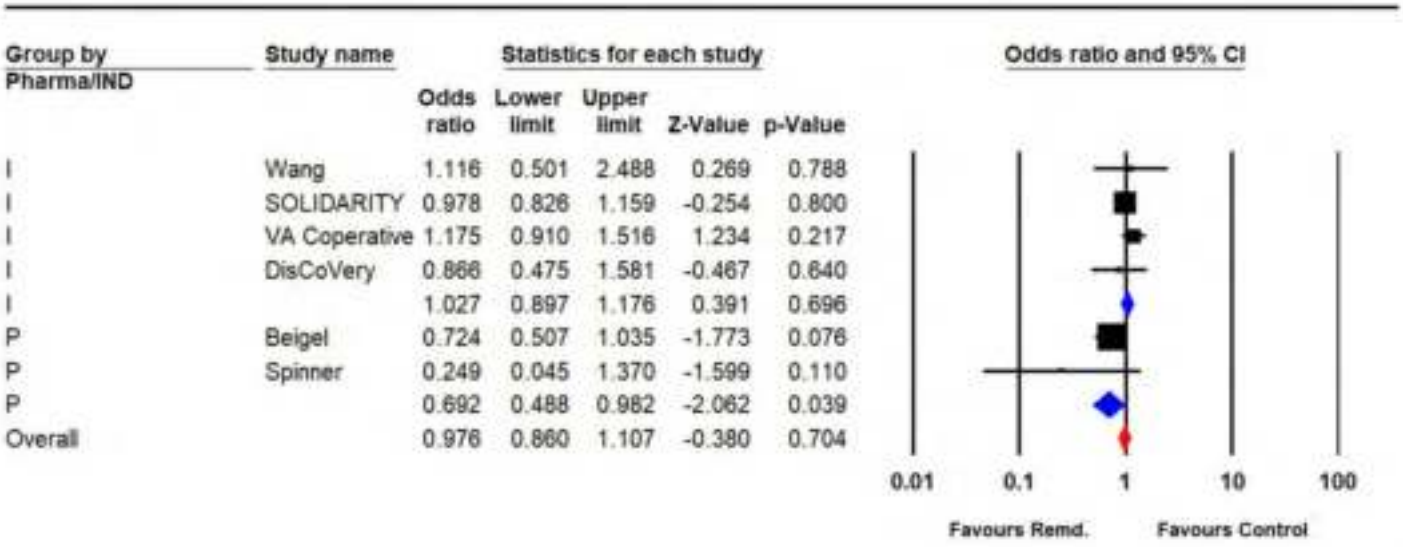


Figure 9. Meta-analysis of the Remdesivir RCTs grouped by independent studies (I) and those done by Gilead™ (P)



5. MATH+ PROTOCOL (for patients admitted to the ICU) [335,336]

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. [292-304] Pulse methylprednisolone 500-1000 mg/day for 3 days (followed by taper) may be required. [302] 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. [337,338] These clinical findings are supported by a genomic study.[204] 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. [116,125,126,339-349]. *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 [350] (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. [351] 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.[350] Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport proteins 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%).[305] 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.[352] 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.[125,126] 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). [353-355] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [356]

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 – 0.8 mg/kg day orally for 5 days or until recovered [23,77-79,162,165-172,287-289,357-363]. A higher dose (up to 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.[291] 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.[36-38]
7. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [364-369] Thiamine may play a role in dampening the cytokine storm. [365,370]
8. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe pro-thrombotic state and increasing the inflammatory response.[206,207,307,308] 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).[221] [371] **AVOID IN PREGNANCY**. [219,224] Bicalutamide 150 mg daily is also an option.
11. Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40 mg daily is an alternative.

5.3 Second line treatments

12. B complex vitamins.
13. Vitamin D3. Dosing as suggested in Table 3.
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. [158] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [372-374]

5.4 Optional Treatments and those of uncertain benefit

17. *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [44-50].
18. *Optional:* JAK inhibitors ruxolitinib or baricitinib.
19. *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). [275,375,376]*
20. *Unclear benefit.* Maraviroc 300 mg BID for 10 days. Maraviroc is a CCR5 antagonist. [263] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19.[260,377] Blocking the CCR5 receptor (CCR5R) repolarizes macrophages/monocytes and decreases the production of proinflammatory cytokines (see section on repolarizing macrophages/monocytes and section on Long-Covid).
21. *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.[284,378,379] 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.
22. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
23. *Not recommended.* Convalescent serum [380-385] nor monoclonal antibodies. [386] However, convalescent serum/ monoclonal antibodies may have a role in patients with hematologic malignancies.[387]
24. *Not recommended.* Colchicine (see above).
25. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [388-392] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [393] Tocilizumab may have of benefit in patients receiving an inadequate dose of corticosteroids.[394] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.
26. 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. [395-397] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [398] 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.
27. 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.
28. 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.
29. 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 [399]
d. Trial of inhaled Flolan (epoprostenol)
e. Attempt proning (cooperative repositioning-proning) [400-403]
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.[404,405] HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. HFNC is preferred over conventional oxygen therapy. [399] Intermittent CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

Figure 10. “Typical” progression of Chest CT findings.

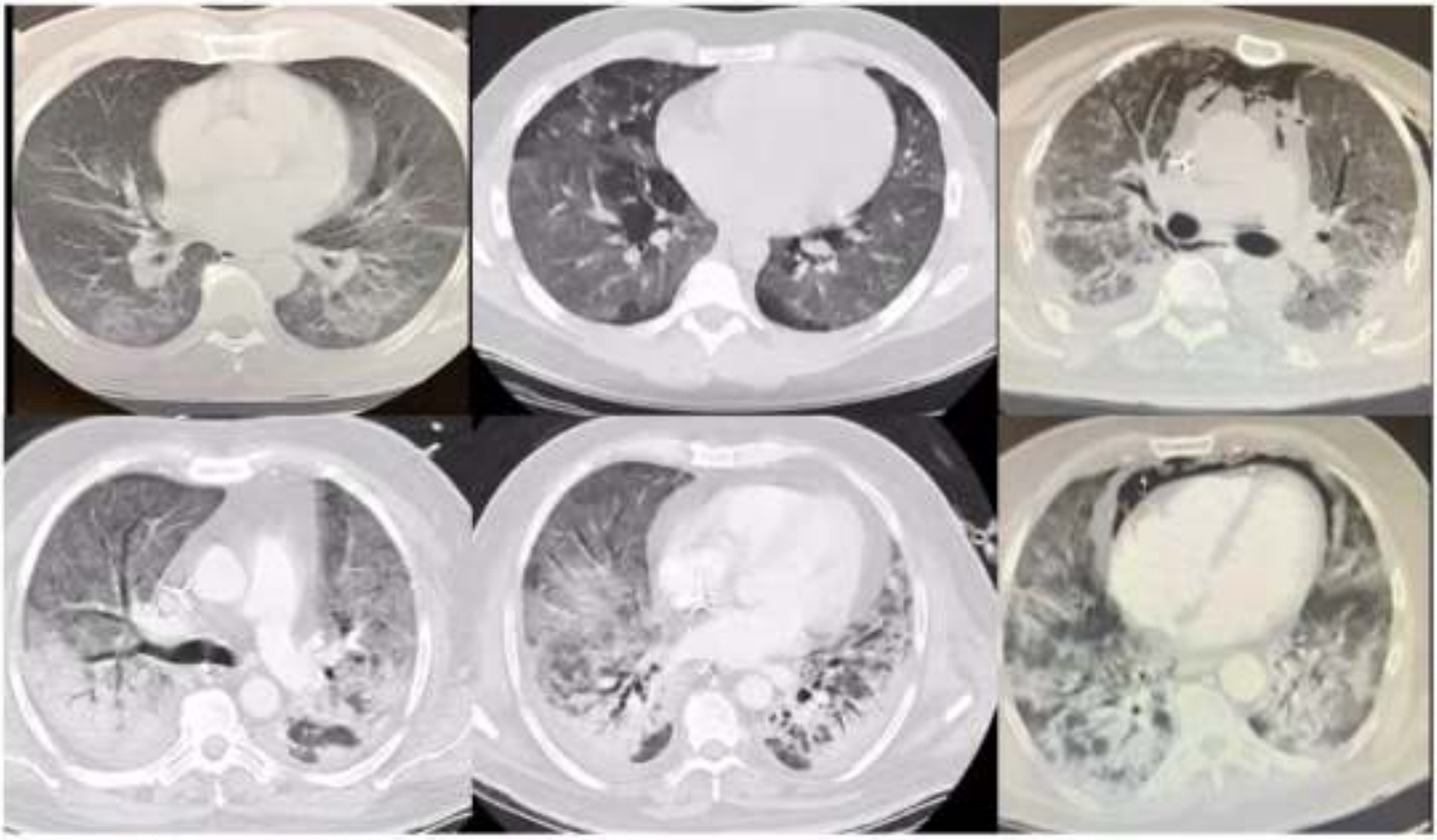


Table 5: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone - Number Need to Treat (NNT)

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. [406] 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. [407] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively (see Figure 10). [406,408-414] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19.[415,416] 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. [406] 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. [300,302]
- Plasma exchange [417-423]. 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.[350,351] (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.[424,425]
- 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". [426-429]
- ECMO [430-432]. 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. [433]
- Lung transplantation. [434]

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. [380-382,384,385] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[435] 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.[436] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [437]
- In patients hospitalized with severe COVID-19, Canakinumab, an anti‑interleukin-1 β antibody failed to improve any outcome measure. [438]
- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [439-442] 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 [443,444] 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). [7,407,445,446]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multisystem organ failure.[447]
- "*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.
- 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. Approach to the Omicron Variant

Omicron, the SARS-CoV-2 variant responsible for a cluster of cases in South Africa and that is now spreading around the world, is the most heavily mutated variant to emerge so far and carries mutations similar to changes seen in previous variants of concern associated with enhanced transmissibility and partial resistance to vaccine induced immunity. [448,449] In South Africa, Omicron has completely displaced the Delta variant, with Omicron being the major variant. [449,450] In total, the variant's genome has around 50 mutations, including more than 30 in the spike protein. One of the omicron variant's mutations leads to "S gene target failure" (or "S gene dropout"), meaning that one of several areas of the gene that are targeted by PCR testing gives a false negative. Omicron is highly infectious, spreading rapidly among communities with neutralizing antibodies against SARS-CoV-2 acquired by natural infection or vaccination appearing to have limited protection. [448,451,452] In a case series of 785 cases from Denmark, 76% of patients were fully vaccinated. [453] Despite the apparent lack of efficacy of vaccination and monoclonal antibodies, antivirals directed at SARS-CoV-2 remain effective. [454] A high infectivity rate has been reported in large group gatherings. [453] While Omicron is highly infectious, it appears to cause much milder disease. Anosmia and ageusia are uncommon, which may distinguish Omicron from previous variants. Furthermore, Omicron appears less likely to cause pulmonary disease; this may be related to altered ACE-2 binding to pulmonary alveolar cells. [455] Nevertheless, the elderly and those with significant comorbidities may suffer severe disease.

At this time the prevention and early treatment for Omicron should not differ from that of the previous variants, i.e., the I-MASK+ protocol should be followed. Early treatment is critical to limit spread of the virus, and as this variant is highly infectious prophylaxis of close contacts is important. Those infected

with omicron should be quarantined for up to 5 days. The optimal dose of ivermectin for early treatment is unclear, however, it is likely that a lower dose may suffice i.e. 0.3- 0.4 mg/kg. It is likely that the early treatment of Omicron may limit the progression to Long Covid.

13. Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[456] A PCT is essential to rule out coexisting bacterial pneumonia.[457]
- 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.[415,458] 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. [459]
- 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. [460,461]
- ECHO as clinically indicated; Patients may develop a severe "septic" cardiomyopathy and/or COVID-19 myocarditis. [462,463]

14. 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
- Atorvastatin 40mg daily

15. Post Hospital Discharge management

a. Patients have an increased risk of thromboembolic events post-discharge. [464,465] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include: [466]
    i. Increased D dimer (> 3 times ULN)
    ii. Increased CRP (> 2 times ULN) [467]
    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 a statin. These agents may reduce this risk of developing the post-COVID syndrome.
d. Nigella sativa and Kefir.
e. Patients should be followed/monitored for developing the post-COVID/long hauler syndrome.

16. Pathophysiology of COVID-19

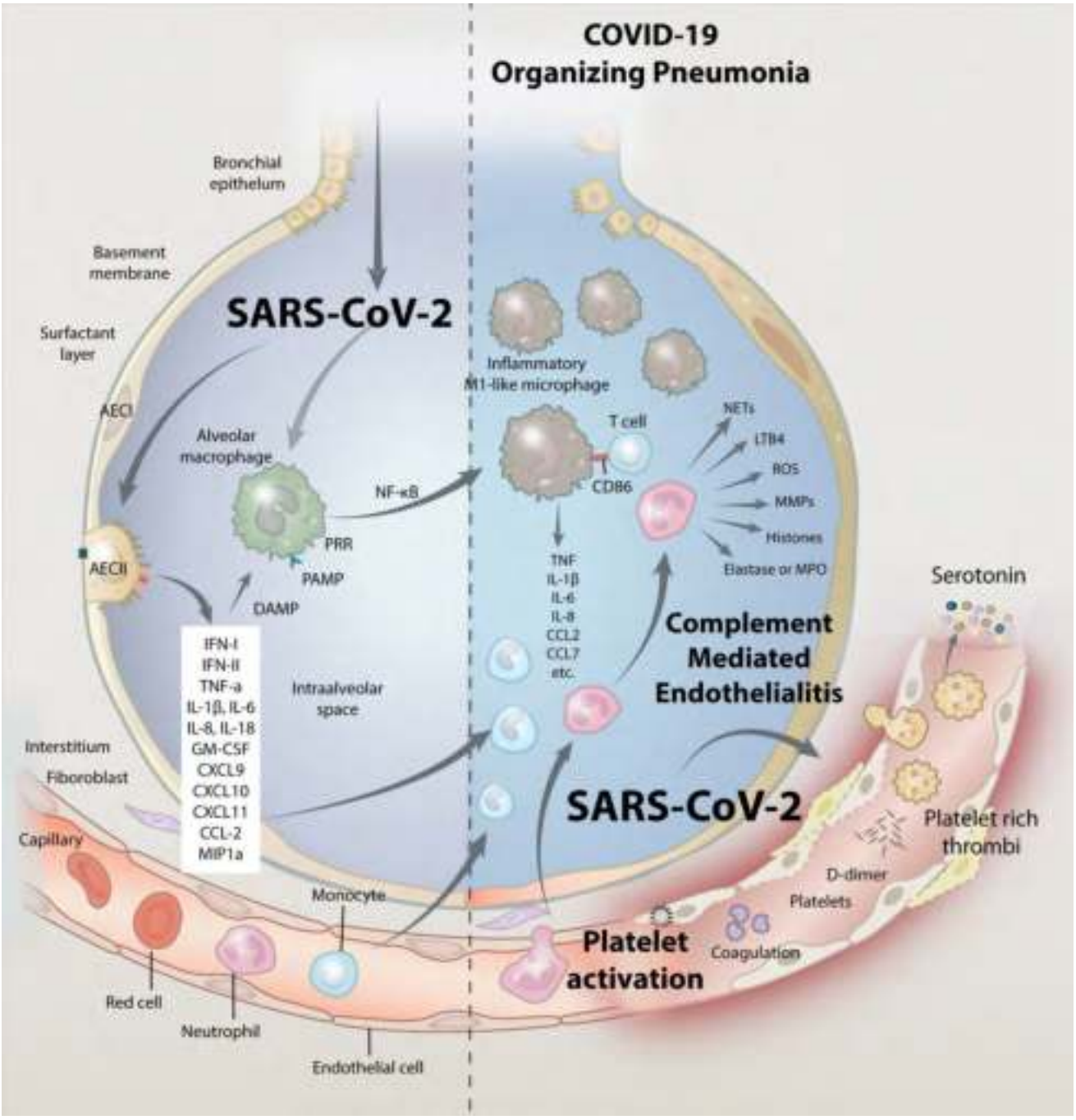
Basic Concept: Need to Understand the Disease to Treat the Disease

The pathophysiology of COVID-19

- Pulmonary Macrophage Activation Syndrome
  - Severe hyperinflammatory status
- Microvascular endothelialitis and thrombosis
  - Activation of clotting esp. platelet thrombi in lung and brain
  - High circulating serotonin
    - Arterial vasoconstriction
    - V/Q mismatch
  - Organ ischemia
- Multiple autoantibodies
- Mast cell activation – histamine release
- ACE-2 deficiency
  - Excess angiotensin II/ angiotensin 1-7
- T cell dysfunction

Based on clinical, proteomic, and genomic studies as well as autopsy data ,severe COVID-19 disease can be considered to be the connection of three basic pathologic processes, namely a pulmonary macrophage activation syndrome with excess production of cytokines and chemokines and uncontrolled inflammation, a complement mediated endothelialitis together with a procoagulant state with a thrombotic microangiopathy (see figure 11). In addition, platelet activation with the release of serotonin and the activation and degranulation of mast cells contributes to the hyper-inflammatory state. Autoantibodies have been demonstrated in a large number of hospitalized patients which adds to the end-organ damage and prothrombotic state. However, activated M1 macrophages appear to be the major driver of severe COVID-19 infection. Similarly, recent data suggests that the Long Haul Covid Syndrome (LHCS) results due to increased circulating levels of activated monocytes with ongoing cytokine production. [377] Interestingly, these monocytes contain high levels of the spike protein. [468] Both activated macrophages and activated monocytes express the same surface activation markers (CD14+, CD16+). This suggests that treatment aimed at repolarizing the macrophage/monocyte should have an important adjunctive role in the treatment of both acute COVID and the LHCS. Those interventions that have been demonstrated to repolarize macrophages/monocytes (from M1 to M2 phenotype) are listed below.

Figure 11. Pathogenetic mechanism of severe COVID-19 disease



17. The Long Haul COVID syndrome (post-COVID syndrome)

The Long Haul COVID Syndrome (LHCS) is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain and cognitive dysfunction.[474-485] Up to 80% of patients experience prolonged illness after Covid-19. LHCS is not only seen after the COVID infection but it is being observed in some people that have received vaccines (likely due to monocyte activation by the spike protein from the vaccine). LHCS 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.[483,486] A puzzling feature of the LHCS syndrome is that it is not predicted by initial disease severity; post-COVID-19 frequently affects mild-to-moderate cases and younger adults that did not require respiratory support or intensive care. [485] The symptom set of LHCS is in majority of the cases very similar to the chronic inflammatory response syndrome (CIRS)/ myalgic encephalomyelitis/chronic fatigue syndrome.[485] An important differentiating factor from CIRS is the observation that LHCS continues to improve on its own albeit slowly in majority of the cases. Another important observation is that LHCS includes more young people compared to severe COVID that affects older people or persons with comorbidities. Furthermore, the similarity between the mast cell activation syndrome and LHCS has been observed, and many consider post-COVID to be a variant of the mast cell activation syndrome.[487]

The LHCS syndrome is highly heterogeneous and likely results from a variety of pathogenetic mechanisms Furthermore, it is likely that delayed treatment (with ivermectin) in the early symptomatic phase will results in a high viral load which increase the risk and severity of LHCS. The following theories have been postulated to explain LHCS: [485]

1. Ongoing respiratory symptoms (SOB, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activate pulmonary macrophages).
2. Monocyte activation syndrome. Persistence of viral debris in monocytes results in an ongoing immune response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments.
3. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[488] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [489] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [490] as well as severe cerebral vasoconstriction. [491] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirions" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[492].
4. An unmasking of mast cell activation syndrome (MCAS), or triggering of mast cell activation syndrome. 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 corticotropin releasing hormone.[493] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation.[493] The "brain-fog", cognitive impairment and general fatigue reported in long-COVID may be due to mast cell related neurovascular inflammation.

Clinical signs and symptoms can be grouped in the following clusters. The reason for this grouping is to allow organ specific targeted therapy/individualized therapy.

1. Respiratory: shortness of breath, congestion, persistent cough, etc.
2. Neurological/psychiatric: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus/concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.

3. Musculoskeletal: myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life (ADL's).
4. Cardiovascular: Palpitations, arrhythmias, Raynaud like syndrome, hypotension, and tachycardia on exertion.
5. Autonomic: Postural tachycardia syndrome (POTs), abnormal sweating.
6. Gastrointestinal disturbance: Anorexia, diarrhea, bloating, vomiting, nausea, etc.
7. Dermatologic: Itching, rashes, dermatographia
8. Mucus membranes: Running nose, sneezing, Burning and itchy eyes.

17.1 Approach to Treatment:

The treatment approach should be individualized according to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g**.** ivermectin) during the acute symptomatic phase and adequate anti-inflammatory/macrophage repolarization therapy (e.g. corticosteroids, statins, omega-3 fatty acids, fluvoxamine, ivermectin, etc.) during the acute phase of COVID-19 are much more likely to develop the Post-COVID-19 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. A CRP should be measured, and extended corticosteroids (titrated to the CRP) offered to these patients. Similar to patients who have recovered from septic shock, [494] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the LHCS. This is likely the consequence of monocyte activation syndrome and monocyte repolarization therapy is therefore indicated. In addition, a cytokine panel may allow targeted anti-inflammatory therapy (Maraviroc in patients with high CCR5 levels). It should be noted that much like omega-3 fatty acids, corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4. [495] 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.[480] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [439-442] 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. [330]

17.2 The I-RECOVER Protocol for the treatment of the "Long-haul COVID Syndrome".

Although numerous reports describe the epidemiology and clinical features of LHCS, [474-484] studies evaluating treatment options are glaringly sparse. [312] Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations. [496] In general, while the treatment of 'Long COVID" should be individualized, the following treatments may have a role in the treatment of this disorder. In addition, the I-RECOVER protocol may have a role in the treatment of post-vaccination syndrome. Patients with Long Covid should be managed by clinicians who have experience treating this troublesome disorder.

- Ivermectin has been reported to have a role in the treatment of post-COVID-19 syndrome. [312] A dose of 0.2-0.4 mg/kg day for 3-5 days, followed by once or twice weekly dosing for ongoing symptoms for up to 4 weeks. A repeat course is recommended in those who respond poorly or relapse once the treatment is stopped. The anti-inflammatory properties of ivermectin may mediate this benefit.
- Prednisone if inadequate response to ivermectin. Prednisone 0.5mg/kg daily for 5 days, 0.25mg/kg for 5 days followed by 0.12 mg/kg for 5 days. Patients with persistent organizing pneumonia may require higher doses for a more prolonged period of time.
- Vitamin C 500 mg BID (vitamin C inhibits histamine and repolarizes monocytes).[125]
- 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 resolvin production. [256,257]
- Melatonin 2- 10 mg at night (slow release/extended release) with attention to sleep hygiene. Increase dose from 2mg as tolerated (may cause severe nightmares at high dosages)
- Curcumin has anti-inflammatory and immunomodulating properties and has been demonstrated to repolarize macrophages. [59]
- Maraviroc (a CCR5 receptor antagonist). C-C chemokine receptor type 5 (CCR5) is a cell surface G protein-coupled receptor expressed on macrophages and dendritic cells. CCR5 interacts with multiple ligands, notably the chemokines CCL3 (macrophage inflammatory protein-1), CCL4 (macrophage inflammatory protein-1), and CCL5 (RANTES). CCR5 and its ligands are overexpressed in COVID-19. [262,263,497] The activated CCR5 pathway may partly explain the persistence of activated monocytes in long-COVID. [377,468] Maraviroc has been extensively used in HIV infected patients, as CCR5 is a co-receptor for HIV. This drug has proven to have a remarkable safety record. [264,498] The approved dose of maraviroc for adults is 300 mg twice daily (BID) in the absence of potent CYP3A inducers or inhibitors. Evolving clinical experience suggests that maraviroc may be particularly effective in the treatment of long-COVID (no published data to date).
- Kefir, probiotic yogurt and/or Bifidobacterium Probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome. Prolonged dysbiosis has been reported following COVID-19 infection. [499]
- *Nigella sativa* which like curcumin has anti-inflammatory and immunomodulating properties.
- Atorvastatin 40 mg daily (increase resolvin synthesis and repolarizes macrophages) [408]
- Functional rehabilitation with light aerobic exercise paced according to individual capacity. [485]
- Behavioral modification, mindfulness therapy [500] and psychological support may help improve survivors' overall well-being and mental health. [485]
- *Optional:* Luteolin 100-200 mg day or quercetin 250 mg day (or mixed flavonoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells,[493,501-504] and have been demonstrated to reduce neuroinflammation. [505]
- *Optional:* Famotidine 20-40 mg day (histamine-2 blocker for Mast Cell Activation syndrome). [487]
- *Optional:* Fluvoxamine, especially in those with neurocognitive issues. Start at 25 mg daily, Increase slowly to 50 -100 mg per day. Monitor response closely as some patients will respond poorly to this medication. 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:* Antiandrogen therapy which results in macrophage repolarization. [471-473] Spironolactone 50-100 mg BID and dutasteride 1mg daily.
- *Optional:* H1 receptor blockers (for mast cell activation syndrome). Loratadine 10mg daily, Cetirizine 5-10mg daily, Fexofenadine 180mg daily.
- *Optional:* H2 receptor blockers (for mast cell activation syndrome). Famotidine 20 mg, or Nizatidine 150 mg – twice daily as tolerated.
- *Optional:* Montelukast 10 mg/day (for mast cell activation syndrome). Caution as may cause depression is some patients.

Macrophage/monocyte Repolarization Therapy for COVID-19 and Long Haul COVID Syndrome

- Corticosteroids [469]
- Statins [309,310]
- Omega-3 fatty acids [251-253]
- Melatonin [470]
- Vitamin C
- Anti-androgen therapy [471-473]
- Curcumin (turmeric) [59]

I-RECOVER

Management Protocol for Long-haul COVID Syndrome (LHCS)

The approach outlined below is a simplified, consensus protocol based on a collaboration led by Dr. Mobeen Syed ("Dr. Been"), Dr. Ram Yogendra, Dr. Bruce Patterson, Dr. Tina Peers, and the FLCCC Alliance. Given the lack of clinical treatment trials of Long-haul Covid Syndrome, these recommendations are based on the pathophysiologic mechanisms of COVID and post-viral illnesses along with our collective experience observing profound and sustained clinical responses achieved with the treatment approaches below.

This protocol has also been used to treat post-vaccine inflammatory syndromes with similar success. As with all FLCCC Alliance protocols, the components, doses, and durations will evolve as more clinical data accumulates. Several members of this collaboration employ various adjunctive therapies they have found beneficial. Info on these approaches can be found on page 3.

Initial therapy of Long-haul Covid Syndrome:

IVERMECTIN

0.2–0.4 mg/kg dose once daily with meals* for 3–5 days (higher doses are sometimes needed in anosmia).

* Take on empty stomach if presenting with nausea/diarrhea/anorexia.

After 3–5 days, change to once or twice weekly depending on the time to symptom recurrence/persistence.

Discontinue after 2–4 weeks if all symptoms have resolved and do not recur.

Relative Contraindications:
- Patients on Warfarin require close monitoring and dose adjustment.
- Pregnant or lactating women require a more in-depth risk/benefit assessment.

If not all symptoms resolve with ivermectin:

CORTICOSTEROID THERAPY

A tapering dose of **prednisone** as follows:

1. 0.5 mg/kg daily for 5 days
2. 0.25 mg/kg daily for 5 days
3. 0.12 mg/kg daily for 5 days

Take in morning to lessen impact on sleep.

Side effects may include: Increased appetite, mood changes, insomnia, raised blood glucose, dyspepsia.

Recommended to support the LHCS therapy:

SUPPLEMENTS

- Vitamin C: 500 mg twice daily.
- Vitamin D3: 2,000–4,000 IU daily.
- Melatonin: 2–10 mg nightly – start with low dose, increase as tolerated in absence of sleep disturbance.

If presenting with neurologic symptoms, i.e. poor concentration, forgetfulness, mood distrubance:

FLUVOXAMINE

50 mg – twice daily for 15 days.

Reduce dose or discontinue if side effects develop. Doses as low as 9 mg twice daily have shown efficacy.

If symptoms still unresolved or recur after ivermectin and corticosteroid regimens:

TREATMENT OF SUSPECTED MAST CELL ACTIVATION

Choose a Type I and Type II antihistamine along with a mast cell stabilizer – for example, Loratidine, Famotidine, and Rupatadine. Change medicines if poor response. US FDA approved doses of many of the below medicines are daily, but can increase to three times daily with caution and close monitoring if poor response.

First-line Therapy
- Low histamine diet

Type I antihistamines:
- Use up to TDS: Loratadine 10 mg, or Cetirizine 10 mg, or Fexofenadine 180 mg

Type II antihistamines:
- twice daily: Famotidine 20 mg, or Nizatidine 150 mg

Mast cells stabilizers:
- Rupatadine 10 mg, or Ketotifen 1 mg, plus or minus
- Sodium Cromoglycate 200 mg TDS (increase slowly) or Quercetin 500 mg TDS

Second-line Therapy
- Montelukast 10 mg (beware depression in some)
- Low Dose Naltrexone (LDN; avoid if taking opiates), start with 0.5 mg daily increasing by 0.5 mg weekly up to 4.5 mg daily
- Diazepam 0.5-1 mg twice daily
- SSRIs

IF PRESENTING WITH SHORTNESS OF BREATH OR LOW OXYGEN LEVELS:

PULMONARY EVALUATION

Refer to lung specialist if available, otherwise perform chest imaging (CT preferred) to assess for secondary organizing Pneumonia (OP).

If findings consistent with secondary OP found, initiate Corticosteroid Therapy as below. May need to repeat or prolong course of treatment if symptoms or oxygen needs persist.

BID	twice daily	mg/kg	dose in mg per kg body weight
CT	computed tomography scan	OP	organizing pneumonia
GIT	gastrointestinal tract	RDA	recommended dietary allowances
IU	international units	TDS	3 times daily

Please regard our disclaimer on page 3.

For more information on the treatment protocols of the FLCCC Alliance please see: flccc.net

18. 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. It is important to focus on the totality of the evidence and not just on RCTs (see figure 11). We are in the midst of a global pandemic and the use of cheap, effective, and safe repurposed drugs has and will continue to have a major role in the prevention and treatment of this disease.
2. 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).
3. 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.
4. 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).
5. 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). [506] COVID-19 is essentially a clinical diagnosis supported by laboratory tests.
6. 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). [507]
7. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, SARS-CoV-2 variant, genetic heterogeneity mutations and polymorphisms, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[295,508-518] 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. [519]
8. The pulmonary phase is characterized by immune dysregulation, [488,511,520-533] a pulmonary microvascular injury (vasculopathy), [488,533-536] with activation of clotting and a procoagulant state together with the characteristics of an organizing pneumonia. [407,537]
9. 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. [488]
10. As patients, progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are two-fold.
    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.
11. 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.

12. The radiographic and pathological findings of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [407,538,539]
13. THIS is NOT ARDS (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS. [540-542] The ground glass infiltrates are peripheral and patchy, [538] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS". [543] 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 an organizing pneumonia with severe ventilation/perfusion mismatch likely due to the microvascular narrowing, thrombosis and vasoplegia.
14. 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.
15. Ivermectin has emerged as a highly effective drug for the prophylaxis and treatment of COVID-19. Ivermectin inhibits viral replication and has potent anti-inflammatory properties. Emerging clinical data (including RCTs) suggest that ivermectin may have an important clinical benefit across the spectrum of phases of the disease, i.e pre-exposure prophylaxis, post-exposure prophylaxis, during the symptomatic phase and during the pulmonary phase. [23,77-79,162,165-171,287-289,357-363,544] In the recommended dosages, ivermectin is remarkably safe and effective against SARS-CoV-2. However, as noted above, there is the potential for serious drug-drug interaction.
16. 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. [545]
17. 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.
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, [546,547] 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. [548] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[549,550] as well as viral replication [170,551]. Most importantly LWWH inhibits heparanase (HPSE).[552] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[552] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [553] 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. [341,346] Vitamin C protects the endothelium from oxidative injury. [125,554-556] Furthermore, vitamin C Increases the expression of interferon-alpha [115] while corticosteroids (alone) decrease expression of this important protein. [557-560] 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. [297,561] 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),[562] genomic data specific for SARS-CoV-2,[204] and a long track record of successful use in inflammatory lung diseases (see Table 2).
22. It should be noted that animal studies have demonstrated that ivermectin has immunostimulatory effects.[563,564] For this reason patients taking ivermectin do not need to stop taking ivermectin when vaccinated. Indeed, ivermectin may boost the immune response to the vaccine.

And finally: "If what you are doing ain't working, change what you are doing."

Figure 12. Evaluating the totality of evidence.

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