EVMS COVID-19 MANAGEMENT PROTOCOL

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

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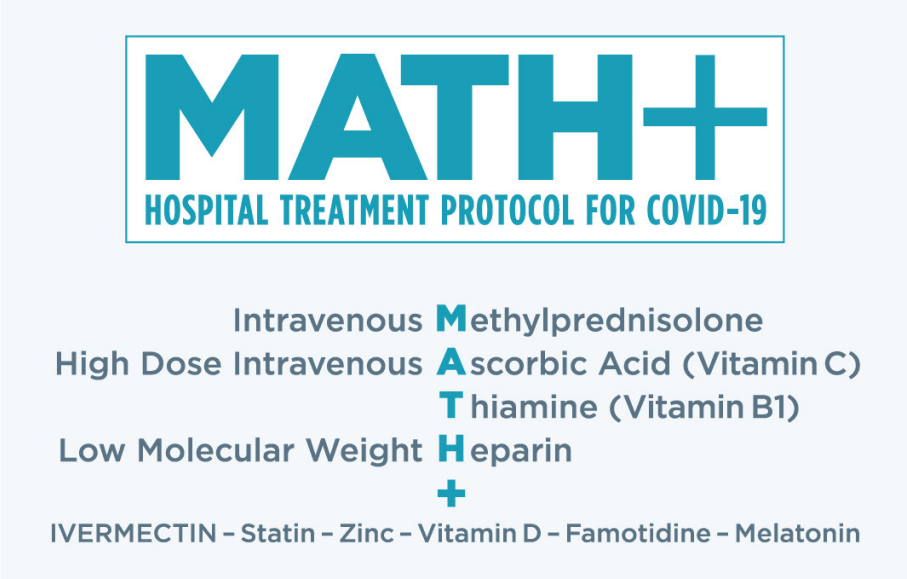
This is our recommended approach to COVID-19 based on the best (and most recent) literature. This is a highly dynamic topic; therefore, we will be updating the guideline as new information emerges.

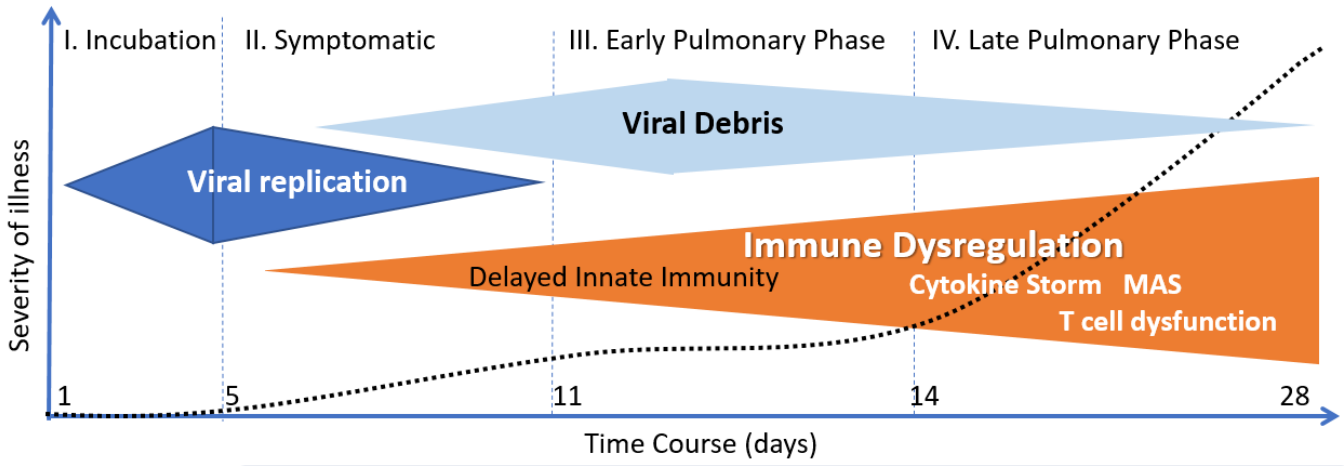
PLEASE NOTE: Updates will no longer be posted on the EVMS Website. Please check on the FLCCC Alliance website for updated versions of this protocol. www.flccc.net



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

Please Note: The NIH has not approved the use of IVERMECTIN for the treatment or prophylaxis of COVID-19.

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



Ground-glass infiltrates	+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory Rx	
Potential therapies	? Interferon-α	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.	
	ASA	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12
	IVERMECTIN 0.2 mg/kg x 2-5 doses	IVERMECTIN 0.3 mg/kg for 5 doses	
	Flavanoid + Zinc + Vit C + Vit D	Flavanoid + Zinc + Vitamin D + IV Vitamin C (6 -50 g/day)	

THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL

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

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

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

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

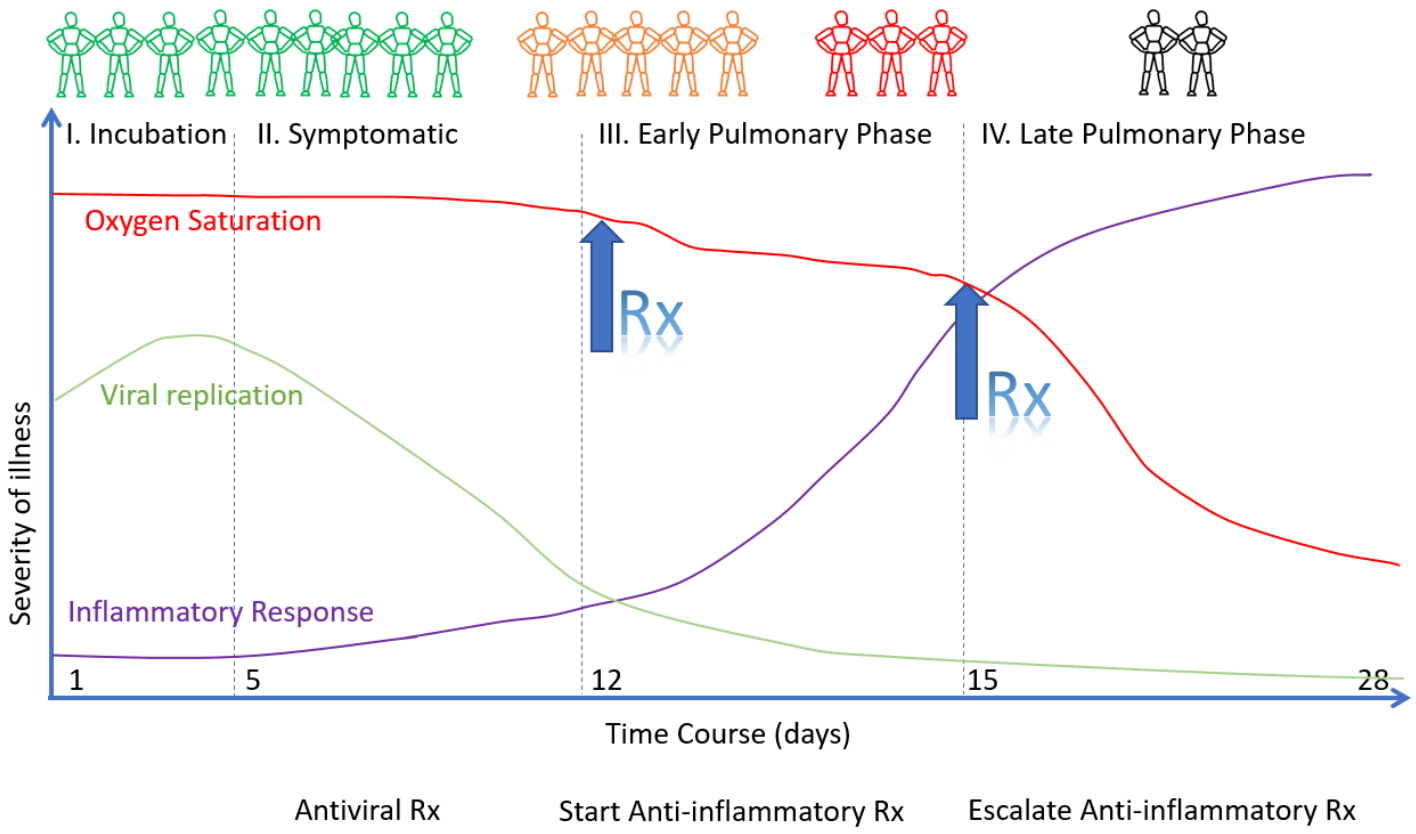


Figure 3. Time course of laboratory tests for COVID-19

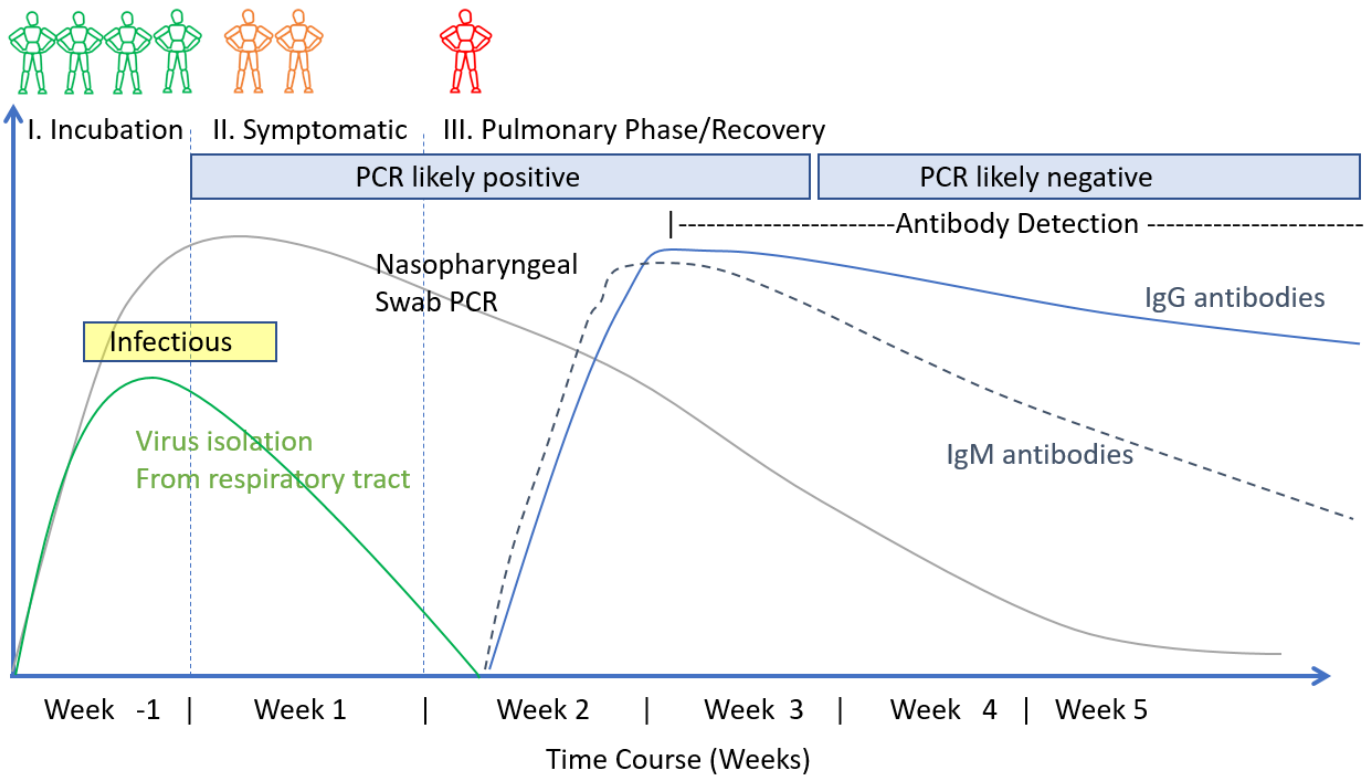
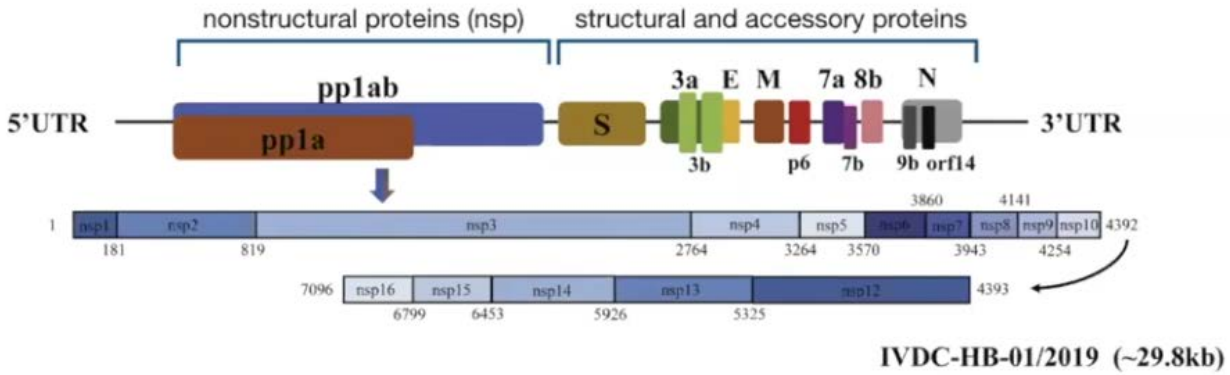


Figure 4. SARS-Co-V-2 RNA genome



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

As the pandemic has played out over the last nine months almost two million patients have died world-wide and the pandemic shows no signs of abating. Hospitals in the USA are now overwhelmed, and many have exceeded their ICU capacity. 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 late pulmonary phase of this disease with the goal of reducing the hospital mortality from COVID-19. However, it has now become blatantly clear that our emphasis needs to shift to the prevention and early treatment of this catastrophic disease to prevent patients progressing to the pulmonary phase and requiring hospitalization (see Figure 5). Hence, we developed the I-MASK+ protocol. While we strongly believe that such an approach can mitigate the development and progression of this disease, limit deaths, and allow the economy to re-open, “Health-Care authorities” across the globe have been silent in this regard, including the WHO, CDC, NIH, etc (see NIH Guidance, Figure 6a and 6b). While vaccination is part of the solution, it will take many months if not years to vaccinate 70-85% of the world’s population of 7.8 billion people required for “herd immunity”. We believe that the I-MASK+ protocol provides a bridge to universal vaccination. Furthermore, mutant strains of SARS-CoV-2 have recently appeared, these stains have demonstrated increased transmissibility.[4,5] Many of these mutations involve the spike protein (against which almost all of the vaccines have targeted), raising the real possibility that the vaccines may become less effective against the mutating strains of SARS-CoV-2.[6]

Figure 5. Treatment Phases of COVID-19

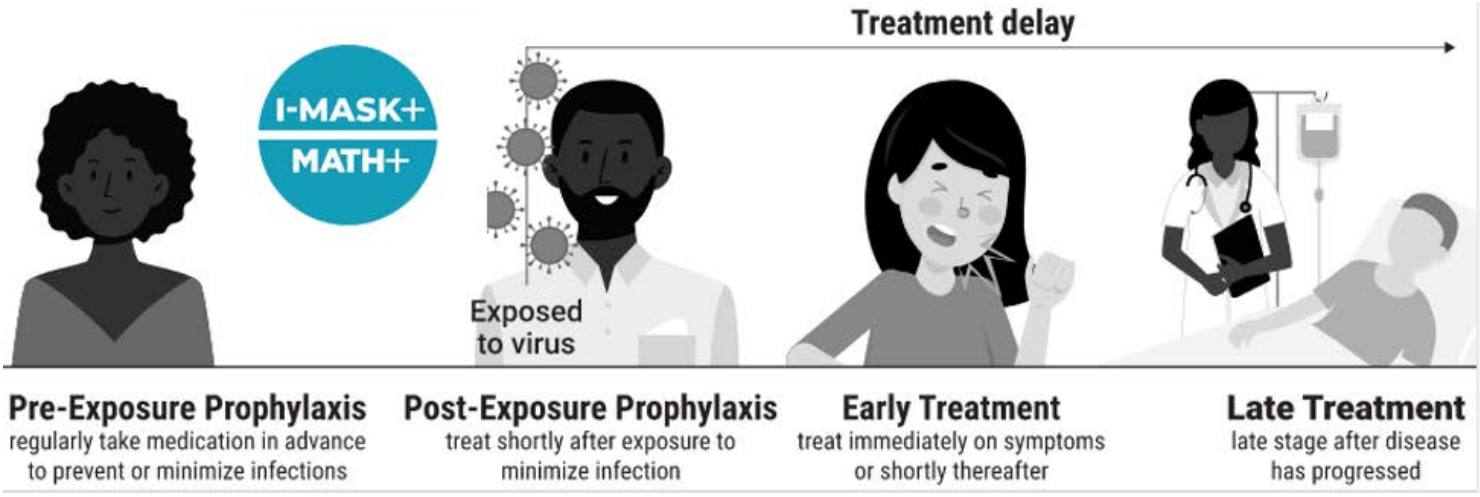


Figure 6a. NIH Recommendations for the Treatment of COVID-19 across the stages of the disease.

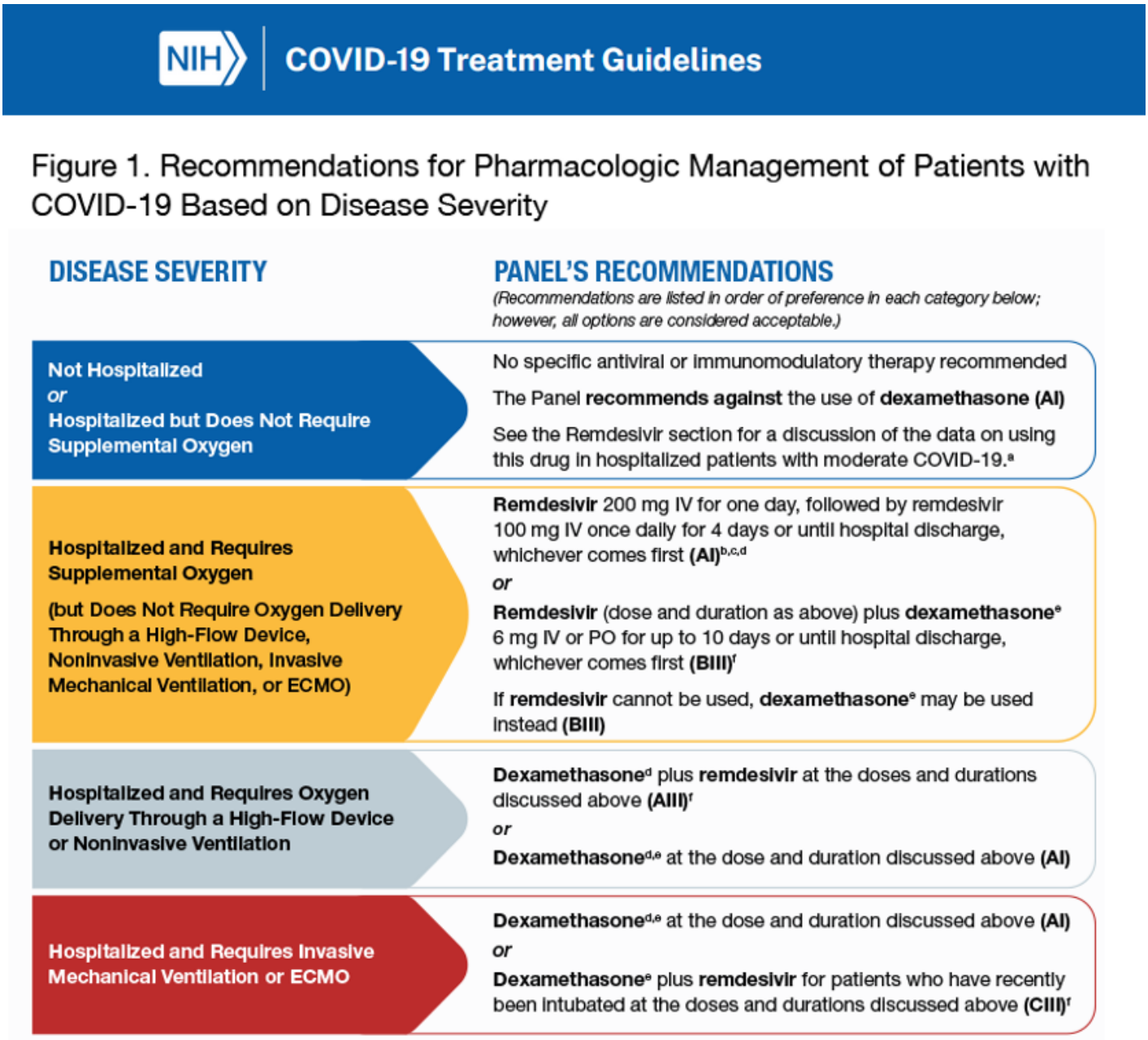
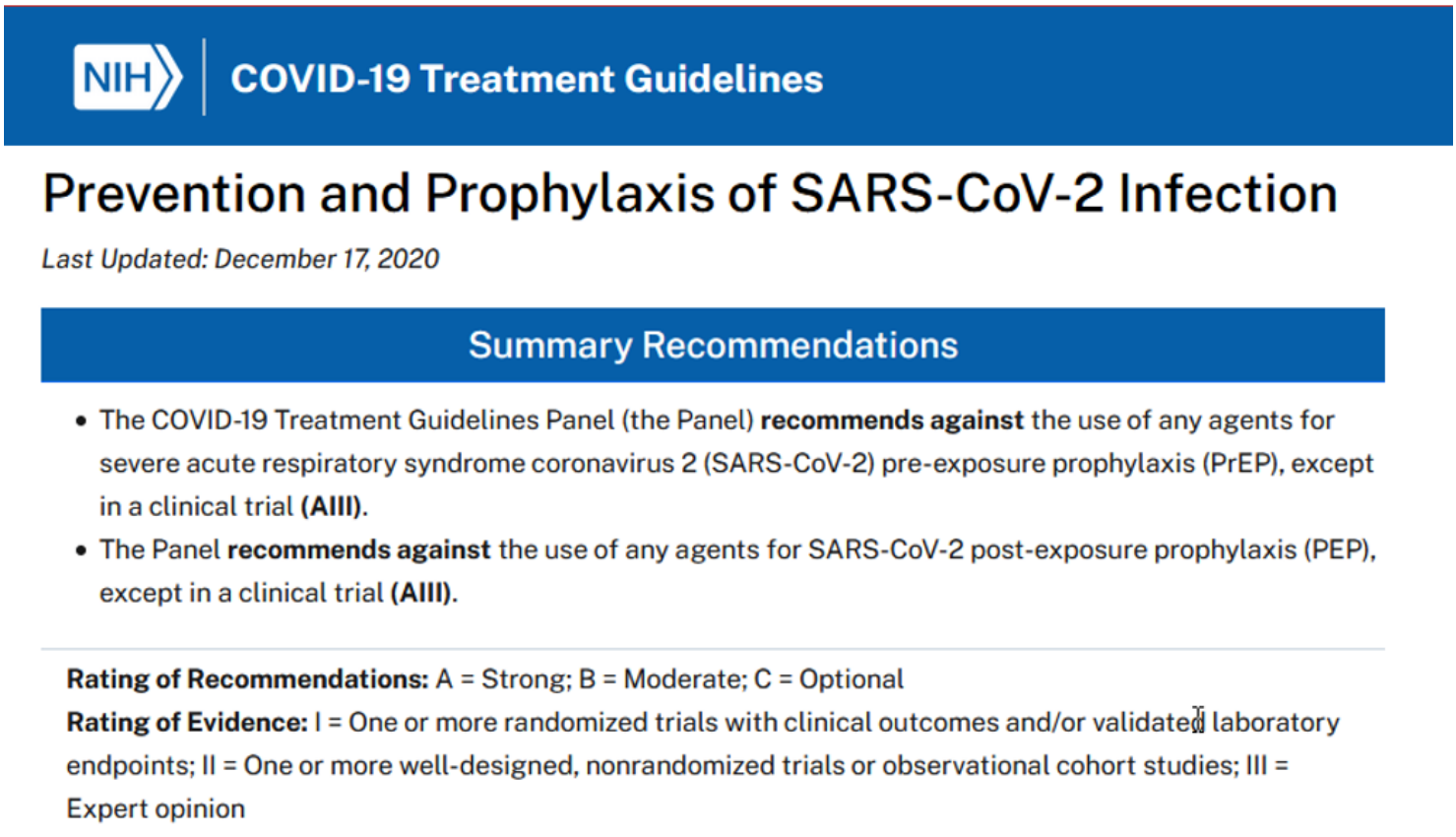


Figure 6b. NIH Recommendations for the prevention prophylaxis of COVID-19.



NIH | COVID-19 Treatment Guidelines

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Summary Recommendations

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

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

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

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

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

I-MASK+

PROPHYLAXIS & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

PROPHYLAXIS PROTOCOL

Ivermectin	***Prophylaxis for high risk individuals*** 0.2 mg/kg* – one dose on day 1, day 3, then continue with one dose every 2 weeks** ***Post COVID-19 exposure prophylaxis**** 0.2 mg/kg* – one dose on day 1 and day 3
Vitamin D3	1,000-3,000 IU/day
Vitamin C	1,000 mg twice a day
Quercetin	250 mg/day
Zinc	50 mg/day
Melatonin	6 mg before bedtime (causes drowsiness)

EARLY OUTPATIENT PROTOCOL****

Ivermectin	0.2 mg/kg* – one dose on day 1 and day 3
Vitamin D3	4,000 IU/day
Vitamin C	2,000 mg 2-3 times daily
Quercetin	250 mg twice a day
Zinc	100 mg/day
Melatonin	10 mg before bedtime (causes drowsiness)
Aspirin	325 mg/day (unless contraindicated)

Behavioral Prophylaxis

WEAR MASKS

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

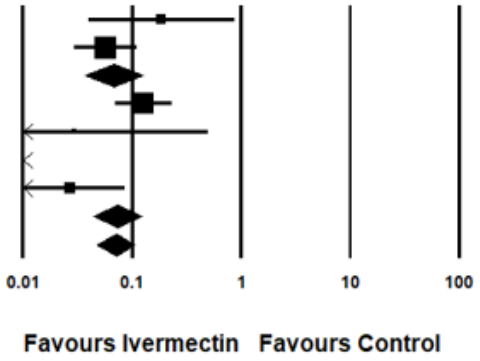
Must wear a N95 mask (without valve) during prolonged exposure to non-household persons in any confined, poorly ventilated area.

KEEP DISTANCE

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

Figure 8. Ivermectin for Pre-and postexposure prophylaxis.

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total: Group-Ivermectin	Symptomatic Infection / Total: Group-Control
Post-exposure	Elgazzar	0.184	0.039	0.861	-2.150	0.032	2 / 100	10 / 100
Post-exposure	Shouman	0.057	0.029	0.110	-8.542	0.000	15 / 203	59 / 101
Post-exposure		0.068	0.037	0.125	-8.701	0.000		
Pre-exposure	Behera	0.127	0.069	0.232	-6.704	0.000	15 / 91	171 / 281
Pre-exposure	Carvallo -1	0.029	0.002	0.497	-2.441	0.015	0 / 131	11 / 98
Pre-exposure	Carvalllo-2	0.000	0.000	0.007	-5.426	0.000	0 / 788	237 / 407
Pre-exposure	Alam	0.027	0.008	0.086	-6.077	0.000	4 / 58	44 / 60
Pre-exposure		0.073	0.044	0.123	-9.900	0.000		
Overall		0.071	0.048	0.105	-13.179	0.000		



Meta Analysis

Components of the I-MASK Prophylactic Protocol

- Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561). 0.2 mg/kg immediately then repeat day 3.
- Ivermectin for pre-exposure prophylaxis (in HCW) and for prophylaxis in high-risk individuals (> 60 years with co-morbidities, morbid obesity, long term care facilities, etc). 0.2 mg/kg Day 1, Day 3 and then bi-weekly. [9-13] (also see ClinTrials.gov NCT04425850). We believe that bi-weekly dosing is likely the most practical, cost effective and safest prophylactic regimen. See dosing Table below and Figures 8 and 9. NB. Ivermectin has a number of potentially serious drug-drug interactions; please check for potential drug interactions at Ivermectin Drug Interactions - Drugs.com. The most important drug-drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs, and certain anti-fungal drugs. While ivermectin has a remarkable safety record, [14] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [15,16]
- Vitamin D3 1000–3000 IU/day. An alternative strategy is 40 000 IU weekly. Note RDA (Recommended Daily Allowance) is 800–1000 IU/day. The safe upper-dose daily limit is likely < 4000 IU/day. [10,17-37] Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. Vitamin D supplementation may therefore prove to be an effective and cheap intervention to lessen the impact of this disease, particularly in vulnerable populations, i.e., the elderly, those of color, obese and those living > 45° latitude. [22-37] 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. This concept is supported by a recent study which demonstrated that residents of a long-term care facility who took vitamin D supplementation had a much lower risk of dying from COVID-19. [38] Furthermore, it should be noted that Former CDC Chief Dr. Tom Frieden has stated "*Coronavirus*

infection risk may be reduced by Vitamin D".
https://preventepidemics.org/covid19/press/former-cdc-chief-dr-tom-frieden-coronavirus-infection-risk-may-be-reduced-by-vitamin-d/

- Vitamin C 500 mg BID (twice daily) and Quercetin 250 mg daily. [39-50] Vitamin C has important anti-inflammatory, antioxidant, and immune enhancing properties, including increased synthesis of type I interferons.[42,51,52] Quercetin has direct viricidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [40,45,50,50,53-60] In addition, quercetin acts as a zinc ionophore. [61] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [2] 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. [62-65] The use of quercetin has rarely been associated with hypothyroidism. The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with sub-clinical thyroidism.[66] In women high consumption of soya was associated with elevated TSH concentrations.[67] 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. [68] In patients taking these drugs it is best to avoid quercetin; if quercetin is taken cyclosporin and tacrolimus levels must be closely monitored.
- Melatonin (slow release): Begin with 0.3 mg and increase as tolerated to 2 mg at night. [1,7,69-75]. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease. 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. [76]
- Zinc 30–50 mg/day (elemental zinc). [46,48,49,77-80] Zinc is essential for innate and adaptive immunity.[78] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[77]
- B complex vitamins [81-85]
- *Optional:* Famotidine 20–40 mg/day [55–61]. 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.[58] Furthermore, a single study suggested that users of PPI's had a significantly increased odds for reporting a positive COVID-19 test when compared with those not taking PPIs, while individuals taking histamine-2 receptor antagonists were not at elevated risk.[62] This data suggest that famotidine may be the drug of choice when acid suppressive therapy is required.
- *Optional/Experimental:* Interferon-α nasal spray for health care workers [54]

Ivermectin dosing: 200 ug/kg or fixed dose of 12 mg (≤ 80kg) or 18 mg (≥ 80kg).[86] Depending on the manufacturer ivermectin is supplied as 3mg, 6 mg or 12 mg tablets.

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

Figure 9. I-MASK prophylaxis protocol.

For illustration purposes, not for brand or dosage endorsement

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

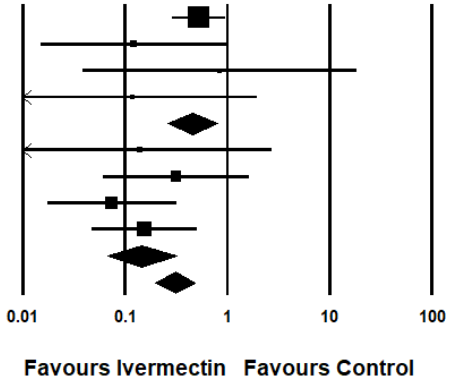
- Ivermectin 0.2 mg/kg on day 1 and day 3 (repeat on day 5 and 7 if poor response). [10,12,14,17-20,87-97] See Table 1, Figure 9 and ClinTrials.gov NCT04523831. See drug-drug interactions above.
- Vitamin C 500 mg BID and Quercetin 250–500 mg BID
- Zinc 75–100 mg/day (elemental zinc)
- Melatonin 10 mg at night (the optimal dose is unknown) [75]
- Vitamin D3 2000–4000 IU/day. Calcifediol 0.2 mg is an alternative. [98]
- ASA 81–325 mg/day (unless contraindicated). ASA has antiinflammatory, antithrombotic, immunomodulatory and antiviral effects.[99-101] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [102]
- B complex vitamins
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction) [103-109].
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed. Omega-3 fatty acids have anti-inflammatory properties and play an important role in the resolution of inflammation. In addition, omega-3 fatty acids may have antiviral properties. [48,110-113]
- *Optional:* Interferon-α/β s/c, nasal spray or inhalation. [114-117] It should be noted that Zinc potentiates the effects of interferon.[118,119]
- 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.[120] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[120] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [121] The following guidance is suggested: [120]
    - Use the index or middle finger; avoid the toes or ear lobe
    - Only accept values associated with a strong pulse signal
    - Observe readings for 30–60 seconds to identify the most common value
    - Remove nail polish from the finger on which measurements are made
    - Warm cold extremities prior to measurement
- *Not recommended:* Hydroxychloroquine (HCQ). The use of HCQ is highly controversial.[122] The best scientific evidence to date suggests that HCQ has no proven benefit for post exposure prophylaxis, for the early symptomatic phase and in hospitalized patients. [123-141] Considering the unique pharmacokinetics of HCQ, it is unlikely that HCQ would be of benefit in patients with COVID-19 infection (it takes 5–10 days to achieve adequate plasma and lung concentrations).[133,142-144] Finally, it should be recognized that those studies which are widely promoted to support the use of HCQ are severely methodologically flawed.[145-148]
- *Not recommended:* Systemic or inhaled corticosteroids *(*budesonide). In the early symptomatic (viral replicative phase), corticosteroids may increase viral replication and disease severity.[149] An OpenSAFELY analysis in patients with COVID-19 demonstrated a higher risk of death in COPD and asthmatic patients using high dose ICS. [150] The role of ICS in the pulmonary phase is unclear as patients require systemic corticosteroids to dampen the cytokine storm, with ICS having little systemic effects.
- *Not recommended:* Azithromycin. [151,152]

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

- Ivermectin 0.2 mg/kg orally on day 1 and day 3 (repeat on day 5 and 7 if poor response) [10,12,14,17-20,87-96]. It should be noted that ivermectin has potent anti-inflammatory properties apart from its antiviral properties.[153-155] See Table 1 and Figure 10. See drug-drug interactions above.
- Vitamin C 500–1000 mg q 6 hourly and Quercetin 250–500 mg BID (if available)
- Zinc 75–100 mg/day
- Melatonin 10 mg at night (the optimal dose is unknown) [75]
- Vitamin D3 20,000–60,000 IU single oral dose. Calcifediol 0.2–0.5 mg is an alternative. [98] This should be followed by 20,000 IU D3 (or 0.2 mg calcifediol) weekly until discharged from hospital. Calcifediol is more efficiently absorbed, achieves 25-OH vitamin D levels quicker and is three times more potent than vitamin D3. [156,157] However, it is important to note that the optimal dose of vitamin D in the acute setting is unknown.[158,159] Very high doses may paradoxically block the vitamin D receptor.
- Enoxaparin 60 mg/day [95,160-173] Consider increasing the dose to 1mg/kg q 12 hourly in those with a high D-Dimer (3-5 x ULN) or an increasing D-Dimer (see Xa monitoring below).
- 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.[174-176]
- Methylprednisolone 40 mg q 12 hourly; 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. [177-189] The role of inhaled corticosteroids (budesonide) is unclear and appears to be rather limited.
- B complex vitamins
- Famotidine 40 mg BID (20–40 mg/day in renal impairment). [103-109] Famotidine may be useful for its protective effect on gastric mucosa, its anti-viral properties and histamine blocking properties.
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily.
- *Optional:* Remdesivir 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [190,191] This agent has been reported to reduce time to recovery (based on an ordinal scale) in patients requiring low levels of supplemental oxygen. [191,192] The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup.[193] Considering the high cost of this agent and the lack of benefit on patient centered outcomes the role of this drug seems very limited. A recent *in vitro* study demonstrated marked synergy between Remdesivir and Ivermectin. [194] Considering the broad antiviral and anti-inflammatory effects of ivermectin, together with its remarkable safety record, this finding suggest that ivermectin should be prescribed in all patients receiving Remdesivir.
- N/C 2L/min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use “Spinhaler” or MDI and spacer if required.
- T/f EARLY to the ICU for increasing respiratory signs/symptoms, increasing oxygen requirements and arterial desaturation.

Figure 10. Metaanalysis of Ivermectin clinical studies (in hospital mortality)

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Ivermectin	Control
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT		0.146	0.067	0.316	-4.868	0.000		
Overall		0.307	0.195	0.483	-5.111	0.000		



Meta Analysis

MATH + PRTOCOL (for patients admitted to the ICU) [195,196]

1. ***Methylprednisolone*** 80 mg loading dose then 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 12 hourly (then 125mg q 12 hourly), then titrate down as appropriate. [177-189] Pulse methylprednisolone 250–500 mg mg/day may be required.[187] As depicted in Table 1, methylprednisolone is the corticosteroid of choice. Methylprednisolone should be weaned slowly over two weeks once oxygen is discontinued to prevent relapse/recurrence. The effect of corticosteroids on the profile of dysregulated immune markers is clearly illustrated in *Figure 11.* [197]
2. ***Ascorbic acid (Vitamin C***) 50 mg/kg q 6 hourly for at least 7 days and/or until transferred out of ICU.[43,51,52,198-207]. *Mega-dose vitamin C* should be considered in severely ill patients, those with progressive respiratory failure and as salvage therapy: 25g 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 [208] (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.[209] 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.[208] Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport and it is difficult to achieve adequate levels with PO administration. However, should IV Vitamin C not be available, it would be acceptable to administer PO vitamin C at a dose of 1g every 4–6 hours.

3. ***Full anticoagulation***: Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e., 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min) in those patients with a D-dimer > 3-5 X ULN and those with a rising D-dimer. Heparin is suggested with CrCl < 15 ml/min. In all other ICU patients, we would suggest medium dose anticoagulation; enoxaparin 0.5 mg/kg q 12 hourly. While observational studies have suggested that full anticoagulation reduces mortality of hospitalized patients with COVID-19 [160,162,163,165-173,210], the ***NIH ACTIV*** anticoagulation trial recently paused enrollment of critically ill COVID-19 patients (Press Release) for? lack of benefit. While the details and results of this study are pending, we still recommend FULL anticoagulation in those patients at highest risk of severe micro- and macro-vascular thrombosis. In our experience we have not observed increased bleeding in patients treated with the full MATH+ protocol. It should be noted that COVID-19 causes a vasculitis (with increased risk of bleeding) and that both corticosteroids and vitamin C are required to limit the vascular injury. Furthermore, vitamin C is a prerequisite for the synthesis of collagen and vitamin C deficiency is classically associated with vascular bleeding.[51,52] This is relevant to COVID-19 as vitamin C levels are undetectable in most COVID-19 patients.[211-213] Due to augmented renal clearance patients may have reduced anti-Xa activity despite standard dosages of LMWH.[214] We therefore recommend monitoring anti-Xa activity aiming for an anti-Xa activity of 0.6–1.1 IU.ml to reduce the risk of both under-dosing and excessive anticoagulation.

Note: A falling SaO2 and the requirement for supplemental oxygen should be a trigger to start anti-inflammatory treatment (see Figure 2).

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

Additional Treatment Components (the Full Monty)

4. Highly recommended: Ivermectin 0.2 mg/kg on day 1 and day 3; repeat on day 5 and day 7 if poor response (see doing above). [14,17-19,87,90-97,153-155,215-221] Note that ivermectin has potent antiviral and ant-inflammatory effects. See Table 1 and Figure 10.
5. Melatonin 10 mg at night (the optimal dose is unknown).
6. Calcifediol 0.2–0.5 mg (25OH Vitamin D). [98] This should be followed by 0.2 mg calcifediol weekly until discharged from hospital. If calcifediol s not available, supplement with vitamin D3 (cholecalciferol) 20,000–60,000 IU single oral dose, followed by 20,000 IU D3 weekly until discharged from hospital. Vitamin D3 takes many days to be converted to 25OH vitamin D; [222] this may explain the lack of benefit of D3 in patients hospitalized with severe COVID-19. [223]
7. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [224-229] Thiamine may play a role in dampening the cytokine storm. [225]
8. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe pro-thrombotic state and increasing the inflammatory response.[174-176] 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. B complex vitamins
10. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [84] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [230-232]
11. Famotidine 40 mg BID (20–40 mg/day in renal impairment). [103-109].
12. *Optional:* Doxycycline 100mg daily for 5 days. Doxycycline is a broad-spectrum antibiotic which has synergistic anti-viral and anti-inflammatory effects when combined with Ivermectin. [21,88,93,233]

13. *Optional (Consider in severe cases).* Anti-serotonin agents. Platelet activation results in the release of serotonin, which may contribute to the "cytokine storm". [234]Therefore, the serotonin receptor blocker cyproheptadine 4–8 mg PO q 6 hours should be considered.
14. *Optional.* Atorvastatin 80 mg/day. Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. In addition, statins decrease expression of PAI-1. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [235] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[236-240] Due to numerous drug-drug interactions simvastatin should be avoided.
15. *Optional:* Vascepa, Lovaza or DHA/EPA 4g day (see above).
16. *Not recommended:* The best information to date suggests that azithromycin is of little benefit in patients with COVID-19.[151,241,242]
17. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
18. *Not recommended.* Convalescent serum [243,244] nor monoclonal antibodies. [245]
19. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [246-250] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising (see Figure 11). [194]
20. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy). Due to the paradox of hyper-inflammation and immune suppression (a major decrease of HLA-DR on CD14 monocytes, T cell dysfunction and decreased CD4 and CD8 counts) secondary bacterial and fungal infections (Candida and Aspergillus species) and viral reactivation is not uncommon. [251-253] While low CD4 counts are typical of severe COVID-19 infection, PJP infections have not been reported; therefore PJP prophylaxis is not required.
21. 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.
22. 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.
23. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible,*** (see Figure 12)
    - 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
    - N/C 1–6 L/min
    - High Flow Nasal canula (HFNC) up to 60–80 L/min
    - Trial of inhaled Flolan (epoprostenol)
    - Attempt proning (cooperative repositioning-proning) [254,255]
    - Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
    - Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cm H_2O.
    - Moderate sedation to prevent self-extubation
    - Trial of inhaled Flolan (epoprostenol)
    - Prone positioning.

There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no evidence to support this fear. HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

A sub-group of patients with COVID-19 deteriorates very rapidly. Intubation and mechanical ventilation may be required in these patients.

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

PUBLISHED RCT's/COHORT STUDIES OF CORTICOSTEROID THERAPY IN COVID-19		ABSOLUTE DIFFERENCE IN MORTALITY RATE (Rx Group vs. Control Group)	ESTIMATED NUMBER NEEDED TO TREAT TO SAVE ONE LIFE
METHYLPREDNISONE – HOSPITAL PATIENTS (Edalatifard et al, Iran)		5.9% vs. 42.9%	2.7
METHYLPREDNISONE – ICU PATIENTS (Salton et al, Italy)		7.2% vs. 23.3%	6.2
METHLPREDNISONE – HOSPITAL PATIENTS, (Fadel et al, USA)		13.6% vs. 26.3%	7.8
METHYLPREDNISONE- ARDS PATIENTS (Wu C et al- China)		46.0% vs. 61.8%	6.3
METHYLPREDNISONE - Pts on oxygen – (Fernandez-Cruz, Spain)		13.9% vs. 23.9%	10.0
CoDEX –DEXAMETHASONE - MECHANICAL VENTILATION		56.3% vs 61.5%	19.2
RECOVERY TRIAL (DEXAMATHASONE)	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4
HYDROCORTISONE -CAPE-COVID – ICU Patients (Dequin et al France)		14.7% vs 27.4%	7.9
HYDROCORTISONE –REMAP-CAP – ICU patients		28%% vs 33%	20.0

Figure 11. Comparison of circulating COVID-19 related biomarkers in response to immunomodulatory therapy.[197]

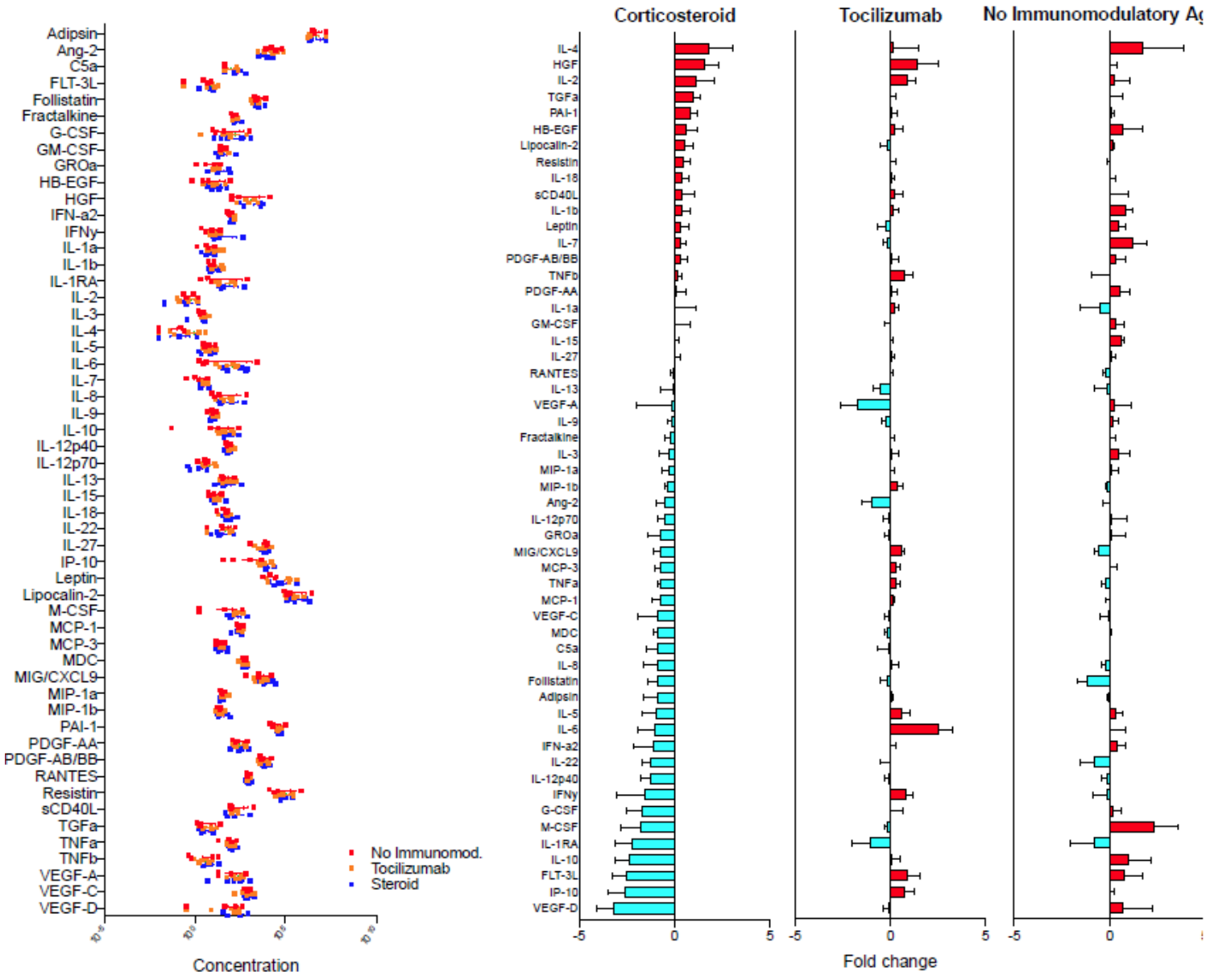


Figure 12.

General schema for respiratory support in patients with COVID-19
Try to avoid intubation if possible

DETERIORATION

Low flow nasal cannula
- Typically set at 1–6 liters/minute

High flow nasal cannula
- Accept permissive hypoxemia (0_2 Saturation > 86%)
- Titrate FiO_2 based on patient's saturation
- Accept flow rates of 60 to 80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative proning)

Invasive mechanical ventilation
- Target tidal volumes of ~6 cc/kg.
- Lowest driving pressure and PEEP
- Sedation to avoid self-extubation
- Trial of inhaled Flolan

Prone positioning
- Exact indication for prone ventilation is unclear.
- Consider in patients with PaO_2/FiO_2 ratio < 150.

Salvage Therapies
- High dose corticosteroids; 120–250 mg methylprednisolone q6–8
- Plasma exchange
- "Half-dose" rTPA

RECOVERY

24. Salvage Treatments

- High dose bolus corticosteroids; 250–1000 mg/day methylprednisolone [185,187]
- Plasma exchange [256-262]. 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.[208,209] (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.[263,264]
- 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". [265-268]
- ECMO [269,270]. Unlike "typical ARDS" COVID-19 patients do not progress into a resolution phase. Rather, patients with COVID-19 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. [271]

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. [243,244,272,273] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[274] 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.[275] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [276]
- Janus Kinase inhibitors downregulate cytokine expression and may have a role in this disease. [277-279] The role of the combination of Baricitinib and Remdesivir is unclear.[280]
- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [281-284] 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 [285,286] This treatment strategy appears to have an extremely limited role.

25. Treatment of Macrophage Activation Syndrome (MAS)

- A sub-group of patients will develop MAS, particularly those patients with severe COVID-19 disease.[287] While the pathophysiology of MAS in the setting of COVID-19 is unclear this appears to be driven by SARS-CoV-2 induced inflammasome activation and increased IL-18 production as well as increased GM-CSF and INFγ production. [288-291] The role of IL-1 and IL-6 in the pathogenesis of MAS is unclear.
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multi-system organ failure.[292]
- "*High dose corticosteroids*." Methylprednisolone 120 mg q 6–8 hourly for at least 3 days, then wean according to Ferritin, CRP, AST/ALT. Ferritin should decrease by at least 15% before weaning corticosteroids.
- Consider plasma exchange.
- The role of inhibition of IL-1 (Anakinra) and IFNγ (emapalumab) is unclear (NCT04324021).

26. Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[293] A PCT is essential to rule out coexisting bacterial pneumonia.[294]
- 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. [295]
- 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. [296,297]
- A CT on admission to the ICU is useful to determine the severity/extent of the organizing pneumonia [298] and to calculate the Ichikado Score.[299,300] Follow-up CXR and chest ultrasound as clinically indicated.
- ECHO as clinically indicated; Patients may develop a severe "septic" cardiomyopathy and/or COVID-19 myocarditis. [301,302]

27. Post ICU management

a. Enoxaparin 40–60 mg s/c daily
b. 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
c. Vitamin C 500 mg PO BID
d. Melatonin 3–6 mg at night
e. Vascepa, Lovaza or DHA/EPA 4g day (important for resolution of inflammation)

28. Post Hospital Discharge management

a. Patients have an increased risk of thromboembolic events post-discharge. [303] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include:[304]
   i. Increased D dimer (> 3 times ULN)
   ii. Increased CRP (> 2 times ULN) [305]
   iii. Age > 60
   iv. Prolonged immobilization

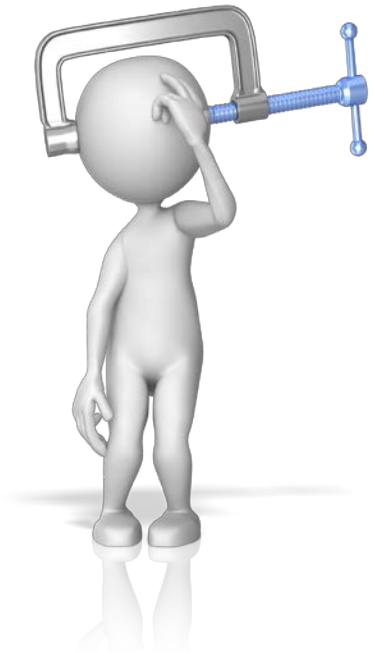
b. ***The post-COVID-19 syndrome (Long haul syndrome)*** is characterized by prolonged malaise, headaches, generalized fatigue, painful joints, dyspnea, chest pain and cognitive dysfunction.[306-311] Up to 50% of patients experience prolonged illness after Covid-19. The post-COVID-19 syndrome may persistent for months after the acute infection and almost half of patients report reduced quality of life. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[287] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [312] Similar to patients who have recovered from septic shock, [313] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the post-COVID-19 syndrome. Consequently, A CRP should be measured prior to discharge and a tapering course of corticosteroids should be considered in those with an elevated CRP. It should be noted that much like omega-3 fatty acids corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4.[314] Other interventions that should be considered include:
   i. Recently Ivermectin has been reported to have a role in the treatment of post-COVID-19 syndrome. [312] The anti-inflammatory properties of ivermectin may mediate this benefit.
   ii. Vascepa, Lovaza or DHA/EPA 4g day; important for resolution of inflammation by inducing resolvin production. [112,113]
   iii. Atorvastatin 40 mg daily (increase resolvin synthesis) [315]
   iv. Continue melatonin.
   v. Multivitamin with adequate vitamin D.

c. *Post-COVID-19 pulmonary fibrosis.* An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [281-284] however additional data is required before this therapy can be more generally recommended.

29. Maintaining mental health and the avoiding the misinformation pandemic

'*Misinformation on the Coronavirus might be the most contagious thing about it"*
Dr. Tedros, WHO Director General

- The Panic and misinformation spread by Social Media travels faster than the pandemic itself. What you can do?
    - Avoid social media as much as possible; excess social media exposure increases the likelihood of anxiety and depression[316]
    - Read the news/information from reliable sources (if you can find one)
    - Have a designated time for checking information
    - People share false claims about COVID-19 partly because they simply fail to think sufficiently about whether or not the content is accurate when deciding what to share. [317]
    - Stay connected to positive people! Remotely!
    - Have a plan for staying in touch with family and friends
    - Identify positive influencers…limit contact with other "worriers"
    - Isolation can cause rumination/anxious thinking to escalate
    - Maintain a sense of *hope, humanity and kindness toward others*
    - Seek professional help if anxiety is overwhelming
- Recognize the things you can control
    - WEAR A MASK when in contact with others
    - Establish social distancing; stand/sit about 6 feet away from others
    - Limit attendance at large gatherings
    - Eliminate your contact with those who are ill
    - DON'T go to work or school if you are sick
    - Practice self-care
        - Good sleep, balanced diet, exercise
        - Mindfulness/Meditation/Relaxation activities



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

This is an extraordinarily complex disease; many of the mysteries are still unravelling. However, a number of concepts are key to the management of this "treatable disease; they include.

1. Patients transition through a number of different phases (clinical stages). The treatment of each phase is distinct ... this is critically important (see Figures 1 & 2).
2. Antiviral therapy is likely to be effective only during the viral replicative phase whereas anti-inflammatory therapy is expected to be effective during the pulmonary phase and possibly the post-COVID-19 phase. While Remdesivir is a non-specific antiviral agent that targets RNA viruses, it is likely that agents specifically designed to target SARS-CoV-2 will be developed.
3. The SARS-CoV-2 PCR remains positive for at least 2 weeks following detection of whole virus (by culture, See figure 3). Patients who progress to the pulmonary phase are usually PCR positive despite cessation of viral replication (and are therefore less likely to be infectious).
4. Due to the imperfect sensitivity of the PCR test as many as 20% of patients who progress to the pulmonary phase will be PCR negative (even on repeat testing). At symptom onset PCR will be positive in approximately 60% of patients; maximal positivity rate is on day 8 (post infection) when 80% of patients will be positive (see Figure3). [318]
5. Symptomatic patients are likely to be infectious during a narrow window starting 2–3 days before the onset of symptoms and to up to 6 days after the onset of symptoms (see Figure 3).[319]
6. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, genetic heterogeneity mutations and polymorphisms, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[180,320-330] 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. [331]
7. The pulmonary phase is characterized by immune dysregulation, [277,279,287,290,291,323,332-341] a pulmonary microvascular injury (vasculopathy),[287,341-344] with activation of clotting and a pro-coagulant state together with the characteristics of an organizing pneumonia. [298,345]
8. Endothelial damage and an imbalance of both innate and adaptive immune responses, with aberrant macrophage activation, plays a central role in the pathogenesis of the severe COVID-19 Disease. [287]
9. As patients, progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are twofold.
    a. Early treatment (of the pulmonary phase) is ESSENTIAL to a good outcome.
    b. Treatment in the late pulmonary phase may require escalation of the dose of corticosteroids as well as the use of salvage methods (i.e., plasma exchange). However, patients who present in the late pulmonary phase may have progressed to the irreversible pulmonary fibroproliferative phase.
10. The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to "supportive care" alone. Furthermore, it is unlikely that there will be a single "silver bullet" to treat severe COVID-19 disease. Rather, patients will require treatment with multiple drugs/interventions that have synergistic and overlapping biological effects. Repurposed FDA approved drugs that are safe, inexpensive, and "readily" available are likely to have a major therapeutic effect on this disease. The impact of COVID-19 on middle- and low-income countries is enormous; these countries are not able to afford expensive propriety "designer" molecules.

11. The radiographic and pathological finding of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [298,346,347]
12. THIS is NOT ARDS (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS.[348-350] The ground glass infiltrates are peripheral and patchy, [346] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS".[351] Extravascular lung water index (EVLWI) is normal or only slightly increased; this by definition excludes non-cardiogenic pulmonary edema (ARDS). Lung compliance is normal (this excludes ARDS). Patients are PEEP unresponsive. Treating patients as if they ARDS is an extremely dangerous approach. The hypoxia is due to a organizing pneumonia with severe ventilation/perfusion mismatch likely due to the microvascular narrowing, thrombosis and vasoplegia.
13. The core principles of the pulmonary phase (MATH+) is the use of anti-inflammatory agents to dampen the "cytokine storms" together with anticoagulation to limit the microvascular and macrovascular clotting and supplemental oxygen to help overcome the hypoxia.
14. Ivermectin has emerged as a highly effective drug for the prophylaxis and treatment COVID-19. Ivermectin inhibits viral replication and has potent anti-inflammatory properties. Emerging clinical data (including RCT's) suggest that ivermectin may have an important clinical benefit across the spectrum of phases of the disease, i.e pre-exposure prophylaxis, postexposure prophylaxis, during the symptomatic phase and during the pulmonary phase. [14,17-19,87,90-96,153-155,215-221,352] In the recommended dosages, Ivermectin is remarkably safe and effective against SARS-CoV-2 (see Table 1 and Figures 8 and 10). However, as noted above there is the potential for serious drug-drug interaction.
15. The pulmonary phase of COVID-19 is characterized by PROLONGED immune dysregulation that may last weeks or even months. The early and abrupt termination of anti-inflammatory agents will likely result in rebound inflammation. [353]
16. SARS-CoV-2 as compared to all other respiratory viruses, upregulates cytokines and chemokines while at the same time down regulating the expression of Interferon alpha (the hosts primary antiviral defence mechanism). [131,155] Low innate antiviral defenses and high pro-inflammatory mediators contribute to ongoing and progressive lung injury.
17. Patients in whom the cytokine storm is not "dampened" will progress into the "H phenotype" characterized by poor lung compliance, severe oxygenation failure and PEEP recruitability. Progression to this phase is exacerbated by ventilator induced lung injury (VILI). The histologic pattern of the "H Phenotype" is characterized by an acute fibrinous and organizing pneumonia (AFOP), with extensive intra-alveolar fibrin deposition called fibrin "balls" with absent or minimal hyaline membranes.[325,347,354-356] Corticosteroids seem to be of little benefit in established AFOP. High dose methylprednisolone and Mega-dose vitamin C should be attempted in the "early phase" of AFOP, however many patients will progress to irreversible pulmonary fibrosis with prolonged ventilator dependency and ultimately death.
18. An unknown percentage of patients with COVID-19 present with "silent hypoxia" with a blunted respiratory response. This phenomenon may be related to involvement of chemoreceptors of the carotid bodies and/or brain stem dysfunction,[357,358] 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.[359] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[360,361] as well as viral replication [95,161]. Most importantly LWWH inhibits heparanase (HPSE).[362] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[362] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [363] 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. [200,205] Vitamin C protects the endothelium from oxidative injury.[51,364-366] Furthermore, vitamin C Increases the expression of interferon-alpha [42] while corticosteroids (alone) decease expression of this important protein. [367-370] 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. [182,371] 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),[372] genomic data specific for SARS-CoV-2,[101] and a long track record of successful use in inflammatory lung diseases. (see Table 1)

Scientific Rationale for MATH+ Treatment Protocol (pulmonary phase)

Three core pathologic processes lead to multi-organ failure and death in COVID-19:

1) **Hyper-inflammation ("Cytokine storm") –** a dysregulated immune system whose cells infiltrate and damage the lungs as well as other organs including the heart and bone marrow. It is now widely accepted that SARS-CoV-2 causes aberrant T lymphocyte and macrophage activation resulting in a "cytokine storm." [277,279,290,291,323,332,334-340] In addition, post-mortem examination has demonstrated features of the "macrophage activation syndrome", with hemophagocytosis and a hemophagocytic lymphohistiocytosis-like disorder.[287] These autopsy studies have shown minimal viral cytopathic effects providing further validation that it is the hosts immune response to the virus rather than the virus itself which is killing the host.[287,373-375]
2) **Hyper-coagulability (increased clotting)** – the dysregulated immune system damages the endothelium and activates blood clotting, causing the formation of micro and macro blood clots. Clotting activation may occur directly due to increased expression of Factor Xa as well as endothelial injury with the release of large aggregates of van Willebrand factor.[102] Furthermore, ACE-2 receptors are present on platelets and this may contribute to the massive platelet aggregation characteristic of severe COVID-19 disease.[174,176,376] These blood clots impair blood flow. [162,163,165-173,343,344,377,378] It should be noted that the thrombotic microangiopathy appears to target predominantly the pulmonary and cerebral circulation. [287]
3) **Severe Hypoxemia (low blood oxygen levels)** –lung inflammation caused by the cytokine storm, together with microthrombosis in the pulmonary circulation severely impairs oxygen absorption resulting in oxygenation failure with a sever V//Q mismatch.

The above pathologies are not novel, although the combined severity in COVID-19 disease is considerable. Our long-standing and more recent experiences show consistently successful treatment if traditional therapeutic principles of ***early and aggressive intervention*** is achieved, before the onset of advanced organ failure. It is our collective opinion that the historically high levels of morbidity and mortality from COVID-19 is due to a single factor: the widespread and inappropriate reluctance amongst hospitalists and intensivists to employ anti-inflammatory and anticoagulant treatments, including corticosteroid therapy *early in the course of a patient's hospitalization.* It is essential to recognize that it is not the virus that is killing the patient, rather it is the patient's overactive immune system. [276,279,287,358] The flames of the "cytokine fire" are out of control and need to be extinguished. Providing supportive care (with ventilators that themselves stoke the fire) and waiting for the cytokine fire to burn itself out simply does not work… this approach has FAILED and has led to the death of tens of thousands of patients.

"If what you are doing ain't working, change what you are doing" – PEM

The systematic failure of critical care systems to adopt corticosteroid therapy (early in this pandemic) resulted from the published recommendations against corticosteroids use by the World Health Organization (as recent as May 27th 2020) [379,380]. This recommendation was then perpetuated by the Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), Infectious Diseases Association of America (IDSA) amongst others. A publication authored one of the members of the Front Line COVID-19 Critical Care (FLCCC) Alliance (UM), identified the errors made by these organizations in their analyses of corticosteroid studies based on the findings of the SARS and H1N1 pandemics.[177,381] Their erroneous recommendation to avoid corticosteroids in the treatment of COVID-19 has led to the development of myriad organ failures which have overwhelmed critical care

systems across the world and led to excess deaths. The recently published results of the RECOVERY-DEXAMETHASONE study provide definitive and unambiguous evidence of the lifesaving benefits of corticosteroids and strong validation of the MATH + protocol. It should be recognized that corticosteroids are the only therapy proven to reduce the mortality in patients with COVID-19.[382] The RECOVERY-DEXAMETHASONE study, randomized 2104 patients to receive dexamethasone 6 mg (equivalent to 32 mg methylprednisolone) once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomized to usual care alone.[149] Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14). The results of this study STRONGLY support the EVMS/MATH+ protocol which recommends the use of corticosteroids for the "pulmonary phase" of COVID-19. It should be noted that we would consider the non-titratable 'fixed" dose of dexamethasone used in the RECOVERY-DEXAMETHASONE study to be very low. Furthermore, as indicated above we consider methylprednisolone to be the corticosteroid of choice for the treatment of COVID-19 pulmonary disease. The benefit of methylprednisolone in improving respiratory function, ventilator dependency and mortality has been confirmed in a number of observational studies, [178,179,185,371,383-385] as well as a randomized controlled study.[187] It should be recognized that the mortality benefit with methylprednisolone was not replicated in a recent Brazilian RCT. [353] However, in this study methylprednisolone was started relatively late (day 13 after symptom onset), but most importantly was stopped on day 5. This failed study reinforces the concept of early and prolonged treatment with methylprednisolone titrated to the patient's clinical response. In patients at high risk of Strongyloides infection, screening and/or treatment of this parasite with ivermectin is suggested prior to treatment with corticosteroids.[386]

Our treatment protocol targeting the key pathologic processes has been highly successful, *if begun within 6 hours* of a COVID19 patient presenting with shortness of breath and/or arterial desaturation and requiring supplemental oxygen. If such early initiation of treatment could be systematically achieved, the need for mechanical ventilators and ICU beds will decrease dramatically.

Further resources:

The reader is referred to the large autopsy series by Bruce and colleagues which clearly outlines the pathophysiology of severe COVID-19 disease.[287]

The scientific rationale for the MATH + protocol is reviewed in this paper.[195,196]

In this U-tube video, Professor Britt Glaunsinger, PhD provides an outstanding review on the molecular virology of SARS-CoV-2: https://www.youtube.com/watch?v=DQVpHyvz4no

Lectures by Paul Marik, MD reviewing clinical aspects of COVID-19.
https://www.youtube.com/channel/UCz9Pvn15m4Rv1uY-aBYRVuw

FLCCC ALLIANCE

Question: My Primary care physician (PCP) will not prescribe Ivermectin. Where can I get a script?

Answer: We understand and empathize with the challenges faced in obtaining a prescription for Ivermectin during the time period prior to its use being formally adopted in national or international COVID-19 treatment guidelines. We are anticipating these treatment guidelines to be updated in the near future. Alternately, please know our scientific review manuscript on ivermectin in COVID-19 is undergoing expedited peer-review at a prominent American medical journal, and if it passes peer review and becomes published, we anticipate that this will also make access to ivermectin more widespread. However, until such a time when its use as both a prophylactic and treatment agent is more widely accepted, many physicians will be reluctant to prescribe. We can only recommend the following approaches:

I. Discuss with your primary health care provider. If they are unconvinced of the data, share with them our manuscript which can be downloaded from the FLCCC Website or from the Pre-print server at https://osf.io/wx3zn/. Please understand that many will prefer to avoid adoption of ivermectin treatment until such a time as the guidelines are updated or the manuscript gets published.
II. The second option is to try one of the doctors on the list below that can provide telemedicine consultation here: Drs Prescribing Ivermectin. https://www.exstnc.com/ Confirm the price of any visit prior to the consultation. We have reports of some doctors charging exorbitant fees.
III. If more pills are desired than can be provided locally, you can order in bulk from the Canadian King Pharmacy, however you will need a prescription. https://www.canadianpharmacyking.com/

Question: Is ivermectin safe and can it be used in patients with liver disease?

Answer: The discovery of Ivermectin in 1975 was awarded the 2015 Nobel Prize in Medicine given its global impact in reducing onchocerciasis (river blindness), lymphatic filariasis, and scabies in endemic areas of central Africa, Latin America, India, and Southeast Asia. It has since been included on the WHO's "List of Essential Medicines with now over 4 billion doses administered. Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of parasites and include itching, rash, swollen lymph nodes, joint paints, fever, and headache. In a study which combined results from trials including over 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa Loa infected patients. Further, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of anti-

tuberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Similarly, we suggest therapeutic monitoring of drug levels such as calcineurin inhibitors such as tacrolimus and cyclosporin and the immunosuppressant sirolimus as potential interactions exist. A longer list of drug interactions can be found on the *drugs.com* database, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given escalating high doses of ivermectin, toxicity is unlikely although a reduced efficacy due to decreased levels may be a concern.

Question: Can I request expert advice or consultation from the FLCCC?

Answer: Given the sheer volume of requests and the limited number of expert clinicians that make up the FLCCC Alliance, the doctors are not able to respond to individual requests for expert consultation on patients ill with COVID-19. Furthermore, we cannot provide treatment recommendations for patients that are not under our direct care. However, we can offer interested patients, families, and health care providers the expertise and guidance contained in our published and pre-published manuscripts which support our understanding and approach to treatment in this disease. Given that the majority of requests for consultation have been on cases where patients are failing standard therapies, we suggest that those interested review the section on "salvage therapies" in this document (#24, Page 21). We also emphasize the importance of recognizing that COVID-19 respiratory disease is not a viral pneumonia, but rather an "organizing pneumonia", and as such, in fulminant cases, typically require high doses of corticosteroids as in our protocol. For support of this, please refer to our paper on "SARS-CoV-2 Organizing Pneumonia" (available on the FLCCC Website). Lastly, we recommend that patents ill with COVID-19 at any stage of disease receive ivermectin, as per the accompanying manuscript which compiles and reviews the large evidence base supporting this therapy.

Question: Will ivermectin interfere with the vaccine and can I continue to take ivermectin once vaccinated?

Answer: Our understanding of the importance of ivermectin in the context of the new vaccines, is that ivermectin prophylaxis should be thought of as complementary bridge to vaccination until the vaccines are made available to all those in need. At this time and speaking with the vaccine experts we do not believe that ivermectin prophylaxis interferes with the efficacy/immune response to the vaccine, however it must also be recognized that no definitive data exists to guide use more specifically on this question. However, given that maximal immunity from the vaccines is only achieved 2 weeks after the second dose of vaccine, it is reasonable to take bi-weekly ivermectin until this time point. The "New' mutated strain of SARS-CoV-2 appears to be less susceptible to pre-existent neutralizing antibodies; this may have potential implications for the current vaccination program.

Question: Shouldn't we wait for more data before widely adopting another medicine that may not work?"

Answer: Making a risk/benefit decision at this time, with the currently available data showing consistent high efficacy and safety with mortality benefits from 24 controlled trials, would far exceed the strength and validity of the rationales used to adopt the entirety of currently employed therapeutics in COVID-19 given all were adopted in the setting of either:

I. Weak clinical impacts measured (Remdesivir, monoclonal antibodies, convalescent plasma),
II. High costs (Remdesivir, monoclonal antibodies, convalescent plasma, vaccines)
III. Significant adverse effects (Remdesivir, vaccines),
IV. Weak, conflicting, or non-existing evidence bases to support use (Remdesivir, monoclonal antibodies, convalescent plasma),
V. Conflicting treatment guidelines (Remdesivir – WHO and NIH recommendations conflict)
VI. Non-peer reviewed studies (Remdesivir, monoclonal antibodies, convalescent plasma)
VII. Absence of even pre-print study data available for wider scientific review (vaccines)

Question: If ivermectin is so effective in COVID-19, how come no countries have adopted it into their national treatment guidelines?

Answer: Multiple countries and regions have formally adopted ivermectin into their treatment guidelines, with several having done so only recently, based on the emerging data compiled by the FLCCC. Examples include:

I. Macedonia - December 23, 2020
II. Belize - December 22,2020
III. Uttar Pradesh in Northern India- a state with 210 million people, adopted early home treatment kits which include ivermectin on October 10, 2020
IV. State of Alto Parana in Paraguay - September 6, 2020
V. Capital City of Lucknow in Uttar Pradesh - August 22, 2020
VI. State of Chiapas, Mexico - August 1, 2020
VII. 8 state health ministries in Peru - Spring/summer 2020
VIII. Lima, Peru - Many clinics, districts use and distribute ivermectin, as of October the hospitals no longer use.

Question: Isn't the promotion of ivermectin the same thing as hydroxychloroquine – everyone claims it works when all the randomized controlled trials showed it did not?

Answer: The decision to adopt hydroxychloroquine was made early in the pandemic, when, despite the lack of clinical trials data to support use, there existed a scientific rationale given pre-clinical data suggesting anti-viral and anti-inflammatory properties. Thus, the decision at that time was likely a sound one based on a risk/benefit calculation given HCQ's low cost, minimal adverse effect profile, wide availability/ease of compounding, and long history of use. Such a decision was also entirely in keeping with Principle 37 of the Helsinki Agreement on Medical Research, first formulated in 1964, which declares that "*physicians may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research*." In keeping with Declaration 37, immediately after the widespread adoption of HCQ, studies were immediately conducted by many centers. Unfortunately, all of the RCT's reported negative results which led to rapid de-adoption with the exception of sporadic continued use

in early phase disease. Note that the current widespread non-adoption of ivermectin in the face of hundreds of thousands of ill and dying, currently violates Declaration 37 in that adoption is being purposely and overtly avoided despite the efficacy/risk assessment of now numerous well controlled trials including over 3,000 total patients which report massive drops in transmission and large decreases in mortality when used in the treatment of COVID-19 patients. The data supporting adoption is now approaching that of corticosteroids, where widespread use began almost immediately upon the reporting of results of the 6,000 patient RECOVERY trial which demonstrated a mortality benefit (with only 2,000 patients treated with corticosteroids in that trial).

Question: Isn't it a problem that all the trials were done in foreign countries and may not be generalizable to our patients here?"

Answer: Such concerns reflect a surprising degree of ethnocentrism that we believe will lead to further harms against humanity. We cannot deny that these concerns currently present a significant barrier for the evidence compiled in our manuscript to influence practice. We recently learned that a COVID-19 therapeutics committee of a large hospital health care system in the Midwest recently reviewed the existing trials data for ivermectin in November and decided not to recommend ivermectin, with one of the stated reasons being that "many of the studies were performed abroad and are likely not generalizable to our patients". The belief that a potent anti-viral medicine only works in foreigners and not in Americans is ludicrous and deserves no further comment or explanation except to note it as an example of the most extreme skepticism that can be displayed by providers who simply "do not believe" in the efficacy of ivermectin.

Question: Shouldn't we wait until there are more randomized controlled trials?

Answer: Fifteen of the 24 controlled trials results are prospective and randomized and include over 3,000 patients. Again, note that the RECOVERY trial which made corticosteroids the standard of care in COVID-19 overnight was a randomized controlled trial which included 2,000 patients treated with dexamethasone. The number of ivermectin treated patients in the RCT's are now approaching 2,000. Further, the number of patients in the 9 observational controlled trials also total over 4,000 patients. Thus, after 7,000 patients and 24 controlled trials of ivermectin in varying sizes and designs and countries, with nearly all resulting in consistent, reproducible, large magnitude, statistically significant findings of efficacy as a prophylactic and in early and late phase disease. Given these marked reductions in transmission, hospitalizations, and death, any further studies using a placebo would be unethical. For any who require more clinical trials data, well-designed observational controlled trials are a perfectly valid alternative and will (and should) be conducted by many, even after adoption as a treatment agent.

Question: How does the NIH arrive at their recommendations for current widely used therapies and why is the rationale for these recommendations so difficult to understand?

Answer: We are unable to identify a consistent approach to the strength and timing of NIH recommendations and/or updates to the recommendations. However, the influence of "Big Pharma" appears undeniable.

Question: Why does the NIH recommends against the use of ivermectin outside of clinical trials?

Answer: This recommendation is from August 27th, is graded IIIA, which means that it was expert opinion only and reflected a "strong" opinion against. Given the amount of data available as of today, December 27, 2020, we must ask the question, "What should the strength and level of recommendation for Ivermectin be updated to by the NIH? First, all must understand how recommendations for medical therapies are created by the NIH. They essentially use the below grading scale which provides an assessment of both the strength of the recommendation and the quality of evidence to support that recommendation.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	**III:** Expert opinion

The last NIH recommendation on ivermectin from August 27th was graded AIII against use as per above table, indicating a strong recommendation based on expert opinion only, despite it being one of the world's safest, cheapest, and most widely available drugs. No rationale or supporting evidence. Further, the grade implies that there was no available clinical evidence at the time to make an "evidence-based" grading, yet we know of a number of trials results available at that time.

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