- Oropharyngeal hygiene with twice daily antiviral mouthwash/gargle (see Figure 7 and below).
- Monoclonal antibodies for postexposure 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%). [36] 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 [37-43]. 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. [40] Furthermore, a number of studies have demonstrated an association between the use of proton pump inhibitors (PPI's) with an increased risk of contracting COVID-19 and with worse outcomes. [44,45] This data suggest that famotidine may be the drug of choice when acid suppressive therapy is required.

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: 200 ug/kg (0.2mg/kg) or fixed dose of 12 mg (≤ 80kg) or 18 mg (≥ 80kg).[46]
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

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.[47-51] Emerging data suggests that curcumin improves the clinical outcome of patients with COVID-19. [52,53]
- *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. [54-61]
- Vitamin D3 1000–3000 IU/day (25-75 mcg). An alternative strategy is 40 000 IU weekly. Note RDA (Recommended Daily Allowance) is 800–1000 IU/day. The safe upper-dose daily limit is likely < 4000 IU/day. Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. [62-86] 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. [68-83,86] 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. [87] 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. [84]
- 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.[88-91] 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 has demonstrated health benefits.[92,93] 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. [94-106] 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.[97,107,108] Quercetin has direct virucidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [95,100,105,105,109-117] Quercetin is a potent inhibitor of inflammasome activation, which believed to play a major role in the pathophysiology of the COVID-19 immune dysfunction.[117] In addition, quercetin acts as a zinc ionophore. [118] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [2] A mixed flavonoid supplement containing quercetin, green tea catechins and anthrocyanins (from berries) may be preferable to a quercetin supplement alone; [119-123] 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. [124-127] 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.[128] In women high consumption of soya was associated with elevated TSH concentrations.[129] 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. [130] 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). [101,103,104,131-135] Zinc is essential for innate and adaptive immunity.[133] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[132] 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. [136] 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 [137-141].

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

Drug Interactions with Ivermectin

Drug Interactions. (From Medscape).
https://reference.medscape.com/drug/stromectol-ivermectin-342657#3

Patents 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

Figure 7a. Naso-oropharyngeal sanitization

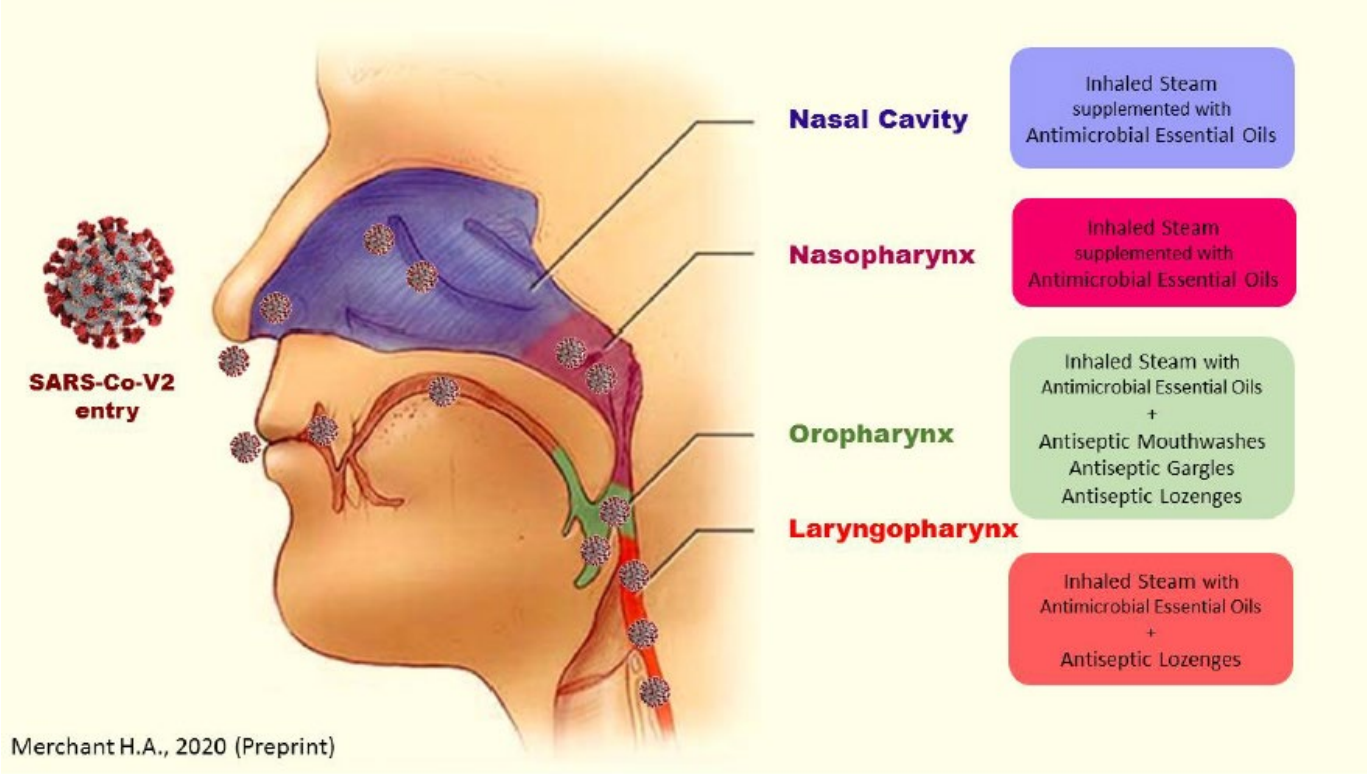

Figure 7b. Commercial products available for naso-oropharyngeal sanitization

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

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

- Ivermectin 0.4- 0.6 mg/kg – one dose daily for 5 days or until recovered. [15,19,62-65,142-157]. Higher doses (0.6 mg/kg) often required in a) regions with more aggressive variants, b) treatment started on or after 5 days of symptoms or c) in patients in pulmonary phase, d) extensive CT involvement or e) extensive comorbidities/risk factors (older age, obesity, diabetes). Ivermectin is best taken with a meal or just following a meal (greater absorption). See 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.[158] The combination of NTZ and ivermectin has been shown to reduce viral clearance and symptom progression in outpatients with COVID-19. [159,160] 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.[161,162] Like ivermectin NTZ has broad spectrum antiviral activity that includes SARS-CoV-2.[162-165] Furthermore, as NTZ and ivermectin have differing modes of action it is likely that these two drugs have synergistic antiviral and anti-inflammatory effects.[160,163,166] 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???
- Oropharyngeal sanitization (see figure 7). [167] Inhaled steam supplemented with antimicrobial essential oils (e.g VapoRub™ inhalations) has been demonstrated to have virucidal activity. [168] 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. [169-176] A mouthwash containing cetylpyridinium chloride (CPC) has broad antimicrobial properties and has been shown to be effective in controlling gingivitis and gingival plaque.[176-178] An *in-vitro* study demonstrated that CPC was highly viricidal against a human coronavirus.[179] 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 morbidly, hospitalization and death. [180] A nasal spray with 1% povidone-iodine (for example Immune Mist ™) administered 2-3 times per day is recommended in postexposure prophylaxis and in symptomatic patients (early phase of COVID-19 infection).[171] 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 mouth wash over a 6-month period was demonstrated to increase serum iodine levels, thyroid function tests remained unchanged. [181] 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.[182-184] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [185-187]
- Melatonin 10 mg at night (the optimal dose is unknown) [31-34] 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. [47-51]
- *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. [56]
- 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 3 - 5000 IU daily (125 mcg). It is important to note that the optimal dose of vitamin D in the acute setting is unknown.[188,189]
- 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).
- 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.[190] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[190] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [191] The following guidance is suggested: [190]
    - 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.[192] In addition androgens are pro-inflammatory.[193]. 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).[194-197] 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.[198] 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. [199,200] Both spironolactone and dutasteride decrease expression of TMPRSS2.[201] 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. [198,202-207] Dutasteride has been used in women with alopecia and reported to be safe. [208,209] 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. [210-214] This SSRI is recommended in those patients with more severe symptoms/more advanced disease. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that activates sigma-1 receptors decreasing cytokine production. [210,211] In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus and inhibits melatonin degradation.[215,216] Antidepressant medications (SSRI) deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation.[217-219] The use of antidepressants has be associated with a lower risk of intubation and death in patients hospitalized with COVID-19. [213,214] Fluoxetine (Prozac; 20-40mg daily), has activity against the sigma-1 receptor and is an alternative should fluvoxamine not be available. [220]
- 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.[221] 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!!! [221] The duration of symptoms was 4 days shorter in the REG-COV2 group. 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.

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.[222-224] As discussed later this is critical in the management of COVID-19. In addition, omega-3 fatty acids may have antiviral properties. [103,225-228]
- *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. [229-231] Preliminary data demonstrated that disruption of the CCR5 axis with monoclonal antibodies was associated with an improved outcomes in patients with COVID-19. [232-234] Maraviroc is a CCR5 blocker that has been extensively used in patients with HIV, with a good safety record. [235-237] Emerging data suggests that maraviroc may be useful as an adjunctive agent in both acute COVID-19 infection and in the long-haul syndrome. 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*) [37-43].*
- *Optional*: Interferon-α/β nasal spray, inhalation or s/c injection. [238-242] It should be noted that Zinc potentiates the effects of interferon.[243,244]
- *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.[245,246] 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, there with no difference in the rate of hospitalization.[247,248] 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. [249,250] 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. [251] 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, [252] 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.[253]
- *Unclear benefit.* Hydroxychloroquine (HCQ). The use of HCQ is highly controversial.[254] Observational studies have demonstrated a benefit of HCQ in postexposure prophylaxis and early treatment. However, randomized controlled trials have failed to demonstrate a benefit of this drug for post exposure prophylaxis, the early symptomatic phase and in hospitalized patients.[255-276] Very high dosages were used in many of the RCTs'. Furthermore, HCQ is a ZINC ionophore and it is noteworthy that none of the RCTs included zinc in the treatment protocol. The use of HCQ is further complicated by the drugs unique pharmacokinetic properties (it takes 5–10 days to achieve adequate plasma and lung concentrations).[265,277-279] In addition, SARS-CoV-2 ejects its genome directly into the cell avoiding being trapped in endosomes/lysosome.[280].Disruption of lysosomes is the main mechanism that HCQ is postulated to have antiviral effects.[280] Finally, it should be recognized that many of the observational studies are severely methodologically flawed.[281-284]
- *Not recommended:* Prophylactic azithromycin, as well as doxycycline, or quinolone antibiotics are of little benefit in patients with COVID-19. [285-287]

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. [15,19,62-65,142-151,153,155-157]. 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.[288-291] See drug-drug interactions above.
- Nitazoxanide (NTZ) 600 mg BID for 7 days.[292] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
- 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. [293-305] 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.[306]
- 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 (the optimal dose is unknown) [31]
- 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**. [198,202,203]

4.2 Second Line and optional treatments

- Active forms of Vitamin D (Calcifediol 25-OH Vitamin D or Calcitriol 1,25-OH Vitamin D). [307] Calcitriol 0.5 mcg (ug) daily for up to 14 days or until hospital discharge. [308] Alternatively, calcifediol 0.5 mg day 1, followed by 0.2 mg weekly until discharged from hospital (this is high dose treatment based on the Spanish study). [307] Patients receiving the active forms of Vitamin D should be monitored for hypercalcemia. Should calcitriol/calcifediol not be available, supplement with vitamin D3 (cholecalciferol) 20,000–60,000 IU single oral dose, followed by 20,000 IU D3 weekly until discharged from hospital. In the acute setting calcifediol/calcitriol

appears to be more effective than vitamin D3. [308,309] Vitamin D3 takes many days to be converted to 25-OH vitamin D; [310] this may explain the lack of benefit of vitamin D3 in patients hospitalized with severe COVID-19. [87]

- 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.[186,187,311,312]
- B complex vitamins
- Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40mg daily is an alternative.
- 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. [313,314] 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. [315] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[316-320] Due to numerous drug-drug interactions (including ivermectin) simvastatin should be avoided.
- *Optional:* Maraviroc 300 mg BID for 10 days (see discussion above).
- *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [37-43] 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.[321] These drugs have been shown to decrease the use of mechanical ventilation and the risk of death. [322] However the role of these drugs is unclear, and they should not be used in combination with corticosteroids. [323]
- *Optional:* The anti-serotonin agent, cyproheptadine 4–8 mg PO q 6 hour should be considered in patients with more severe disease. [324,325] 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. [324,326-328] 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. [329-332] Furthermore, serotonin itself enhances platelet aggregation creating a propagating immuno-thrombotic cycle.[333] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [334]
- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. [335] Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed
- *Optional:* Remdesivir 200 mg IV loading dose day 1, followed by 100 mg day IV for 9 days. [336,337] This agent has been reported to reduce time to recovery (based on an ordinal scale) in patients requiring low levels of supplemental oxygen. [337,338] The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup.[339] The VA study showed no mortality benefit with Remdesivir and a longer length of hospital stay.[340] Most recently, the DisCoVeRy trial reported no outcome benefit from remdesivir.[341] Considering the high cost of this agent and the lack of benefit on patient centered outcomes the role of this drug seems very limited. An in vitro study demonstrated marked synergy between Remdesivir and Ivermectin. [342] Considering the broad antiviral and anti-inflammatory effects of ivermectin, together with its remarkable safety record, this finding suggests that ivermectin should be prescribed in all patients receiving Remdesivir. However, Remdesivir should only be prescribed in the early viral replicative phase of COVID-19.