I-CARE℠

EARLY COVID TREATMENT

A guide to early treatment of COVID-19

April 2024

- Updates: Added short-term use of fluvoxamine to second line treatments

FLCCC® ALLIANCE

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Summary of Suggested Therapies

First Line Treatments *(in order of priority, not all required)*	**Second Line Treatments**
Ivermectin 0.4 to 0.6 mg/kg one dose daily for at least 5 days, or until symptoms resolve	Nitazoxanide (NTZ) 500 mg twice a day for 5 days
Hydroxychloroquine (HCQ) 200 mg twice a day for 5-10 days	Fluvoxamine 25-50 mg daily for 7 days (use with great caution in patients with acute COVID infection, especially in young patients)
Mouthwash and nasal spray three times a day	Vitamin D (see dosing chart)
Quercetin 250–500 mg twice a day	Lactoferrin 100-400 mg daily Diphenhydramine (Benadryl) 25-50 mg every 6 hours until symptoms resolve
Nigella sativa (black cumin) If using seeds, take 80 mg/kg once a day (or 400 to 500 mg of encapsulated oil twice a day)	B complex vitamins
Honey 1 g/kg one to two times a day	N-acetyl cysteine (NAC) 600-1200 mg orally twice a day
Melatonin 5-10 mg at night	Omega-3 fatty acids 4 g daily
Curcumin (turmeric) 500 mg twice a day	
Zinc 75–100 mg daily	
Aspirin (unless contraindicated) 325 mg daily	
Bifidobacterium Probiotics (avoid added sugars)	
Vitamin C 500–1000 mg twice a day	
Home pulse oximetry monitoring	

Disclaimer

The information in this document is our recommended approach to COVID-19 based on the best (and most recent) literature. It is provided as guidance to healthcare providers worldwide on the early 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 provider before starting any medical treatment.

As this is a highly dynamic topic, we will update these guidelines as new information emerges. Please ensure you are using the latest version of this protocol.

The Use of "Off-Label" Drugs

Once the FDA approves a prescription medication, federal laws allow any U.S. physician to prescribe the duly approved drug for any reason. In fact, 30 percent of all prescriptions are for off-label uses, written by American doctors exercising their medical judgment.

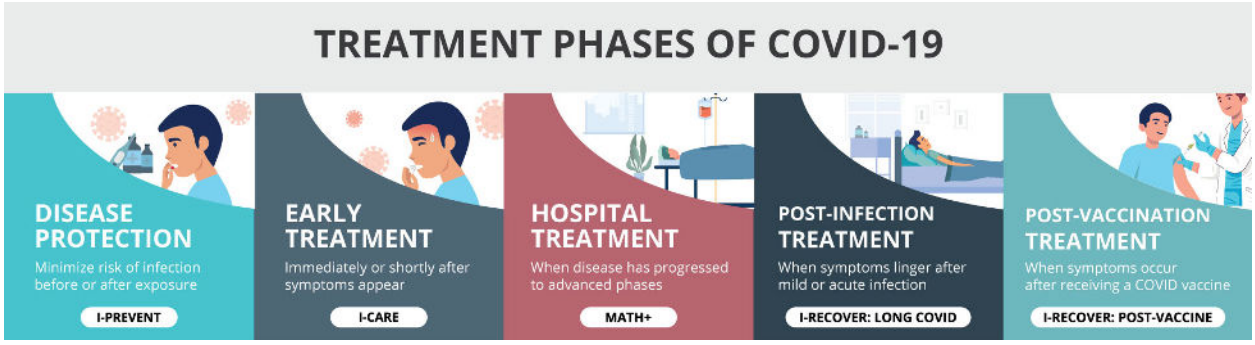
Many states — including Nebraska, Tennessee, and Missouri — have asserted the right of physicians to prescribe, and pharmacists to dispense, off-label drugs such as ivermectin and hydroxychloroquine for the treatment of COVID-19. For example, Nebraska's Attorney General, Doug Peterson, released a legal opinion in October 2021 saying he did not see data to justify legal action against healthcare professionals who prescribe ivermectin or hydroxychloroquine. (1) In May 2022, Tennessee approved a standing order allowing ivermectin to be dispensed over the counter.

Overview of I-CARE

At the beginning of the pandemic, FLCCC developed the MATH+ protocol to provide guidance for treating the pulmonary phase of COVID-19, with the goal of reducing hospital mortality. However, it soon became obvious that our emphasis needed to shift to prevention and early treatment to protect patients from requiring hospitalization and dying from this largely preventable disease.

It is critical to recognize that infection with SARS-CoV-2, the virus that causes the disease, progresses through several stages. Treatment is therefore highly stage-specific (see Figures 1-3 and Table 1). COVID-19 is a clinical diagnosis; a confirmatory antigen or PCR test is not required. Treatment should be initiated immediately after the onset of flu-like symptoms.

Figure 1. Treatment Phases of COVID-19



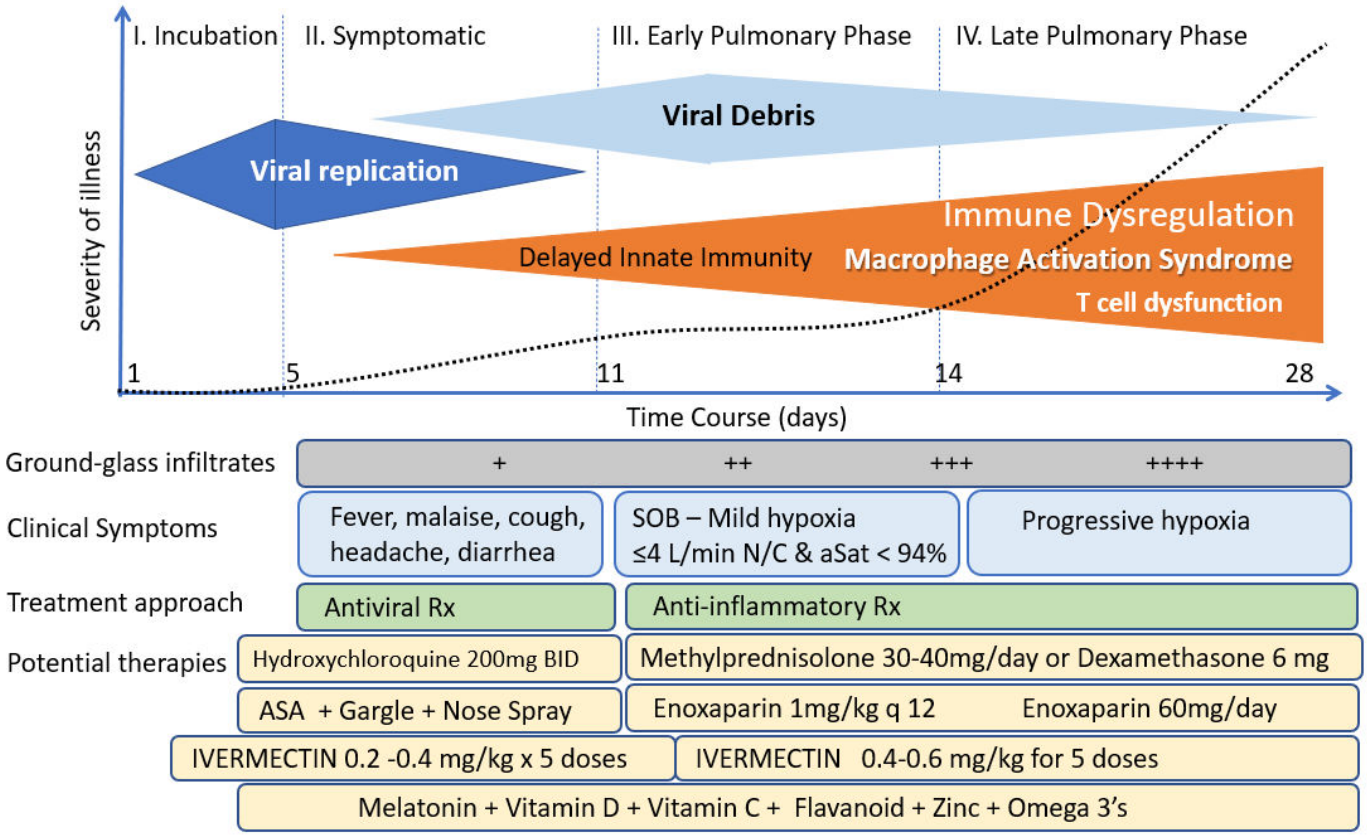
Source: FLCCC

It is likely that no single drug will be effective in treating this complex disease and that multiple therapies and drugs with different mechanisms of action used in specific phases of the disease will be required. A growing body of evidence suggests that many of these agents may act synergistically during various phases of the disease. (2-4)

While there is no cure or "magic bullet" for COVID-19, a number of therapeutic agents have shown benefit for early treatment (see Figure 4). The drugs that are the most clinically useful include ivermectin, hydroxychloroquine, zinc, quercetin, melatonin, fluvoxamine, curcumin (turmeric) and *Nigella sativa.*

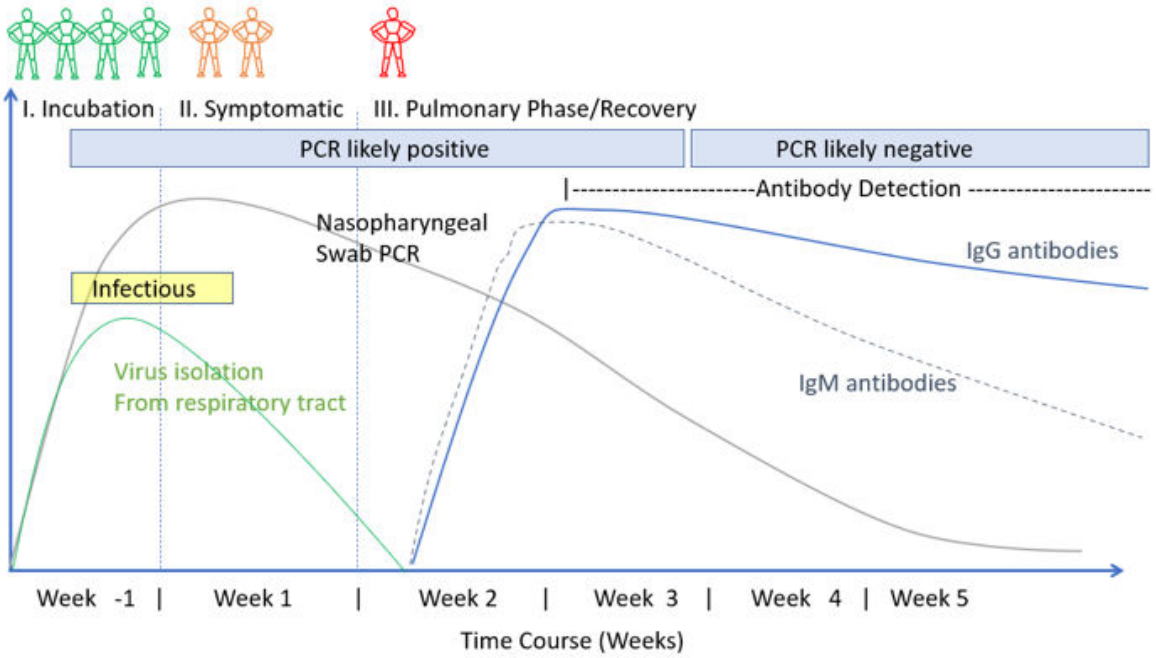
Early treatment is critical and the most important factor in managing this disease. The relentless malpractice of deliberately withholding effective early COVID treatments, and of forcing the use of toxic remdesivir in hospitalized patients, may have unnecessarily killed up to 800,000 Americans. (5)

Figure 2. The Course of COVID-19 and General Approach to Treatment



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Figure 3. Time Course of Laboratory Tests for COVID-19



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Figure 4. Meta-Analysis of Early Treatment Studies

Source: c19early.com

Figure 4b

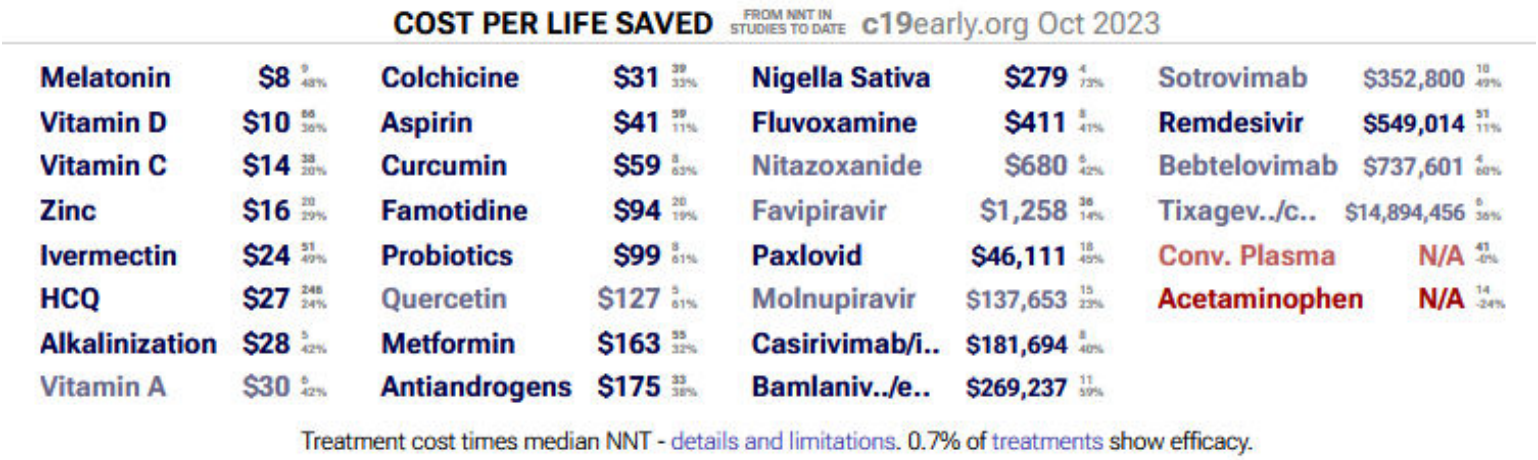


Figure 5a. Meta-Analysis of Ivermectin for COVID-19

Source: ivmmeta.com

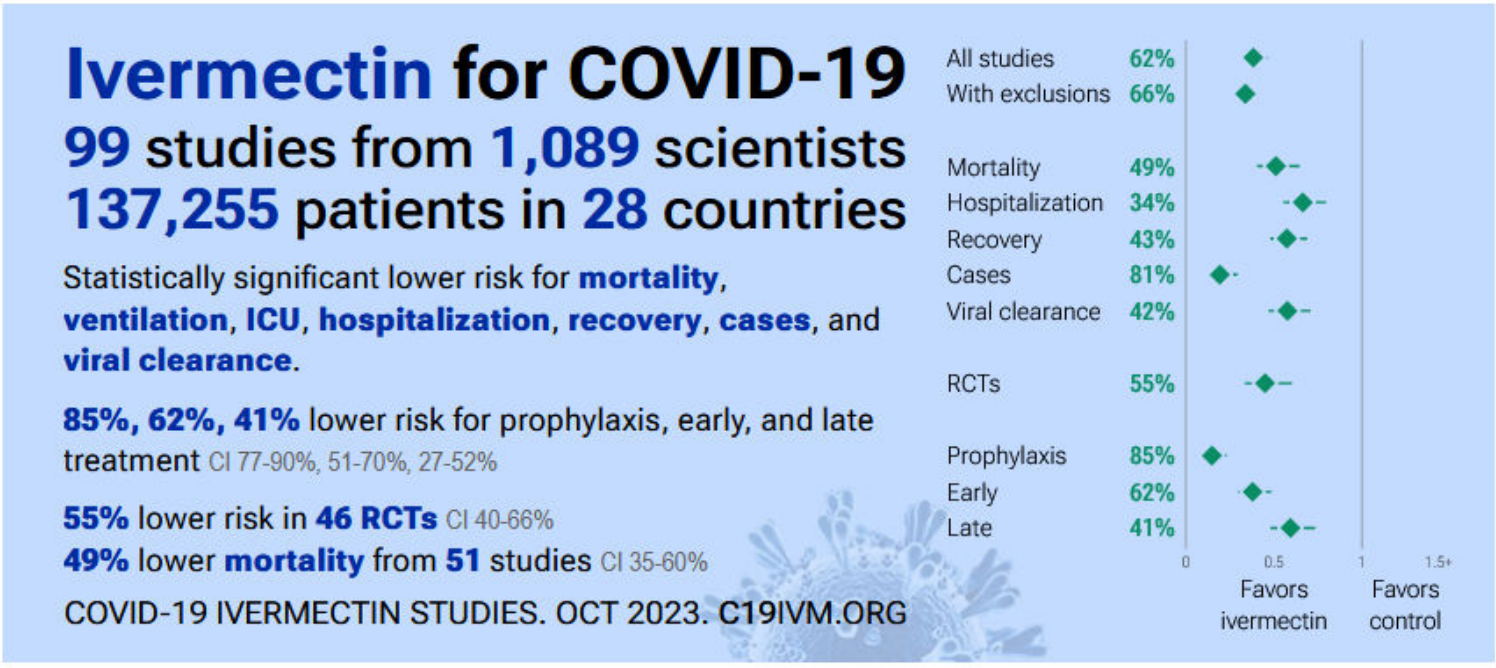


Figure 5b. Meta-Analysis of Ivermectin for Early Treatment Studies

Source: ivmmeta.com

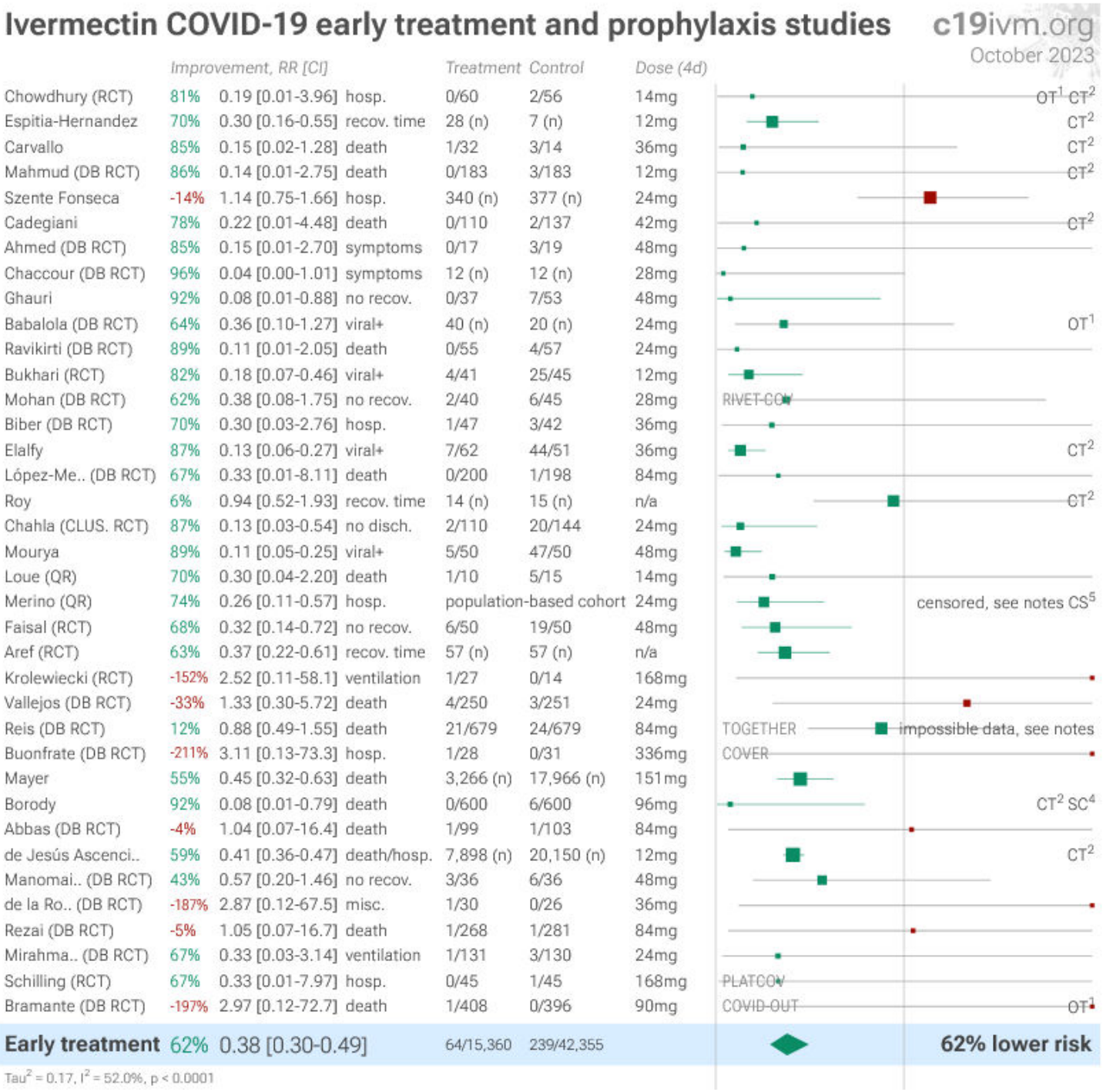


Table 1. Pharmacological Therapy for COVID-19 by Stage of Illness: What has worked and what has failed

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Corticosteroids	n/a	Trend to harm	BENEFIT
Anti-androgen Rx	? Benefit	Benefit	BENEFIT
LMWH	n/a	n/a	BENEFIT
Paxlovid/Molnupiravir	n/a	No Benefit	n/a
Monoclonal Abs	No Benefit	No benefit	HARM
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

Source: FLCCC

First Line Treatments

(in order of priority, not all required)

- **Ivermectin** 0.4 to 0.6 mg/kg – one dose daily for at least 5 days, or until symptoms resolve. Multiday treatment has been shown to be more clinically effective than single-day dosing. If symptoms persist longer than 7 days, consult a healthcare provider.

  Ivermectin has been demonstrated to be highly effective against the Omicron variant at a dose 0.4 mg/kg, when taken early. (6) Higher doses (0.6 mg/kg) may be required in:

  - Cases where treatment starts on or after 5 days of symptoms;
  - Regions with more aggressive variants;
  - Patients in the pulmonary phase of disease;
  - Patients with extensive CT involvement; or
  - Patients with extensive comorbidities or risk factors (i.e., older age, obesity, diabetes, etc.)

  Ivermectin is a remarkably safe drug with minimal adverse reactions (almost all minor). (7) However, potential drug-drug interactions should be reviewed before prescribing ivermectin (see Table 2). The most important drug-drug interactions occur with *cyclosporin, tacrolimus, antiretroviral drugs*, and certain antifungal drugs.

  Due to a possible interaction between quercetin and ivermectin, these drugs should not be taken simultaneously. Instead, they should be staggered throughout the day. For COVID treatment, ivermectin is best taken with a meal or just following a meal, for greater absorption (see Table 3).

Table 2. Drug Interactions with Ivermectin

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

SERIOUS (5) Use Alternative	MONITOR CLOSELY (50)	
erdafitinib	amiodarone	lonafarnib
lasmiditan	atorvastatin	loratadine
quinidine	berotralstat	lovastatin
sotorasib	bosutinib	nefazodone
tepotinib	clarithromycin	nicardipine
	clotrimazole	nifedipine
	dronedarone	nilotinib
	elagolix	phenobarbital
	eliglustat	phenytoin
	erythromycin base	ponatinib
	erythromycin ethylsuccinate	quercetin
	erythromycin lactobionate	ranolazine
	erythromycin stearate	rifampin
	felodipine	ritonavir
	fosphenytoin	sarecycline
	fostamatinib	simvastatin
	glecaprevir/pibrentasvir	sirolimus
	indinavir	St John's Wort
	istradefylline	stiripentol
	itraconazole	tacrolimus
	ivacaftor	tolvaptan
	ketoconazole	trazodone
	lapatinib	tucatinib
	levoketoconazole	verapamil
	lomitapide	warfarin

Source: Medscape

- **Hydroxychloroquine (HCQ)** 200 mg twice a day for 5-10 days. (8-11) Best taken with zinc. HCQ may be taken in place of, or together with, ivermectin. While ivermectin should be avoided in pregnancy, the FDA considers HCQ safe in pregnancy.

  As the Omicron variant uses the lysosomal pathway to gain cell entry, HCQ may be the preferred drug for this variant. (12)

  Some 200 peer-reviewed studies (C19Study.com) by government and independent researchers deem HCQ safe and effective against coronavirus, especially when taken prophylactically or when taken in the initial stages of illness, along with zinc. Unfortunately, most of the RCTs conducted to date used toxic doses of HCQ and/or were given very late in the disease, and appear to have been clearly designed to fail. (5) Instead of using the standard treatment dose of 400 mg/day, the 17 WHO studies administered a borderline lethal *daily* dose starting with 2,400 mg on day 1 and using 800 mg/day thereafter. Brazilian prosecutors have accused the authors of one study of committing homicide by purposefully poisoning and murdering the elderly subjects of their study. (13)

- **Naso-Oropharyngeal hygiene** (see figures 6 and 7). (14)
  MOUTHWASH: Antiseptic-antimicrobial mouthwashes have been shown in research studies to inhibit SARS-CoV-2 replication and reduce viral load. Look for products containing chlorhexidine, povidone-iodine, cetylpyridinium chloride and the combination of eucalyptus, menthol and thymol (Listerine™). In patients with symptomatic disease treated at home, a 1% povidone-iodine mouthwash/gargle — together with nasal drops — resulted in a dramatic reduction in morbidity, hospitalization and death. (15) Note that some mouthwashes have reportedly contributed to temporary tooth staining in certain individuals. Discontinue use and try a different product if this problem arises.

  NASAL SPRAY: A nasal spray with 1% povidone-iodine (for example Immune Mist™, CofixRX™, Viraldine™ or IoNovo™) administered 2-3 times per day is recommended in symptomatic patients. Carrageenans are potent inhibitors of SARS-CoV-2, and a carrageenan nasal spray dramatically alters the course of infection. (15-21) Nasal irrigations/nasal spray with saline, neutral electrolyzed water (22, 23) and Nitric Oxide (NO) (24) have proven clinical benefit. Similarly, a saline/Xylitol (Xlear™) nasal spray is likely to be beneficial. Oropharyngeal hygiene will likely reduce the viral load in the upper airways, thereby reducing the risk of symptomatic disease and disease severity.

- **Quercetin** 250–500 mg twice a day. Quercetin is a plant phytochemical (flavonoid) with broad spectrum anti-inflammatory, antioxidant, antiviral, anticoagulant, and immune-

modulatory properties. (25-32) Quercetin inhibits SARS-COV-2 replication by a number of mechanisms. (29, 32-34) In addition, quercetin inhibits mast cells, (35) and has been demonstrated to reduce neuroinflammation. (36) The major limitation of supplemental quercetin is its poor solubility and low oral absorption. (37) A lecithin-based formulation (Quercetin Phytosome®, Life Extension Bio-Quercetin) and a nanoparticle formulation have shown markedly improved bioavailability. (38, 39) Quercetin Phytosome (250-500 mg twice a day) has shown promising results in both the prevention and treatment of symptomatic COVID-19. (40, 41)

Due to the possible drug interaction between quercetin and ivermectin these drugs should not be taken simultaneously (i.e., should be staggered morning and night). See Table 3 for a recommended medication schedule. The use of quercetin has rarely been associated with hypothyroidism. (42) The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with subclinical thyroidism. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored. The safety of quercetin and flavonoids in pregnancy has not been established and they should probably be avoided.

- ***Nigella sativa*** **(black cumin)** If using seeds, take 80 mg/kg once a day (or 400 to 500 mg of encapsulated oil twice a day) and honey 1 g/kg one to two times a day. A randomized placebo-controlled study demonstrated that the combination of honey and *Nigella sativa* hastened recovery, decreased viral shedding**,** and reduced mortality in patients with both moderate and severe COVID-19 infection. (43) In addition, it should be noted that *Nigella sativa* is a zinc ionophore.

- **Melatonin** 5-10 mg at night. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 infections. Some patients are intolerant to melatonin, having very disturbing and vivid dreams; in these patients it may be best to start with a 1-2 mg slow-release tablet and increase slowly, as tolerated. Melatonin undergoes significant first pass metabolism in the liver with marked individual variation; this explains the wide dosing requirement. Slow- or extended-release preparations are preferred, as this minimizes the risk of bad dreams.

- **Curcumin (turmeric)** 500 mg twice a day. Curcumin, the active ingredient in turmeric, has antiviral activity against SARS-CoV-2. In addition, this spice has anti-inflammatory and immune-modulating properties. (44-48) Curcumin has low solubility in water and is poorly absorbed by the body; (49) consequently, it is traditionally taken with full fat milk and black pepper, which enhance its absorption. Nano-curcumin preparations or formulations designed to enhance absorption are recommended. (50-53) Due to the

rare complication of hepatic injury (hepatitis), long-term treatment (> 14 days) is not suggested. (54)

- **Zinc** 75–100 mg/day**.** Take with HCQ. Zinc supplements come in various forms, including zinc sulfate, zinc citrate, zinc gluconate, and zinc oxide.

- **Aspirin (acetylsalicylic acid or ASA)** 325 mg daily (unless contraindicated). Aspirin has anti-inflammatory, antithrombotic, immunomodulatory, and antiviral effects. (55-57) Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. (58-60)

- **Bifidobacterium Probiotics** (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome. Suggested probiotics include Megasporebiotic (Microbiome labs), TrueBifidoPro (US Enzymes) and yourgutplus+. (61) NOTE: Depending on the brand, these products can be very high in sugar, which promotes inflammation. Look for brands without added sugar or fruit jellies and choose products with more than one strain of lactobacillus and bifidobacteria. Try to choose probiotics that are also gluten-free, casein-free, and soy-free.

- **Vitamin C** 500–1000 mg twice a day.

- **Metformin**. In the COVID-OUT trial, an incrementing dose of metformin over 14 days was demonstrated to reduce the rate of hospitalization, (62) however more importantly the cumulative incidence of long COVID by day 300 was 6·3% in participants who received metformin and 10·4% in those who received identical metformin placebo (hazard ratio [HR] 0·59, 95% CI 0·39–0·89; p=0·012). (63) The metformin dose was titrated over 6 days: 500 mg on day 1, 500 mg twice daily on days 2–5, then 500 mg in the morning and 1000 mg in the evening up to day 14. It should be noted that in the COVID-OUT trial patients did not receive aggressive early treatment of COVID-19. Nevertheless, metformin should be considered in patients with acute Covid-19 at increased risk of long COVID, i.e. female sex, obesity, more severe symptoms, lower socioeconomic class, smoking as well as co-morbidities. (64, 65)

- **Home pulse oximetry** monitoring is recommended in symptomatic patients, due to asymptomatic hypoxia. The limitations of home pulse oximeters should be recognized, and validated devices are preferred. (66) Take multiple readings over the course of the day, and regard any downward trend as ominous. (66) Baseline or ambulatory desaturation under 94% should prompt consultation with primary or telehealth

provider, or evaluation in an emergency room. (67) We suggest the following guidance: (66)

- Only accept values associated with a strong pulse signal
- Observe readings for 30–60 seconds to identify the most common value
- Warm up extremities prior to taking a measurement
- Use the middle or ring finger
- Remove nail polish from the finger on which measurements are made

Table 3. Proposed Medication Schedule for First Line Treatments

	Breakfast	Lunch	Dinner	Bedtime
Ivermectin		√		
Hydroxychloroquine	√		√	
Mouthwash/nasal spray	√	√	√	
Quercetin	√		√	
Nigella sativa		√		
Melatonin				√
Curcumin	√		√	
Zinc	√		√	
Aspirin	√			
Probiotics		√		
Vitamin C	√		√	
Pulse oximetry	√	√	√	

Source: FLCCC

Table 4. How to Calculate Ivermectin Dose

Note that ivermectin is available in different strengths (e.g., 3, 6 or 12 mg) and administration forms (tablets, capsules, drops, etc.). Note that tablets can be halved for more accurate dosing, while capsules cannot.

How much do I weigh?		What dose does the protocol say?			
In pounds	In kilos	0.2 mg/kg	0.3 mg/kg	0.4 mg/kg	0.6 mg/kg
70–90	32–41	6-8 mg	10-12 mg	13-16 mg	19-25 mg
91–110	41–50	8-10 mg	12-15 mg	17-20 mg	25-30 mg
111–130	50–59	10-12 mg	15-18 mg	20-24 mg	30-35 mg
131–150	60–68	12-14 mg	18-20 mg	24-27 mg	36-41 mg
151–170	69–77	14-15 mg	21-23 mg	27-31 mg	41-46 mg
171–190	78–86	16-17 mg	23-26 mg	31-35 mg	47-52 mg
191–210	87–95	17-19 mg	26-29 mg	35-38 mg	52-57 mg
211–230	96–105	19-21 mg	29-31 mg	38-42 mg	58-63 mg
231–250	105–114	21-23 mg	32-34 mg	42-45 mg	63-68 mg
251–270	114–123	23-25 mg	34-37 mg	46-49 mg	68-74 mg
271–290	123–132	25-26 mg	37-40 mg	49-53 mg	74-79 mg
291–310	132–141	26-28 mg	40-42 mg	53-56 mg	79-85 mg

Treatment of Current Circulating Omicron variants

Limited data is available on the clinical implications of the current circulating Omicron 'subvariants'. The subvariants are spiking globally because they spread faster than other circulating subvariants. Furthermore, these variants have demonstrated 'neutralization escape' from both the mRNA vaccine and from previous infection. (68) Indeed, previous vaccination appears to be a risk factor for symptomatic disease. The newer variants appear to differ clinically from previous variants due to the early onset of bacterial pneumonia. However, available data suggests the risk of hospitalization and death is similar between the current variants and earlier omicron variants (BA.1 and BA.2). (69, 70)

While the optimal treatment approach to the symptomatic patient is unclear, it is best to risk stratify symptomatic patients. Risk factors for hospitalization and death include age over 60, comorbidities especially obesity and the metabolic syndrome, poor ambulatory status, delayed treatment, high D-dimer, recently vaccinated, and severe symptoms. As has been our approach throughout the pandemic early treatment is critical and it is important to start treatment at the earliest signs of infection and not to delay treatment based on confirmatory tests. Ideally, all susceptible patients should have a "What-if" kit available at home.

In low-risk patients we suggest the following treatment approach (in order of priority).

- Hydroxychloroquine 200 mg twice daily or 400 mg daily for 5 days **or**
- Ivermectin 0.4-0.6 mg/kg once daily for 5 days (take with a fatty meal**) or**
- Nitazoxanide 500 mg three times a day for 5 days (taken with a fatty meal).
- Zinc 75-100 mg for 5 days.
- Antiseptic/antimicrobial mouthwash 3 times daily.
- Nasal spray with 1% povidone-iodine, Carrageenan, Nitric Oxide, or nasal irrigations with saline or neutral electrolyzed water 2-3 times daily.
- Melatonin 5-10 mg at night (slow-release formulation preferred).
- *Nigella sativa* seeds 80 mg/kg once a day (or 400-500 mg encapsulated oil twice a day) with or without honey 1 g/kg
- Aspirin (acetylsalicylic acid or ASA) 325 mg daily (unless contraindicated).
- Home pulse oximetry.

High-risk patients:

- The combination of both HCQ and ivermectin
- Nattokinase 2000-4000 FU/day for 15 days ***OR*** Apixaban 5 mg daily for 15 days ***OR*** Rivaroxaban 10 mg daily for 15 days. The escalated use of anticoagulants should only be considered in patients with a low risk of bleeding. Furthermore, the risk of serious bleeding increases as the number of anticoagulant drugs is increased.
- Spironolactone 200 mg once daily for 7 days (avoid in patients with impaired renal function).

If symptoms have not markedly improved by day 3 of treatment, the following medications should be started. NOTE: physicians should provide scripts for these medications at first visit.

- Prednisolone 60 mg daily for 5 days.
- Oral antibiotic:
    - Doxycycline 100 mg twice daily for 5 days (Doxycycline may act synergistically with ivermectin and maybe the antibiotic of first choice.) (71-76); ***OR***
    - Azithromycin (Z-pack) 500 mg day 1, then 250 mg daily for 4 days; ***OR***
    - Amoxicillin/Clavulanate (Augmentin) 500 mg/125 mg tablet twice daily for 7 days.

Figure 6. Naso-Oropharyngeal Hygiene

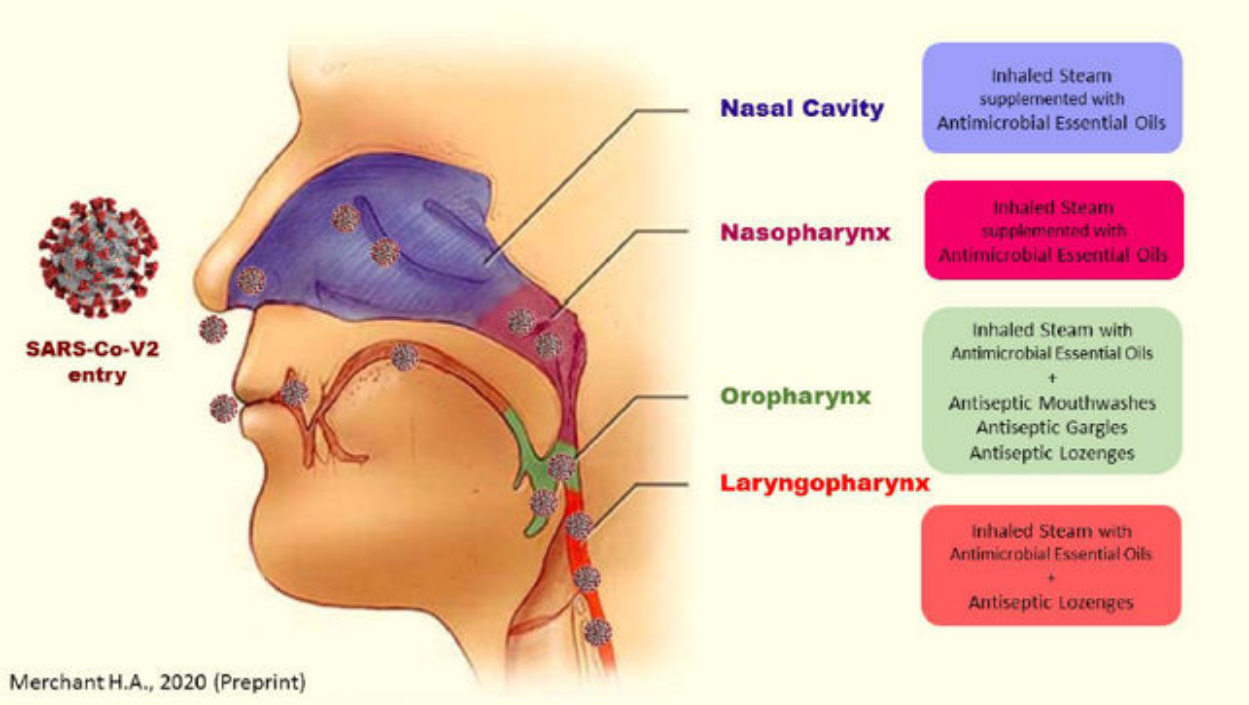


Figure 7. Commercial Products Available for Naso-Oropharyngeal Hygiene

Source: FLCCC

Second Line Treatments

- **Nitazoxanide (NTZ)** 500 mg twice a day for 5 days was shown to reduce disease progression, hospitalization and death when used early in outpatients with mild to moderate disease. (77, 78) NTZ should be taken with a meal (preferably fatty food) as this enhances absorption. The combination of NTZ and ivermectin has been shown to reduce viral clearance and symptom progression in outpatients with COVID-19. (79, 80) NTZ should be considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. 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. (81, 82) Like ivermectin, NTZ has broad spectrum antiviral activity that includes SARS-CoV-2. (82-85) Furthermore, as NTZ and ivermectin have differing modes of action, it is likely that these two drugs have synergistic antiviral and anti-inflammatory effects. (80, 83, 86) It should be noted that while NTZ is relatively cheap in most of the world, it is very expensive in the United States and has therefore been moved to second line treatments.

- **Fluvoxamine combination therapy.** Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that activates sigma-1 receptors decreasing cytokine production. (87, 88) In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus, and inhibits melatonin degradation. (89, 90) SSRIs deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation. (91-93) The use of antidepressants has been associated with a lower risk of intubation and death in patients hospitalized with COVID-19. (94-97) Previous studies have demonstrated that fluvoxamine 25-50 mg twice a day for 1 week improves the outcome of patients with COVID-19. (87, 88, 94, 95, 98-101) A recent multi-arm, placebo-controlled study demonstrated that the addition of bromhexine (8 mg twice a day for 10 days) or cyproheptadine 4 mg three times a day for 14 days) resulted in significantly better outcomes than fluvoxamine alone in patients with mildly symptomatic COVID-19 randomized within 48 hours of symptom onset.(102) In this study, all the patients receiving fluvoxamine had more rapid symptom resolution, greater viral clearance and lower risk of hospitalization than those receiving placebo. Fluvoxamine was dosed in a dose escalation/de-escalation protocol, namely, 50 mg orally, one tablet in the morning and one tablet at bedtime for the first two days, then escalated to one 50 mg one tablet in the morning and two tablets before bedtime for days 3 through 12, ending with one 50 mg one tablet in the morning and one tablet at bedtime for days 13 and 14.

NOTE: Fluvoxamine is a Selective Serotonin Reuptake Inhibitor (SSRI), a class of drugs that is associated with significant side effects, particularly with prolonged use (see 'Managing Depression' monograph). Short-term fluvoxamine should be used with great caution in patients with acute COVID infection, especially in young patients. Some individuals who are prescribed fluvoxamine experience acute anxiety, which may progress to mania. This serious side effect may occur after the first dose. (103) Patients prescribed this medication should be cautioned about this side effect and carefully monitored to prevent escalation to suicidal or violent behavior.

- **Vitamin D**. For patients with acute COVID-19 infection, CALCIFEDIOL as dosed in Table 5 is suggested (**CALCIFEDIOL** and not Vitamin D3 or calcitriol is suggested). Vitamin D3 requires hydroxylation in the liver to become the 25(OH)D, causing a lag of about 3-4 days. (104) This may explain the lack of benefit of Vitamin D3 in patients with severe COVID-19. Calcifediol is already 25-hydroxylated and, thus, it bypasses the liver and become available in the circulation within four hours of administration. Among other benefits, it permits boosting the immune system and improving the functions of other systems within a day. Orally administered, a single dose of calcifediol raises serum 25(OH)D concentration within four hours. (105-109) We recommend against the use of **calcitriol**, [1,25(OH)2D] which has minimal effect on immune cells. Moreover, the effective dose (ED50) and toxic level overlap at the dose currently suggested for COVID-19. (110)

- **Lactoferrin and diphenhydramine (Benadryl).** Lactoferrin 100-400 mg daily; Diphenhydramine 25-50 mg every 6 hours until symptom relief. Lactoferrin, a protein found in milk which is also available as an over-the-counter supplement, is a natural antiviral and antibacterial. It also helps the body transport and absorb iron and can inhibit SARS-CoV-2 infectivity. (111)

  The antihistamine diphenhydramine (Benadryl), with on-target binding to the Histamine-1 receptor, has known off-target effects at the sigma-1 receptor. (112) Diphenhydramine has been demonstrated to inhibit SARS-CoV-2 infectivity. (113)

  Lactoferrin is a naturally occurring, non-toxic glycoprotein that is orally available as a nutritional supplement and has established in vitro antiviral efficacy against a wide range of viruses, including SARS-CoV-2. (114-118) In addition, lactoferrin is synthesized by exocrine glands and neutrophils and possesses immunomodulatory and anti-inflammatory effects. (116)

  An in vivo experiment demonstrated that oral and intranasal bovine lactoferrin resulted in more rapid clearance of SARS-CoV-2 in COVID-19 infected patients. (119) In an in-vitro

model, Ostrov et al demonstrated that the combination of lactoferrin and diphenhydramine inhibited 99.97% of N-protein RNA copies, a 3-log reduction that was highly significant. (111) These data demonstrate that the combination of two over-the-counter compounds with well characterized safety profiles has synergistic effects on inhibition of SARS-CoV-2.

- **B complex vitamins.**

- **N-acetyl cysteine (NAC) 600-1200 mg orally twice a day.** NAC is the precursor of reduced glutathione. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis. (120) Based on a broad range of antioxidant, anti-inflammatory and immune-modulating mechanisms, the oral administration of NAC likely plays an adjuvant role in attenuating the severity of COVID-19. (120-125) Several studies showed that NAC is well absorbed by the intestine and that a supplementation with NAC is effective for increasing GSH levels. Oral glutathione is poorly absorbed and is generally not recommended. (126, 127) However, acetyl glutathione is more lipophilic than glutathione, sufficiently so to be taken up intact by cells, and has been shown to rapidly raise intracellular GSH levels. A combination supplement that contains acetyl glutathione, NAC and Vitamin C may enhance the bioavailability of glutathione. In addition, liposomal glutathione has been demonstrated to increase tissue levels, antioxidant capacity and immune function. (128)

- **Omega-3 fatty acids**. Vascepa (Ethyl eicosapentaenoic acid) 4 g daily or Lovaza (EPA/DHA) 4 g daily; alternative DHA/EPA 4 g 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, (129-131) which is critical in the management of COVID-19. In addition, Omega-3 fatty acids may have antiviral properties. (132-136)

Table 5. A Single-Dose Regimen of Calcifediol to Rapidly Raise Serum 25(OH)D above 50 ng/mL

Using a regimen of calcifediol * to rapidly raise serum 25(OH)D concentration above 50 ng/mL (125 nmol/L) in medical emergencies (i.e., to raise serum levels within four hours). ** A single body weight based, oral dose is calculated: 0.014 mg/kg body weight.

Weight (lbs)	Weight (kg)	Calcifediol ~ (mg) #	If Calcifediol Is Not Available: Bolus/Loading Dose of Vitamin D_3 ##
8–14	4–6	0.05	20,000
15–21	7–10	0.1	40,000
22–30	10–14	0.15	60,000
31–40	15–18	0.2	80,000
41–50	19–23	0.3	100,000
51–60	24–27	0.4	150,000
61–70	28–32	0.5	200,000
71–85	33–39	0.6	240,000
86–100	40–45	0.7	280,000
101–150	46–68	0.8	320,000
151–200	69–90	1.0	400,000
201–300	91–136	1.5	600,000
>300	>137	2.0	800,000

Source: SJ Wimalawansa (with permission)(137)

* Calcifediol [partially activated vitamin D3, 25(OH)D]. ** Use the earliest possible in person with COVID-19, sepsis, Kawasaki disease, multisystem inflammatory syndrome, acute respiratory distress syndrome, burns, and vitamin D deficiency in early pregnancy and other clinical emergencies. # Measurement (or the concentration) of serum 25(OH)D is unnecessary. ## If calcifediol is unavailable, the equivalent dose of vitamin D is administered, preferably in divided doses over three to five days. Irrespective of the regimen used, daily or weekly follow-up maintenance vitamin D dose is necessary as described in the text.

Optional Treatments (and those of unclear benefit)

- **Optional: Anti-androgen therapy**. Multiple clinical studies support the notion that androgens exacerbate COVID-19, and that anti-androgen therapy improves clinical outcomes. Androgens augment SARS-CoV-2 infectivity by promoting the expression of transmembrane protease (TMPRSS2) that primes the spike viral entry protein. (138) In addition androgens are pro-inflammatory. (139)

  Anti-androgen therapy should be considered in seriously ill patients, those that are treated late in the course of their illness, and patients with serious comorbidities.

  In both men and women, the anti-androgens dutasteride, proxalutamide, and spironolactone have been demonstrated to reduce time to viral clearance, improve time to recovery, and reduce hospitalization (outpatients) as well as reduce mortality in hospitalized patients. (140-146)

  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). (147-150) The optimal anti-androgenic dose of spironolactone appears to be 100 mg twice a day.

  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. (151, 152) Both spironolactone and dutasteride decrease expression of TMPRSS2. (153) Dutasteride has been used in women with alopecia and reported to be safe. (154, 155) However, this agent **MUST** be avoided in pregnant women. We recommend dutasteride 2 mg day 1, followed by 1 mg for 10 days.

- **Optional: Famotidine** 40 mg twice a day (reduce dose in patients with renal dysfunction).

- **Optional: Green Tea Extract** 500-1000 mg daily. Epigallocatechin-3-gallate (EGCG), the major component of green tea, has several beneficial properties, including antiviral activity against SARS-CoV-2. (156, 157) Mechanistic studies revealed that EGCG blocks infection at the entry step through interfering with the engagement of the receptor binding domain (RBD) of the viral spikes to angiotensin-converting enzyme 2 (ACE2) receptor of the host cells. (158-160) Furthermore, Shin-Ya et al demonstrated that

Omicron subvariants were effectively inactivated by green tea, Matcha, and black tea. (161)

- **Optional: Dandelion** (Taraxacum officinale). The root, flower and leaves of dandelion contain an array of phytochemicals that have anti-inflammatory, antioxidant, hypolipidemic, antimicrobial and anticoagulant properties**.** (162, 163) An *in vitro* study demonstrated that a dandelion leaf extract altered the binding of SARS-CoV-2 spike protein to the ACE-2 receptor**.** (164) Dandelion extract would therefore appear to be of theoretical benefit for the prevention and early treatment of COVD-19. There is, however, no clinical data to support this hypothesis.

  The European Scientific Cooperative on Phytotherapy recommends a dose of 4-10 g three times a day (20-30 mg/ml in hot water). (165) Note that dandelion extract is considered contraindicated in those with liver and biliary disease, bile duct obstruction, gallstones, cholangitis and active peptic ulcer. (165) Furthermore, dandelion is rich in potassium and should be used cautiously in patients with kidney failure.

- **Unclear benefit: Angiotensin II Receptor Blockers (ARBs)** such as Losartan 50-100 mg daily (reduce to 25-50 mg with impaired renal function) or telmisartan 40-80 mg twice a day (reduce to 40 mg daily/twice a day with impaired renal function).

  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.

  The role of ARBs in patients with COVID-19 is controversial, as clinical studies have produced conflicting results. (166, 167) However, it should be noted that ARBs may act synergistically with statins. ARBs are **contraindicated in pregnancy.**

- **Unclear benefit: Inhaled corticosteroids (budesonide)***.* Two recent RCTs have demonstrated more rapid symptomatic improvement in ambulatory patients with COVID-19 treated with inhaled budesonide, however, with no difference in the rate of hospitalization. (168, 169) It should be noted that both these studies were open label (no placebo in the control arm) and that the primary endpoint 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. (170, 171) In a more recent RCT, the inhaled corticosteroid Ciclesonide failed to achieve the primary efficacy end point of reduced time to alleviation of all COVID-19 related symptoms. Based on these data, the role of inhaled corticosteroids in the early phase of COVID-19 is unclear.

- **Unclear benefit (best avoided): Colchicine** 0.6 mg twice a day for 3 days, then reduce to 0.6 mg 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. (172) 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, (173) together with its marginal benefit, colchicine is best avoided.

- **Not recommended. Monoclonal antibodies**. The use of monoclonal antibodies within 3 days of symptom onset was previously associated with a modest reduction in hospitalization, with no mortality benefit. Almost all the monoclonal antibodies in current use have no activity against the Omicron variant.

- **Not recommended: Molnupiravir**. This is a 'Pharma recycled' mutagenic drug that appears to have little role in the treatment of COVID-19. (174-177) Data from the post-interim analysis enrollment demonstrated that there were fewer placebo patients who were hospitalized or died by day 29 versus patients receiving the intervention (4.7% vs 6.2%, respectively). (178)

- **Not recommended: Paxlovid**. In the "pivotal" Pfizer study testing Paxlovid in unvaccinated ambulatory patients with symptomatic disease, disease progression was reported to be less in the Paxlovid arm. (179) In a follow up post-marketing study, Paxlovid proved to be ineffective in patients less than 65 years of age and in those who were vaccinated. (180) Furthermore, rebound infections (once the drug is stopped) appear common with Paxlovid (this does not occur with ivermectin or hydroxychloroquine. (181) In a prospective RCT, Paxlovid was ineffective for the prevention of symptomatic COVID infection in household contacts (according to the press release). Furthermore, in a June 2022 press release, Pfizer stated it is suspending the use of Paxlovid for "standard-risk patients." Paxlovid has numerous drug-drug interactions and the utility and safety of this drug have yet to be established.

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