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MEDICAL GROUP

EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

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

EVMS COVID website: https://www.evms.edu/covid-19/medical_information_resources/
Short url: evms.edu/covidcare

Disclaimer: The information provided in this protocol is to provide guidance to physicians on the prevention of infection with SARS -CoV-2 as well as the early treatment and management of the hyper-inflammatory cytokine "storm" of COVID-19. Our guidance should only be used by medical professionals in formulating their approach to COVID-19. Patients should always consult with their physician before starting any medical treatment.

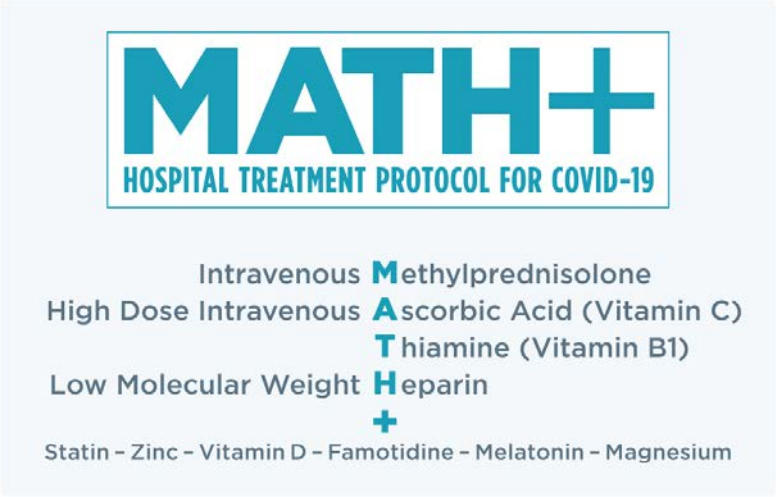

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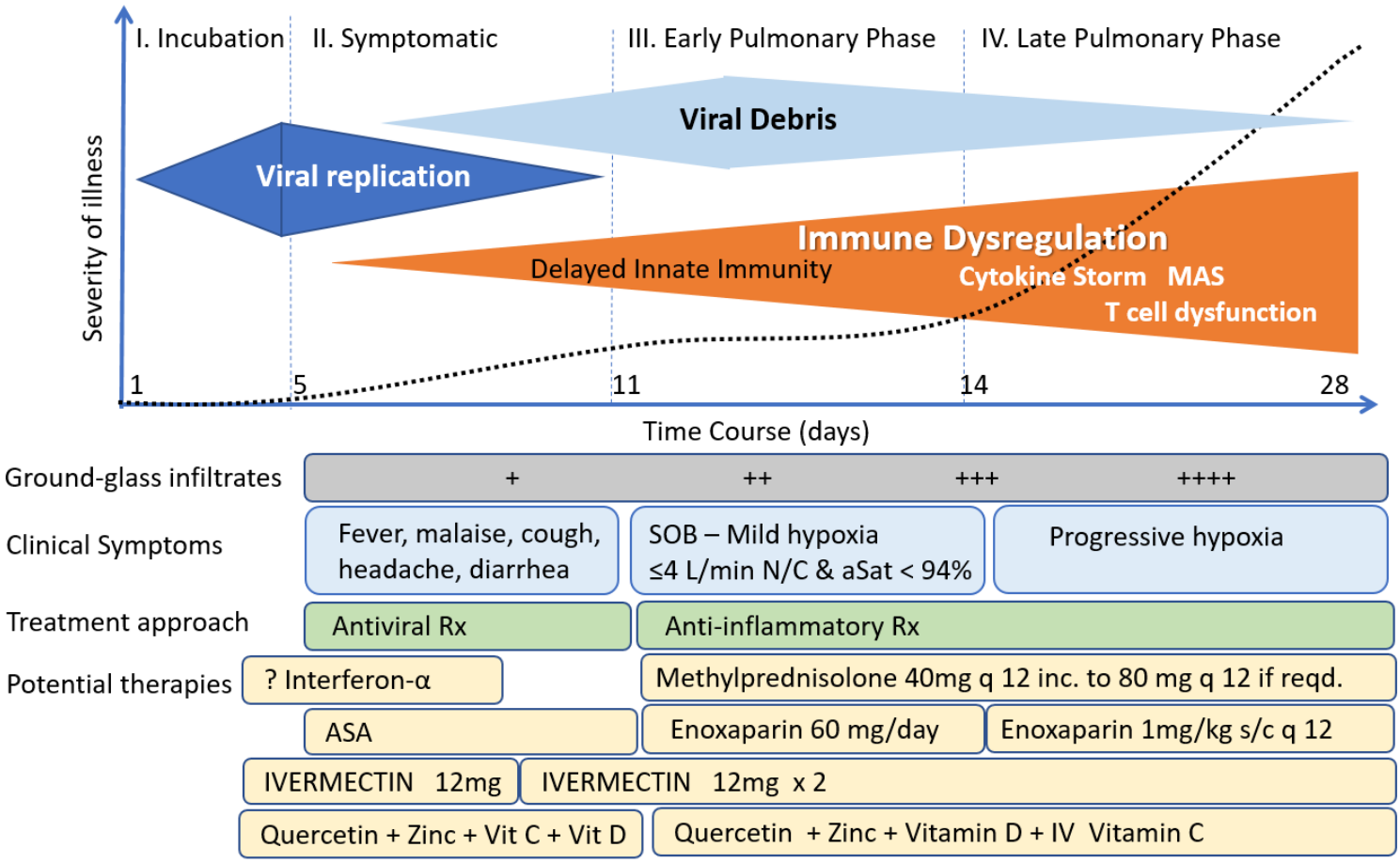
Figure 1. The course of COVID-19 and General Approach to treatment



THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL

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

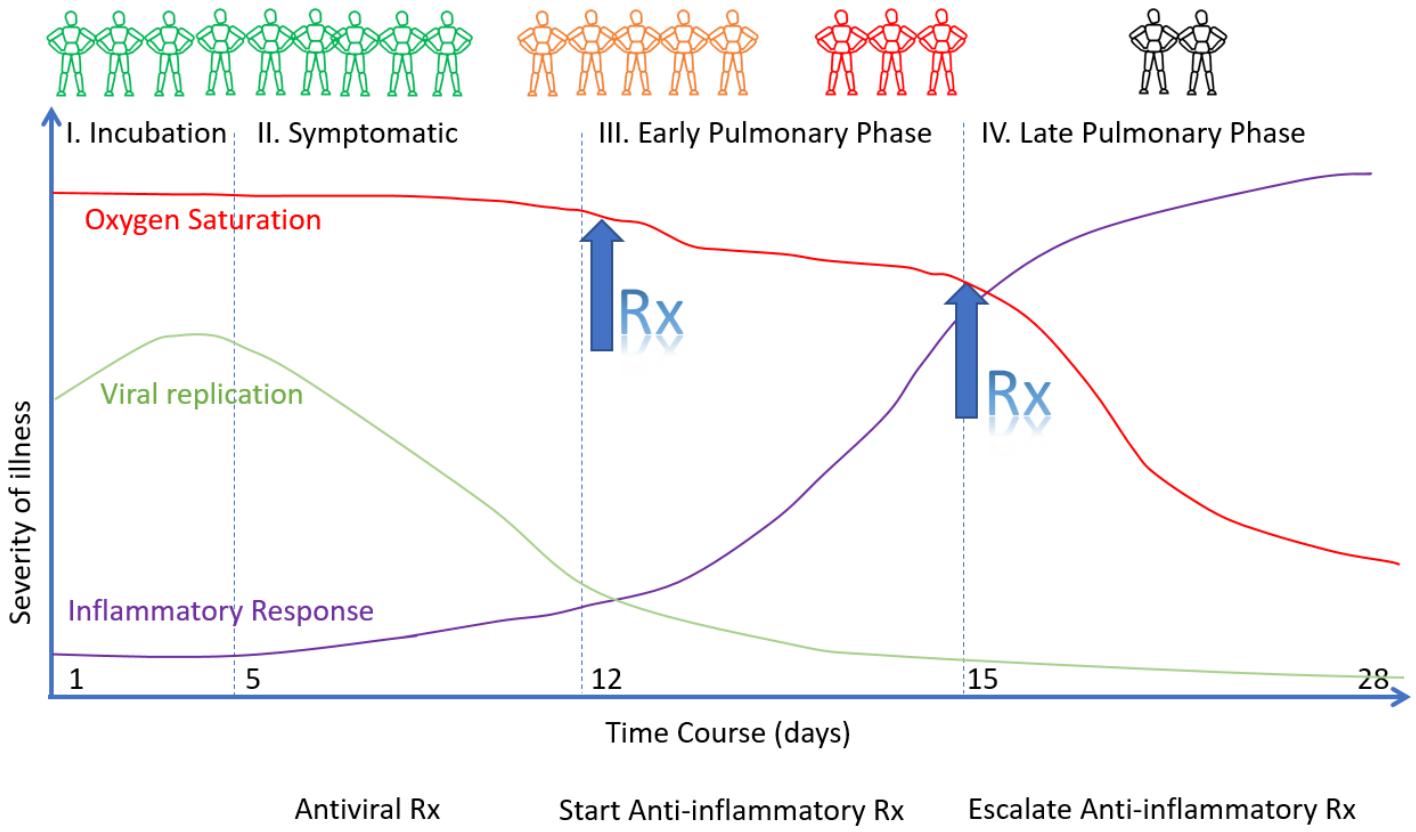


Figure 3. Time course of laboratory tests for COVID-19

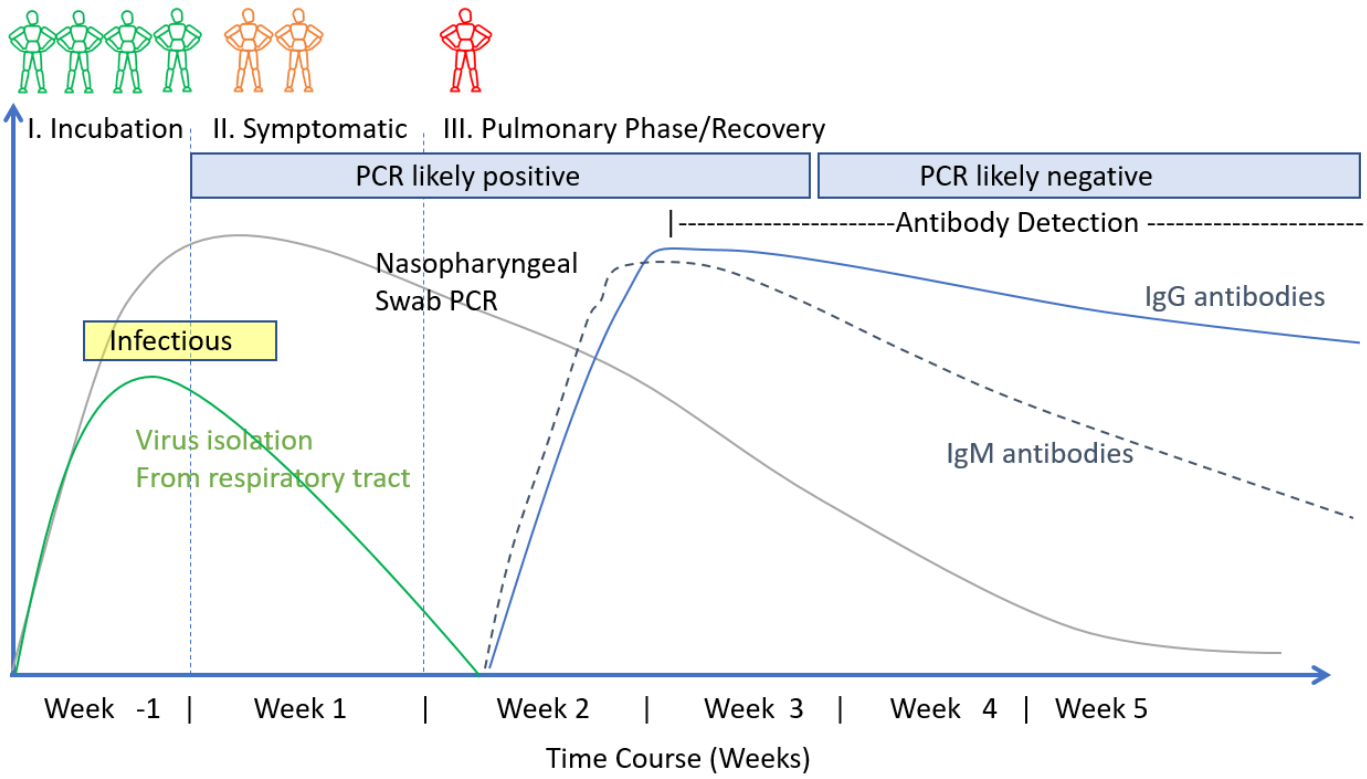
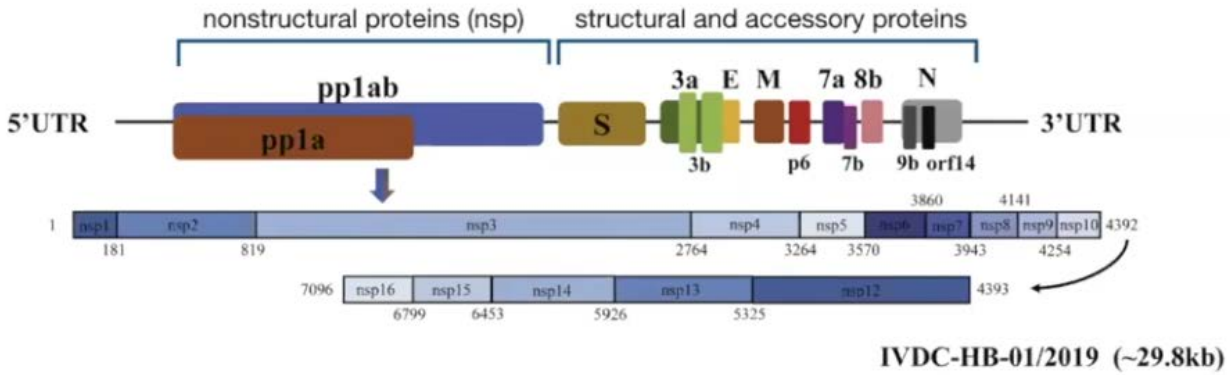


Figure 4. SARS-Co-V-2 RNA genome



It should be noted that there is no cure or "Magic-bullet" for the prevention or treatment of COVID-19. However, recently, a number of therapeutic agents have shown promise for both the prevention and treatment of COVID-19 including ivermectin, Vitamin D, quercetin, melatonin and corticosteroids. Furthermore, it is likely that no single drug will be effective in treating this complex disease and that multiple drugs with different mechanisms of action and used in specific phases of the disease will be required.

Prophylaxis

While there is no "Level 1 evidence" that this "cocktail" will prevent/mitigate against COVID-19 we believe there is significant evidence supporting the efficacy of the individual agents included in the prophylactic protocol. This 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. Furthermore, it should be noted that there is emerging evidence suggesting that IVERMECTIN may be highly effective in the prevention and treatment of COVID-19. It is important to emphasize that ALL of the medications included in our prophylactic regimen are inexpensive, safe, and widely available.

- Vitamin D3 1000-3000 iu/day. Note RDA (Recommended Daily Allowance) is 800-1000 iu/day. The safe upper-dose daily limit is likely < 4000 iu/day. [1-22] 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. [7-22]
- Vitamin C 500 mg BID (twice daily) and Quercetin 250 mg daily. [23-34] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [35] 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. [36-39] 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.[40] In women high consumption of soya was associated with elevated TSH concentrations.[41] 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. [42] 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. [43-50]
- Zinc 30-50 mg/day (elemental zinc). [23,30,32,33,51-55]
- B complex vitamins [56-60]
- Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561). 200 ug/kg (12 mg) 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). 150-200 ug/kg (or 12 mg) Day 1, Day 3 and then every 4 weeks. [5,61,62] (also see ClinTrials.gov NCT04425850). NB. Ivermectin has a number of potentially serious drug-drug interactions. Please check for potential drug interaction at Ivermectin Drug Interactions - Drugs.com. The most important drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs and certain anti-fungal drugs.

- *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]

Symptomatic patients at home **(for the duration of acute symptoms)**

- 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) [50]
- Vitamin D3 2000-4000 iu/day. Calcifediol 200 µg is an alternative. [63]
- Highly recommended: Ivermectin 150-200 ug/kg orally (repeat on day 3). [1-5,62,64-74] See Table 1, Figure 5 and ClinTrials.gov NCT04523831. See drug-drug interactions above.
- ASA 81 -325 mg/day (unless contraindicated). ASA has antiinflammatory, antithrombotic, and antiviral effects.[75,76] Platelet activation may play a major role in propagating the prothrombotic state associated with COVID-19. [77]
- B complex vitamins
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction) [78-84].
- *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. [32,85-88]
- *Optional:* Interferon-α/β s/c, nasal spray or inhalation. [89-92] It should be noted that Zinc potentiates the effects of interferon.[93,94]
- 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.[95] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[95] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [96] The following guidance is suggested: [95]
    - 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 extremely controversial.[97] 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. [98-115] 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).[107,116-118] Finally, it should be recognized that those studies which are widely promoted to support the use of HCQ are severely methodologically flawed.[119-122]

- *Not recommended:* Systemic or inhaled corticosteroids *(*budesonide). In the early symptomatic (viral replicative phase), corticosteroids may increase viral replication and disease severity.[123] An OpenSAFELY analysis in patients with COVID-19 demonstrated a higher risk of death in COPD and asthmatic patients using high dose ICS. [124] 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.

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FRONT LINE COVID-19 CRITICAL CARE ALLIANCE
PROPHYLAXIS & TREATMENT PROTOCOLS FOR COVID-19

I-MASK+

PROPHYLAXIS & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

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PROPHYLAXIS PROTOCOL

Ivermectin	***Prophylaxis for high risk individuals*** 0.2 mg/kg* – one dose on day 1 and day 3, then take one dose every 4 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
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.

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