

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

A Guide to the Management of COVID-19

(Updated as of January 20, 2022)

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for the Front Line COVID-19 Critical Care Alliance (FLCCC)

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 guidelines as new information emerges. Please check on the FLCCC Alliance website (www.flccc.net) for updated versions of this protocol.

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

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I-MASK+
PROPHYLAXIS & EARLY OUTPATIENT
TREATMENT PROTOCOL FOR COVID-19

MATH+
HOSPITAL TREATMENT PROTOCOL
FOR COVID-19

I-RECOVER
MANAGEMENT PROTOCOL FOR
LONG HAUL COVID-19 SYNDROME

Updates in this version:

- Virus mutations and vaccine efficacy (page 4)
- Hydroxychloroquine in I-MASK+ protocol (page 12)
- Vitamin D and Vitamin C in I-MASK+ protocol (pages 13 and 14)
- N-acetyl cysteine in I-MASK+ protocol (page 20)
- Management of Pediatric Patients (CHILD CARE protocol) (page 22)
- Vitamin D and N-acetyl cysteine for mildly symptomatic hospital patients (page 27)
- N-acetyl cysteine and Calcifediol for severe COVID pulmonary disease (page 38)
- Approach to treatment of “long-haul” COVID (I-RECOVER protocol) (page 44)

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1. Introduction

1.1. *The Vacuum of Truth*

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

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

We are living through a period of time characterized by a **“*Vacuum of Truth*,”** with misinformation, disinformation, blatant lies, censorship, and nefarious intentions being the order of the day. It is difficult to dissect out the actual truth and discern whom to trust. Furthermore, it is no longer controversial to acknowledge that drug makers rigorously control medical publishing and that *The Lancet*, *New England Journal of Medicine (NEJM)*, and *Journal of the American Medical Association (JAMA)* are utterly corrupted instruments of Big Pharma.

The Lancet editor, Richard Horton has stated ,[1] “Journals have devolved into information laundering operations for the pharmaceutical industry.” Dr. Marcia Angell, who served as an *NEJM* editor for 20 years, says journals are “primarily a marketing machine.” [2] Pharma, she says, has co-opted “every institution that might stand in its way. Complex scientific and moral problems are not resolved through censorship of dissenting opinions, deleting content from the Internet, or defaming scientists and authors who present information challenging to those in power. Censorship leads instead to greater distrust of both government institutions and large corporations. [3]

1.2 *The Use of “Off Label” Drugs*

Once the FDA approves a prescription medication, federal laws allow any U.S. physician to prescribe the duly approved drug for any reason. [4] Thirty percent of all prescriptions written by American doctors, exercising their medical judgment, are for off-label uses. The Attorney General of Nevada,[5] as well as many other states have asserted the right of physicians to prescribe “off label” drugs such as ivermectin and hydroxychloroquine for the treatment of COVID-19. The office of Nebraska Attorney General Doug Peterson released a legal opinion on October 15 2021 saying it didn’t see data to justify legal action against health care professionals who prescribe ivermectin or hydroxychloroquine. [5]

1.3. *An Overview of the Treatment of COVID-19*

While there is **no cure or “magic bullet”** for COVID-19, recently, a number of therapeutic agents have shown great promise for both the prevention and treatment of this disease. These include ivermectin, Vitamin D, quercetin, melatonin, fluvoxamine, spironolactone, corticosteroids, curcumin (turmeric), *Nigella sativa* and antiandrogen therapy. It is critical to recognize that infection with SARS-CoV-2 progresses through a number of stages/phases and that treatment is highly stage-specific (see Figures 1-4 and Table 1). It is likely that no single drug will be effective in treating this complex disease and that multiple drugs with different mechanisms of action used in specific phases of the disease will be required. A growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [6-8] Furthermore, an understanding of the structure of SARS-CoV-2 (see Figure 5) as well as the pathophysiology/pathogenesis of COVID-19 is critical in treating the disease. [9]

Finally, the relentless malpractice of deliberately withholding effective early COVID treatments, and of forcing the use of toxic remdesivir in hospitalized patients, may have unnecessarily killed up to 500,000 Americans (see Figures 6a-c). [3]

As the pandemic has played out over the last year, over four million patients have died worldwide, and the pandemic shows no signs of abating. Most countries across the globe have limited resources to manage this humanitarian crisis. We developed the **MATH+ protocol** to provide guidance for the treatment of the pulmonary phase of this disease with the goal of reducing hospital mortality from this devastating disease.

However, it soon became obvious that our emphasis needed to shift to the prevention and early (home) treatment 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, so-called “health care authorities” across the globe have been silent in this regard, including the WHO, CDC, NIH, and others (see NIH Guidance, Figure 6a and 6b).

While vaccination may be part of the solution to the COVID-19 pandemic, it will take many months — if not years — to vaccinate the 70-85 percent of the world’s population required for “herd immunity.” Mutant strains of SARS-CoV-2 have recently appeared, demonstrating increased transmissibility. [10-13] Many of these mutations involve the spike protein (which almost all of the vaccines have targeted), raising the real possibility that the vaccines may become less effective (or ineffective) against the mutating strains. [10,11,14-19] Indeed, the protective immunity of the vaccines against both the Delta and Omicron variants has come into question. [16-20] We believe that the **I-MASK+ protocol** provides both a bridge and an alternative to universal vaccination.

And, finally the post-COVID syndrome or “long-hauler syndrome” has emerged as a common and disabling disorder, and its pathophysiology is poorly understood. We offer the **I-RECOVER protocol** to help treat this disabling disorder. Recently, post-vaccination syndrome has emerged as a problematic entity; we believe the **I-RECOVER protocol** has utility in treating this syndrome as well.

Figure 1. Treatment Phases of COVID-19

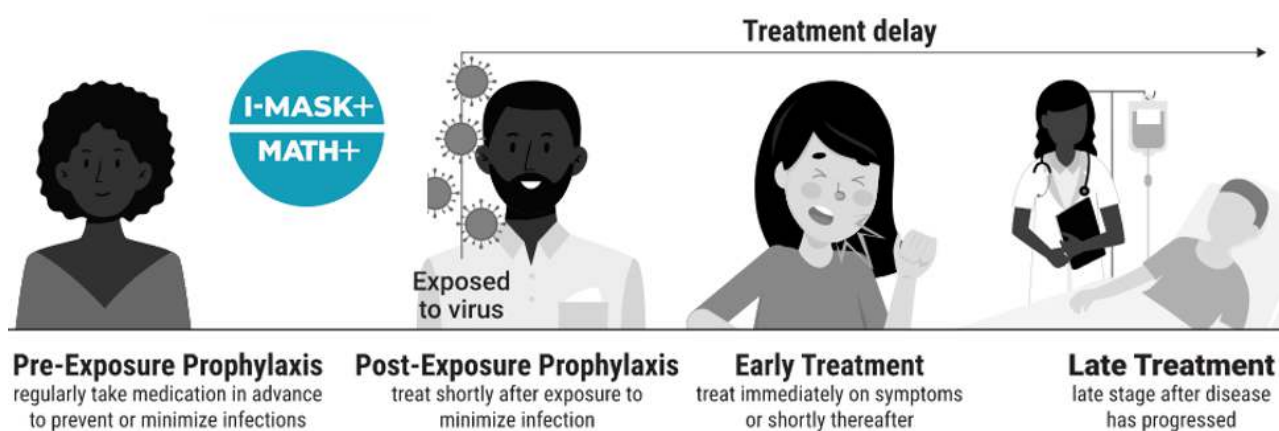
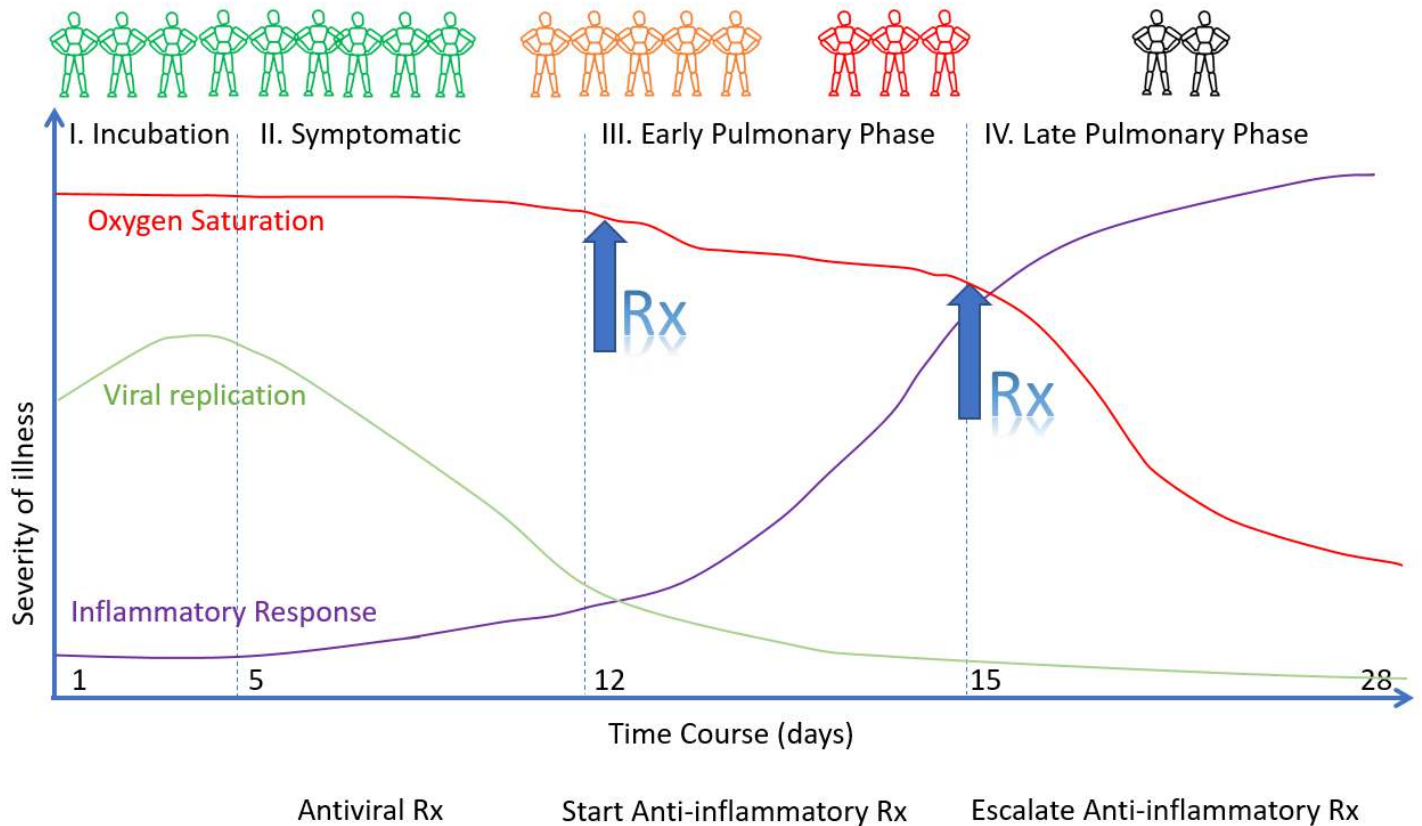


Figure 3. Timing of the Initiation of Anti-Inflammatory Therapy



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

Figure 4. Time Course of Laboratory Tests for COVID-19

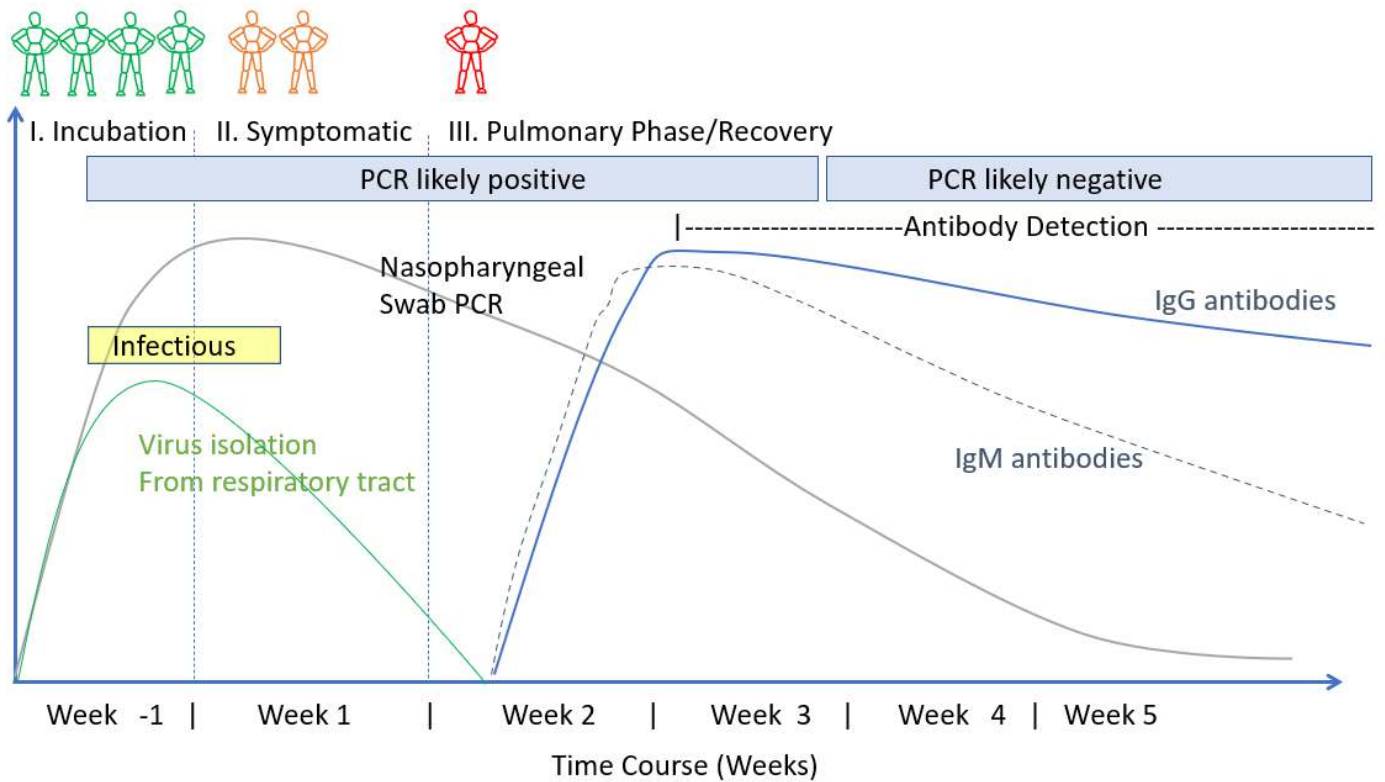


Figure 5. SARS-Co-V-2 Structure and RNA Genome

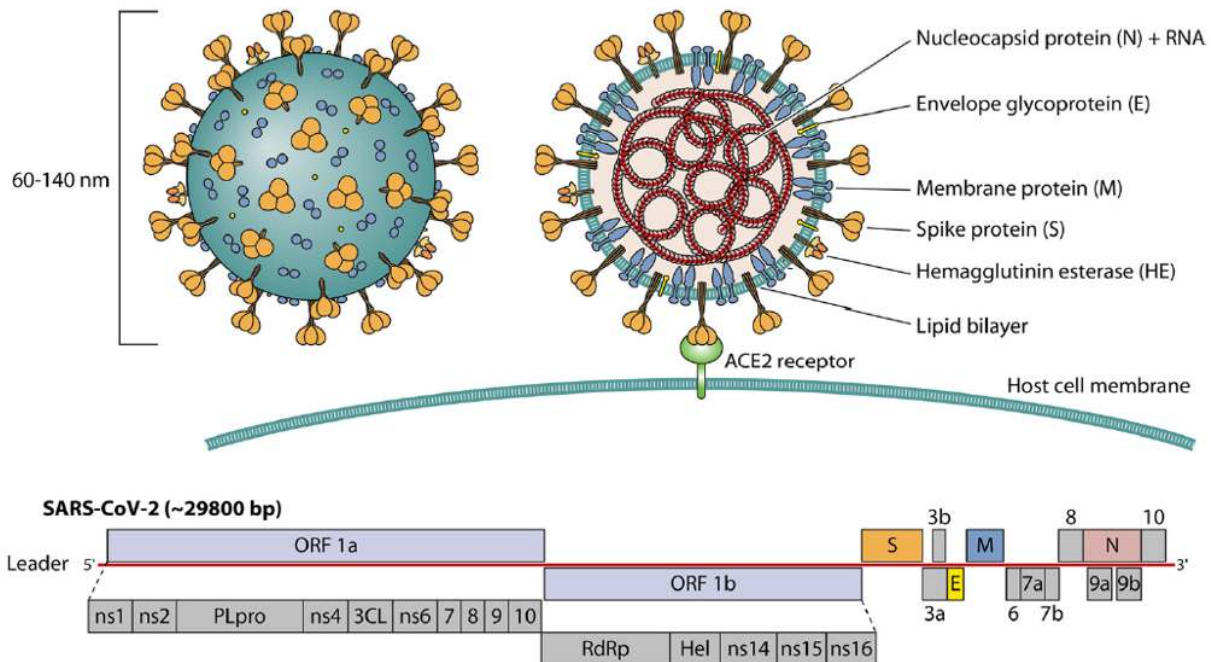


Table 1. Pharmacological Therapy for COVID-19 by Stage of Illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Anti-androgen Rx	Benefit	BENEFIT	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Corticosteroids	n/a	Trend to harm	BENEFIT
LMWH	n/a	n/a	BENEFIT
Monoclonal Abs	BENEFIT	BENEFIT (early)	HARM
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Remdesivir	n/a	? Benefit	HARM
Lopinavir-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ? Benefit	No benefit	Harm
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

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

** Due to extensive fraudulent activity around the design and conduct of RCTs, the benefit of HCQ is supported largely by numerous consistently positive observational trials.

Figure 6a. NIH Recommendations for the Treatment of COVID-19 Across the Stages of the Disease (Last Updated: October 19, 2021)

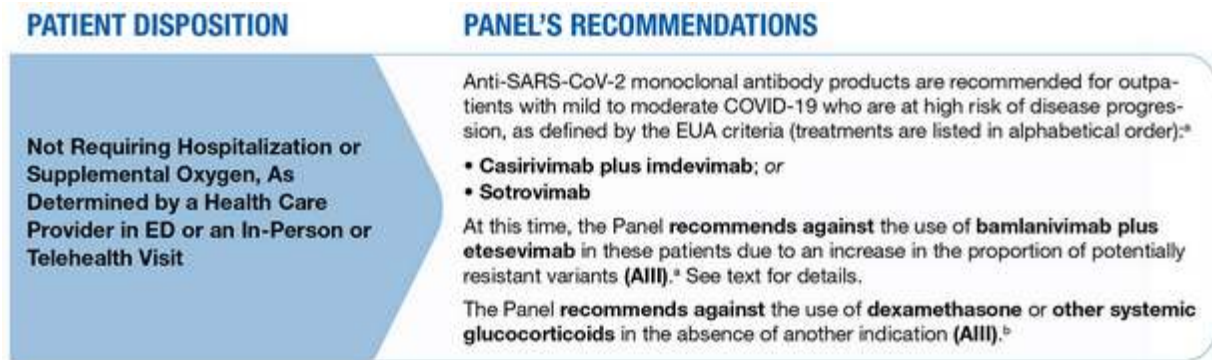
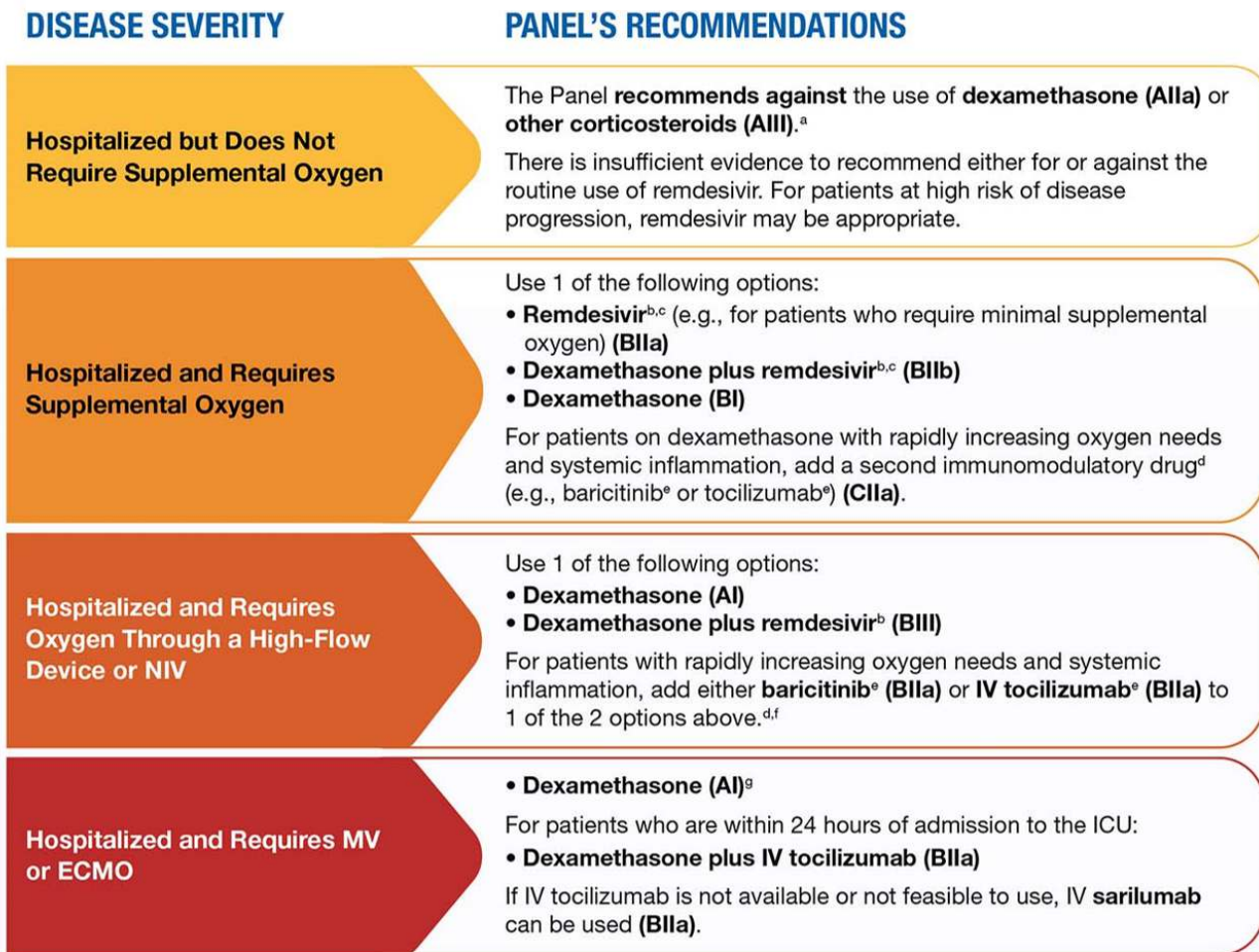


Figure 6b. NIH Recommended Therapeutic Management of Hospitalized Adults with COVID-19, Based on Disease Severity (Last Updated: December 16, 2021)



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

Figure 6c. NIH Recommendations for Prevention of SARS-CoV-2 Infection (Last Updated: December 16, 2021)

Summary Recommendations
<ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible according to the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (AI).• The Panel recommends using 1 of the following anti-SARS-CoV-2 monoclonal antibodies (listed alphabetically) as post-exposure prophylaxis (PEP) for people who are at high risk of progressing to severe COVID-19 if infected with SARS-CoV-2 AND who have the vaccination status AND exposure history outlined in the text below:<ul style="list-style-type: none">◦ Bamlanivimab 700 mg plus etesevimab 1,400 mg administered as an intravenous (IV) infusion (BIII); <i>or</i>◦ Casirivimab 600 mg plus imdevimab 600 mg administered as subcutaneous injections (AI) or an IV infusion (BIII).• The Panel recommends against the use of hydroxychloroquine for SARS-CoV-2 PEP (AI).• The Panel recommends against the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).• The Panel recommends against the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

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

The components of the I-MASK+ Prophylaxis and Early Treatment protocol are illustrated in Figures 7a-c. Recent data suggests that ivermectin, melatonin, as well as the combination of quercetin (or mixed flavonoids) and Vitamin C, as well as oropharyngeal sanitation, may play an important role in both pre-exposure and post-exposure prophylaxis. [7,21-24] The evidence supporting the use of ivermectin for the prophylaxis of COVID-19 is provided by the comprehensive review by Kory et al. [25] It is important to emphasize that ALL of the medications included in our prophylactic regimen are inexpensive, safe, and widely available. The I-MASK+ protocol MUST be part of an overall strategy that includes common-sense public health measures, i.e., masks (only for prolonged exposure in confined, poorly ventilated environments), short term quarantine of infected patients, and high risk individuals (advanced aged and comorbidities) avoiding large public and family gatherings. [26] Standard surgical and cloth masks likely only reduce risk of transmission for finite periods in confined environments. For prolonged protection in such settings, N95 type masks would be required.

2.1 Core Components of the I-MASK+ Prophylactic Protocol

- **Ivermectin** for postexposure prophylaxis; 0.4 mg/kg immediately, then repeat second dose in 48 hours. Ivermectin is best taken with a meal or just following a meal (greater absorption). [27] Oropharyngeal sanitation also suggested (see section on home treatment below).
- Ivermectin for pre-exposure prophylaxis (in healthcare workers) and for prophylaxis in high-risk individuals (> 60 years with co-morbidities, morbid obesity, long term care facilities, etc). 0.2 mg/kg per dose; start treatment with one dose, take second dose 48 hours later, then 1 dose every 7 days (i.e. weekly). [28-33]
- For those at high risk of contracting COVID-19, we now recommend twice weekly dosing. See Dosing Table below.
- Ivermectin has a number of potentially serious drug-drug interactions); please check for potential drug interactions at [Ivermectin Drug Interactions - Drugs.com](https://www.drugs.com/interactions-check.php?drug=ivermectin) (also see Table 4 below). The most important drug-drug interactions occur with *cyclosporin*, *tacrolimus*, *anti-retroviral drugs*, and certain antifungal drugs. While ivermectin has a remarkable safety record, [34] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [35,36] While hepatitis is commonly quoted as a side effect, we are aware of one published case report of reversible hepatitis. [37]
- The safety of ivermectin in pregnancy has not been determined. [38] Ivermectin may increase the risk of congenital malformations, particularly when used in the first trimester. [38] US Food and Drug Administration (FDA) has classified ivermectin as pregnancy category C — i.e, “Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.” In pregnant patients with symptomatic COVID-19 infections, the risk and benefits of ivermectin should be discussed with the patient, and informed consent obtained from the patient should the drug be prescribed. Additionally, women should be counselled that low concentrations of ivermectin are present in breast milk; the implications of this finding are unclear. [39]

- **Hydroxychloroquine (HCQ)** 200 mg BID for 5 days together with ZINC (75-100mg elemental zinc) post COVID-19 exposure. [40-43] HCQ may be used as an alternative to ivermectin. HCQ has been approved by the FDA for use in pregnancy.
- **Melatonin** (slow release/extended release): Begin with 1 mg and increase as tolerated to 6 mg at night. [6,21,44-50]. Some patients are intolerant to melatonin, having very disturbing and vivid dreams; in these patients it may be best to start with a 0.3 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.
- Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease. [51-53] Multiple studies have demonstrated the benefit of melatonin at various stages of the disease. [54-56] A large retrospective study demonstrated that the use of melatonin in intubated patients with COVID-19 significantly reduced the risk of death (HR 0.1; p<0.0001). [52] 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. [57] Similarly, children have high levels of circulating melatonin approximating those of bats, while elderly people — particularly those over the age of 60 — have very low melatonin levels; this may partly explain the increased vulnerability of the elderly to COVID-19.
- The slow release (extended release) formulations of melatonin are preferred as they more closely replicate the normal circadian rhythm. [44] There is marked inter-individual variation in the metabolism of melatonin (first pass metabolism), hence the dose must be individualized. [44] High serum levels are associated with hyper-REM sleep and bad dreams. Rapid release melatonin (usual over-the-counter formulation) results in early high peaks that do not replicate the normal circadian pattern; hence it is important to take the slow release/extended-release formulation.
- **Oropharyngeal hygiene** with twice daily antiviral mouthwash/gargle (see Figure 7 and below).
- **Monoclonal antibodies** for 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 percent (7.8% to 1.5%). [58] 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 [59-65]. 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. [62] Furthermore, a number of studies have demonstrated an association between the use of proton pump inhibitors (PPIs) with an increased risk of contracting COVID-19 and with worse outcomes. [66,67] 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. Use in the first trimester should be avoided. Please discuss with your physician.*

Ivermectin dosing table: 200 ug/kg (0.2 mg/kg) or fixed dose of 12 mg (\leq 80kg) or 18 mg (\geq 80kg). [68] Depending on the manufacturer, ivermectin is supplied as 3mg, 6 mg or 12 mg tablets.

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

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

- **Vitamin D.** Vitamin D deficiency is common in the Middle East and some countries in Asia, Europe, and North America. [69,70] Less sun exposure, sunscreen use, increased body mass index (BMI), less physical activity, and poor socioeconomic status predicts lower serum 25(OH)D concentrations.
- Vitamin D receptors are present on immune cells with this vitamin playing a critical role in both innate and adaptive host immunity.[71,72] Vitamin D has numerous immunological properties that play a vital role in limiting the acquisition and severity of COVID-19.[73] Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. [74-100]
- Vitamin D supplementation is likely a highly 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 $> 45^\circ$ latitude. [80-95,98] In addition, vitamin D supplementation may be important in pregnant patients. [101]
- 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. [102] This concept is supported by a recent study that demonstrated that residents of a long-term care facility who took vitamin D supplementation had a much lower risk of dying from COVID-19. [96]
- The dosing recommendations for vitamin D supplementation vary widely. The OPTIMAL target vitamin D level is > 50 ng/ml; at this level the risk of dying from COVID-19 is extremely low. [103] It may take many months/years to achieve optimal levels in a patient with a vitamin D level of < 12 ng/ml taking the standard recommended dose of 5000 IU /day. It is therefore **EXTREMELY IMPORTANT** to stress that the optimal regimen for Vitamin D supplementation for both the prophylaxis and treatment of COVID-19 should be based on the baseline vitamin D level (see Table 2). The highest dose of commercial vitamin D₃ is 50,000 IU capsules. Due to the availability, affordability, and better gastrointestinal absorption, we recommend using 50,000 IU D₃ capsules for non-urgent, outpatients and community setups. Together, a number of these capsules can be taken as a bolus dose [i.e., single upfront doses such as 100,000 to 400,000 IU. However, the liver has a limited 25-hydroxylase capacity to convert vitamin D to 25(OH)D: thus, taking 50,000 IU capsules over a few days provides better bioavailability. Table 2 presents a safe and practical treatment schedule for raising blood 25(OH)D concentrations and tissue storage without adverse effects in non-urgent situations (modified from SJ Wimalawansa with permission). [104] The dosing schedule

illustrated in Table 3 should be used when recent serum 25(OH)D concentration is unavailable (from SJ Wimalawansa with permission). [104]

- It is optional to measure blood concentrations two to four weeks after a course of vitamin D to assess whether the desired serum 25(OH)D concentrations are achieved. It is best to include both vitamin K2 and magnesium (250 -500 mg/day) when doses of vitamin D > 8000 IU/day are taken. [105,106]
- **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. [107-111] Emerging data suggests that curcumin improves the clinical outcome of patients with COVID-19. [112,113]
- ***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. [114-121] It should be noted that thymoquinone (the active ingredient of *Nigella Sativa*) decreases the absorption of cyclosporine and phenytoin. [122] Patients taking these drugs should therefore avoid taking *Nigella Sativa*. Furthermore, two cases of serotonin syndrome have been reported in patients taking *Nigella Sativa* who underwent general anaesthesia (probable interaction with fentanyl). [123]
- **Vitamin C 500 – 1000 mg BID (twice daily).** Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties, including increased synthesis of type I interferons. [23,24,124-126]
- **Quercetin 250 mg daily.** [126-138] Quercetin has direct virucidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [128,132,137,137,139-147] Quercetin is a potent inhibitor of inflammasome activation, which is believed to play a major role in the pathophysiology of the COVID-19 immune dysfunction. [147] In addition, quercetin acts as a zinc ionophore. [148] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [7]
- **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).**
- A mixed flavonoid supplement containing quercetin, green tea catechins, resveratrol, curcumin, rutin and anthocyanins (from berries) may be preferable to a quercetin supplement alone; [149-153] 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. [154-157]
- 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. [158] In women, high consumption of soya was associated with elevated TSH concentrations. [159] 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. [160] 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).** [133,135,136,161-165] Zinc is essential for innate and adaptive immunity. [163] In addition, zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-

2 virus. [162] 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. [166]

- 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 zinc sulfate contains 50 mg elemental zinc.**
- **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. [167-170] COVID-19 depletes the microbiome of Bifidobacterium, which may then increase the severity and duration of COVID-19 symptoms. Kefir (a fermented milk drink) is high in Bifidobacterium and other probiotics that have demonstrated health benefits. [171,172] 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.
- **B complex vitamins** [173-177].

2.3 Prevention Protocol in Children and Adolescents

- Multivitamin with age-appropriate dosages of Vitamins 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

In children, the risk of serious disease (including hospitalization and death) is increased in those with obesity (very important risk factor) and those with comorbidities. [178-180] Prophylactic measures are especially important in these high-risk children.



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

Achieving serum 25(OH)D concentrations above 50 ng/mL based on serum 25(OH)D concentration in non-emergency situations in a 70 kg adult *				
Serum vitamin D (ng/mL) **	Vitamin D dose, 50,000 IU capsules: Initial and weekly ‡		Duration (weeks)	Total amount for deficit correction (IU, in millions) #
	Initial Dose (IU)	Weekly dose: (50,000 IU caps)		
< 10	300,000	x 3	8 to 10	1.5 to 1.8
11–15	200,000	x 2	8 to 10	1.0 to 1.2
16–20	200,000	x 2	6 to 8	0.8 to 1.0
21–30	100,000	x 2	4 to 6	0.5 to 0.7
31–40	100,000	x 2	2 to 4	0.3 to 0.5
41–50	100,000	x 1	2 to 4	0.2 to 0.3

* A suitable daily or weekly maintenance dose should start after completing the schedule.
 ** For conversion of ng/mL to nmol/L, multiply by 2.5.
 ‡ Mentioned replacement doses can be taken as single cumulative doses or spread out through the week.
 # Estimated deficit of vitamin D needed to replenish body stores.

(From SJ Wimalawansa with permission).

Table 3. Vitamin D dosing in the absence of a baseline vitamin D level

Longer-term maintenance of serum 25(OH)D concentrations above 50 ng/mL based on body weight *			
Body-weight category	Dose (IU) kg/day	Dose (IU)/day	
		Daily dose (IU)	Once a week
BMI ≤19 (under-weight)	40 to 70	≈ 2,000 – 4,000	~25,000
BMI 20-29 (non-obese person)	70 to 100	≈ 5,000 – 7,000	~50,000
BMI 30-39 (obese persons)	100 to 150	≈ 9,000 – 15,000	~75,000
BMI ≥40 (morbidly obese persons)	150 to 200	≈ 16,000 – 30,000	~100,000

(From SJ Wimalawansa with permission).

Table 4. Drug interactions with ivermectin (From Medscape).

<https://reference.medscape.com/drug/stromectol-ivermectin-342657#3>

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

DRUG INTERACTIONS WITH IVERMECTIN			
SERIOUS (4) Use Alternative	MONITOR CLOSELY (possible) (49) Especially those with (*)		
Erdafitinib	Amiodarone	Glecaprevir/Pibrentasvir	Phenytoin
Lasmiditan	Atorvastatin	Indinavir	Ponatinib
Quinidine	Berotrastat	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

4. Symptomatic Patients At Home (I-MASK+ Early Treatment Protocol)

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

- **Ivermectin** 0.3 - 0.6 mg/kg – one dose daily for 5 days or until recovered. [30,34,74-77,181-196]. Higher doses (0.6 mg/kg) are often required: a) in regions with more aggressive variants, b) if treatment started on or after 5 days of symptoms or c) in patients in pulmonary phase, d) extensive CT involvement or e) extensive comorbidities/risk factors (older age, obesity, diabetes). **A dose of 0.3-0.4 mg/kg may be appropriate for the Omicron variant.** Ivermectin is best taken with a meal or just following a meal (greater absorption). See drug-drug interactions above. It should be noted that multiday treatment has been shown to be more clinically effective than single-day dosing.
- **Nitazoxanide (NTZ)** 600 mg BID for 5 days was shown to reduce disease progression, hospitalization and death when used early in outpatients with mild to moderate disease. [197] The combination of NTZ and ivermectin has been shown to reduce viral clearance and symptom progression in outpatients with COVID-19. [198,199] 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. [200,201] Like ivermectin, NTZ has broad spectrum antiviral activity that includes SARS-CoV-2. [201-204] Furthermore, as NTZ and ivermectin have differing modes of action, it is likely that these two drugs have synergistic antiviral and anti-inflammatory effects.[199,202,205] NTZ should therefore be considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA.
- **Oropharyngeal sanitization** (see figure 7b and c). [206] Inhaled steam supplemented with antimicrobial essential oils (e.g VapoRub™ inhalations) have been demonstrated to have virucidal activity. [207] Antimicrobial essential oils include lavender oil, thyme oil, peppermint oil, cinnamon oil, eucalyptus oil and sage oil. [207-211] Antimicrobial 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. [212-219] A mouthwash containing cetylpyridinium chloride (CPC) has broad antimicrobial properties and has been shown to be effective in controlling gingivitis and gingival plaque. [219-221] An *in-vitro* study demonstrated that CPC was highly viricidal against a human coronavirus. [222] In a primary prophylaxis study, a povidone-iodine throat spray administered three times daily proved to be highly effective in reducing the risk of laboratory confirmed SARS-CoV-2 infection. In patients with symptomatic disease treated at home with a 1% povidone iodine mouthwash/gargle, together with nasal and eye drops, resulted in a dramatic reduction in morbidity, hospitalization and death. [223] A nasal spray with 1% povidone-iodine (for example Immune Mist™) administered 2-3 times per day is recommended in post-exposure prophylaxis and in symptomatic patients (early phase of COVID-19 infection). [214] Due to low level systemic absorption, povidone-iodine nasal spray should not be used for longer than 5-7 days in pregnant women. While the use of an iodine-containing mouthwash over a six-month period was demonstrated to increase serum iodine levels, thyroid function tests remained unchanged. [224] 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. [225-227] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [228-230]
- **Melatonin 10 mg at night.** [50-56] 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. [107-111]
- ***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. [116]
- **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.
- The optimal dose of **Vitamin D3** in the acute setting is controversial. [231,232] A dosing schedule as outlined in Tables 2 and 3 are suggested.
- **Vitamin C 500 – 1000 mg BID and Quercetin 250 mg BID** (or mixed flavonoid supplement). **Due to the possible drug interaction between quercetin and ivermectin (see above) these drugs should not be taken simultaneously** (i.e., should be staggered morning and night).
- **Zinc 75–100 mg/day** (elemental zinc).
- **Hydroxychloroquine (HCQ) 200 mg BID for 5-10 days.** [40-43] HCQ may be taken in place of ivermectin or together with ivermectin. While ivermectin should be avoided in pregnancy, the FDA considers HCQ safe in pregnancy. Some 200 peer-reviewed studies (C19Study.com) by government and independent researchers deem HCQ safe and effective against Coronavirus, especially when taken prophylactically or when taken in the initial stages of illness along with zinc and azithromycin. Unfortunately, most of the RCTs that have been conducted to date used toxic doses of HCQ and/or were given very late in the disease and were clearly designed by the “captured” agencies to fail. [3] Instead of using the standard treatment dose of 400 mg/day, the 17 WHO studies administered a borderline lethal *daily* dose starting with 2,400 mg on Day 1 and using 800 mg/day thereafter. Brazilian prosecutors have accused the authors of one study with committing homicide by purposefully poisoning and murdering the elderly subjects of their study. [233]
- 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. [234] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous. [234] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [235] The following guidance is suggested: [234]
 - 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. [236] In addition androgens are pro-inflammatory. [237] 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). [238-241] 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. [242] 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. [243,244] Both spironolactone and dutasteride decrease expression of TMPRSS2. [245] 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. [242,246-251] Dutasteride has been used in women with alopecia and reported to be safe. [252,253] 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. [254-261] This selective serotonin reuptake inhibitor (SSRI) is recommended in those patients with more severe symptoms/more advanced disease. Fluvoxamine is a SSRI that activates sigma-1 receptors decreasing cytokine production. [254,255] In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus and inhibits melatonin degradation.[262,263] Antidepressant medications (SSRI) deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation. [264-266] The use of antidepressants has been associated with a lower risk of intubation and death in patients hospitalized with COVID-19. [257,258,267,268] Fluoxetine (Prozac; 20-40mg daily), has activity against the sigma-1 receptor and is an alternative should fluvoxamine not be available. [269]
- **N-acetyl cysteine (NAC)** 600 – 1200 mg PO BID. NAC is the precursor of reduced glutathione. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis.[270] Based on a broad range of antioxidant, anti-inflammatory and immunomodulating mechanisms, the oral administration of NAC likely plays an adjuvant role in attenuating the severity of COVID-19. [270-274] It is unclear if NAC has an additive benefit over the administration of other antioxidant/anti-inflammatory agents (i.e., melatonin, flavonoids, vitamin C, fluvoxamine, etc). However, this exceedingly cheap medication is devoid of any significant adverse effects.

- **Monoclonal antibodies** for early outpatient treatment (within 7 days of symptom onset; ideally within 4 days). 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. [275] 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!!! [275] The duration of symptoms was 4 days shorter in the REG-COV2 group. Monoclonal antibodies appear to reduce the risk of hospitalization in patients with mild to moderate disease if administered within 4 days of symptoms.[276,277] The timely administration of monoclonal antibodies are recommended in high-risk individuals, namely, > 65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunosuppressed, coronary heart disease, etc. See infusioncenter.org and call 1-877-332-6585 In USA for eligibility and location. Sotrovimab is a monoclonal antibody that neutralizes SARS-CoV-2 by targeting an evolutionarily conserved epitope that lies outside the rapidly evolving receptor binding motif. [278] *In vitro*, data suggests that Sotrovimab retained activity against variants of interest and concern (VOC), including the alpha, beta, gamma, delta, and lambda variants. With the rapid emergence of VOC Sotrovimab may be the preferred monoclonal antibody.

3.3 Optional Treatments (and those of uncertain benefit)

- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed. Omega-3 fatty acids have anti-inflammatory properties and play an important role in the resolution of inflammation. Omega-3 fatty acids reprogram macrophages/monocytes from a M1 phenotype to a M2 phenotype.[279-281] As discussed later this is critical in the management of COVID-19. In addition, omega-3 fatty acids may have antiviral properties. [135,282-285]
- *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. [286-288] Preliminary data demonstrated that disruption of the CCR5 axis with monoclonal antibodies was associated with an improved outcome in patients with COVID-19. [289-291] Maraviroc is a CCR5 blocker that has been extensively used in patients with HIV, with a good safety record. [292-294] Clinical data suggests that maraviroc may be useful as an adjunctive agent in both acute COVID-19 infection and in the long-haul syndrome. However, at this time there is limited published data on the utility of this drug. Due to the very low risk of hepatotoxicity monitoring LFT's are recommended. Price and availability may however be an issue.
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction) [59-65].
- *Optional:* Interferon- α/β nasal spray, inhalation or s/c injection. [295-299] It should be noted that Zinc potentiates the effects of interferon. [300,301]

- *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. [302,303] However, it should be noted that ARBs may act synergistically with statins. [302] ARBs are *contraindicated in pregnancy*.
- *Unclear benefit: Inhaled corticosteroids (budesonide).* Two recent RCTs have demonstrated more rapid symptomatic improvement in ambulatory patients with COVID-19 treated with inhaled budesonide, however, with no difference in the rate of hospitalization. [304,305] 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. [306,307] 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. [308] 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. [309] 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, [310] 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. [311]
- *Not recommended: Prophylactic azithromycin, as well as doxycycline, or quinolone antibiotics* are of little benefit in patients with COVID-19. [312-314]

3.4 Management of Pediatric Patients (CHILD CARE Protocol)

In children, the risk of serious disease (including hospitalization and death) is increased in those with obesity and comorbidities. [178-180] Treatment with ivermectin/HCQ, under the supervision of a pediatrician, should be considered in those with comorbidities and those who are severely symptomatic.

- **C:** Chronic conditions should receive optimal management
 - Diabetes, congenital heart disease, obesity, chronic lung disease
- **H:** Hydroxychloroquine
 - Children and adolescents
 - 4-5 mg/kg day in 1 or 2 divided doses; max of 400 mg/day

- **I:** Ivermectin
 - 0.2-0.3 mg/kg day for 5 days
 - Appears safe in children < 15 kg [315]
- **L:** Lifestyle
 - Nutrition, sleep hygiene, movement/exercise, supportive relationships
- **D:** Vitamin D
 - Doses: depends on latitude, skin color, sun exposure, etc.
 - Infants: 400-800 IU/d
 - Toddlers: 1000-2000 IU/d
 - Elementary: 2000-4000 IU/d
 - Adolescents: 4000-5000 IU/d
- **C:** Vitamin C
 - 0–12 months: 100 mg/day
 - 1-3 years: 200 mg/day
 - 4-8 years: 500 mg/day or 250 mg BID
 - 9-13 years: 500mg BID
 - 14-18 years 500mg TID
- **A:** Vitamin A
 - 1-3 years: 300 mcg/day (1000 units)
 - 3-8 years: 400 mcg/day (1333 units)
 - 9-13 years: 600 mcg/day (2000 units)
 - > 14 years males: 900 mcg/day (3000 units)
 - > 14 years females: 700 mcg/day (2333 units)
- **R:** Recovery (survival rate 99.998%). Social Reintegration.
- **E:** Et cetera: Zinc, Quercetin, Melatonin, oropharyngeal sanitization, Kefir and probiotics.
 - Zinc: lozenges/chewable 3-5mg/day
 - Quercetin: 250mg daily
 - Melatonin: 0.3mg - 3 mg at night. Avoid in toddlers < 12 months



7a. I-MASK+ Early Treatment Protocol

I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

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EARLY TREATMENT PROTOCOL⁵ (for Omicron/Delta variants)

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

ANTI-VIRALS

Ivermectin²: 0.4–0.6 mg/kg per dose (take with or after a meal) — one dose daily, take for 5 days or until recovered. Use upper dose if: **1)** in regions with aggressive variants (e.g. Delta); **2)** treatment started on or after day 5 of symptoms or in pulmonary phase; or **3)** multiple comorbidities/risk factors.

and/or **Hydroxychloroquine** (preferred for Omicron): 200 mg PO twice daily; take for 5 days or until recovered.

ANTI-SEPTIC ANTI-VIRALS

Antiviral mouthwash: Gargle 3 x daily (do not swallow; must contain chlorhexidine, povidone-iodine, or cetylpyridinium chloride). **Iodine nasal spray/drops**: Use 1% povidone-iodine commercial product as per instructions 2–3 x daily. If 1%-product not available, must first dilute the more widely available 10%-solution⁶ and apply 4–5 drops to each nostril every 4 hours. (No more than 5 days in pregnancy.)

ANTI-COAGULANTS / IMMUNE FORTIFYING

Aspirin 325 mg daily (unless contraindicated)
Vitamin D3 Optimal approach to dosing requires testing of 25(OH)D level. *For dosing guidance, see Table 1 if level is known and Table 2 if level is unknown.*
Melatonin 10 mg before bedtime (causes drowsiness)

SYNERGISTIC THERAPIES

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

NUTRITIONAL THERAPEUTICS (for 14 days)⁴

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

PULSE OXIMETER

Monitoring of oxygen saturation is recommended (for instructions see page 4)

Figure 7b. Naso-Oropharyngeal Sanitization

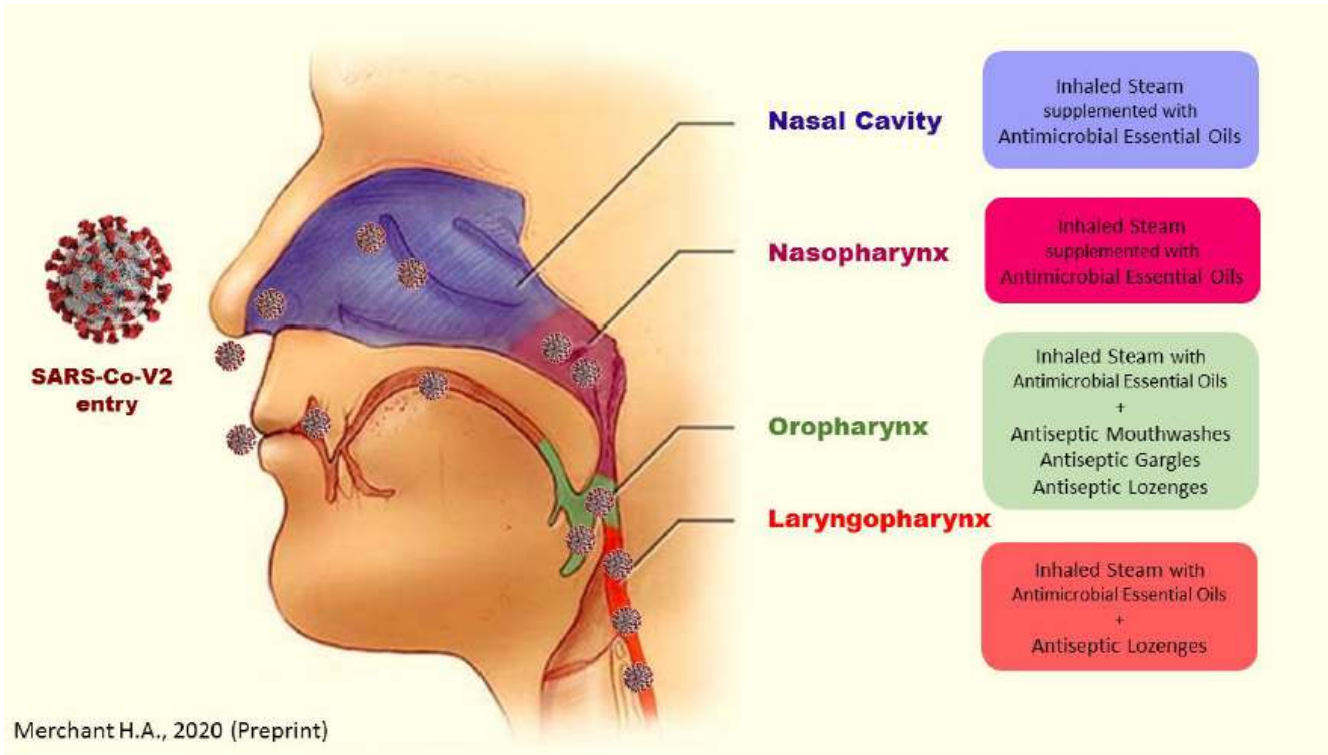


Figure 7c. Commercial Products Available for Naso-Oropharyngeal Sanitization

Cetylpyridinium Chloride



Thymol Menthol Eucalyptus:
Listerine™ Antiseptic



Povidine-Iodine



Steam Inhalation with antimicrobial oils



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. [30,34,74-77,181-190,192,194-196]. 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. [316-319] Preliminary data suggest that ivermectin in a dose of 0.3-0.4 mg/kg is highly effective against the Omicron variant; however, in keeping with the general treatment principles, early treatment is preferred. See drug-drug interactions above.
- **Nitazoxanide** (NTZ) 600 mg BID for 7 days. [320] NTZ should therefore be considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA.
- **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. [321-333] 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.[334]
- **Vitamin C** 500–1000 mg q 6 hourly and Quercetin 250–500 mg BID (if available)
- **Zinc** 75–100 mg/day (elemental zinc)
- **Melatonin** 6 mg at night. [50-56]
- **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.** [242,246,247]
- **Fluvoxamine** 50 -100 mg BID. Fluoxetine 20-40mg daily is an alternative.

4.2 Second Line and Optional Treatments

- **Vitamin D.** For patients hospitalized with COVID-19 the dosing scheme as listed 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 to 4 days [335]. This may explain the lack of benefit of vitamin D3 in patients hospitalized with severe COVID-19.[102] 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 single dose of calcifediol raise serum 25(OH)D concentration within four hours. Therefore, calcifediol is particularly useful in acute infections like, COVID-19 and in sepsis. [99,336-339] The single oral calcifediol dose is calculated, 0.014 mg/kg body weight (Table 6). To be most effective, a loading dose of vitamin D3 dose should be administered with or within the first week of administration of calcifediol (Table 6, column 5). We recommend against the use of **calcitriol** [1,25(OH)2D]. Calcitriol has minimal effect on immune cells. Moreover, the effective dose (ED50) and toxic level overlap at the dose currently suggested for COVID-19. [340]
- **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. [229,230,341,342]
- **B complex** vitamins
- **N-acetyl cysteine** 600-1200 mg PO BID. [270-273]
- **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. [343,344] 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. [345] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19. [346-350] Due to numerous drug-drug interactions (including ivermectin) simvastatin should be avoided.
- *Optional:* **Maraviroc** 300 mg BID for 10 days (see above and section on Long-Covid).
- *Optional:* **Famotidine** 40 mg BID (20–40 mg/day in renal impairment). [59-65] 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. [351] These drugs have been shown to decrease the use of mechanical ventilation and the risk of death. [352,353] In these studies low doses of corticosteroids were used. The role of JAK inhibitors with appropriate corticosteroid dosing is unclear. JAK inhibitors should be used with caution in patients with severe renal impairment as well as those with lymphopenia (< 500) and neutropenia (< 1000). The safety of these drugs is uncertain as they are nephrotoxic and myelosuppressive.

- *Optional:* The anti-serotonin agent, **cyproheptadine** 4–8 mg PO q 6 hour should be considered in patients with more severe disease. [354,355] 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. [354,356-358] 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. [359-362] Furthermore, serotonin itself enhances platelet aggregation creating a propagating immuno-thrombotic cycle.[363] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [364]
- *Optional:* **Vascepa** (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. [365] Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed
- *Not recommended:* Remdesivir. The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup. [366] The VA study showed no mortality benefit with remdesivir and a longer length of hospital stay. [367] Most recently, the DisCoVeRy trial reported no outcome benefit from remdesivir. [368] A meta-analysis of the six published RCTS demonstrate no mortality reduction with remdesivir; interestingly enough, the independent studies demonstrate a trend to harm while the two studies conducted by Gilead demonstrate a mortality benefit. (See figure 9).
- Not recommended: Azithromycin, doxycycline, or quinolone antibiotics. [172,173]
- Not recommended: Colchicine. Recruitment to the colchicine arm of the RECOVERY trial has been closed as no mortality benefit was noted with colchicine (Mortality 20% colchicine, 19% standard of care). In addition, potentially serious drug-drug interactions exist with the use of colchicine and CYP 3A4 and p-glycoprotein inhibitors (ivermectin, macrolide antibiotics, cyclosporin, etc) as well as with the use of statins. [310]

N/C 2L/min if required (max 4 L/min; consider early t/f to ICU for escalation of care).

Avoid Nebulization and Respiratory treatments. Use “Spinhaler” or MDI and spacer if required.

T/f EARLY to the ICU for increasing respiratory signs/symptoms, increasing oxygen requirements and arterial desaturation.

Figure 8. Ivermectin Real-Time Meta-Analysis of 73 Studies (from ivmeta.com)

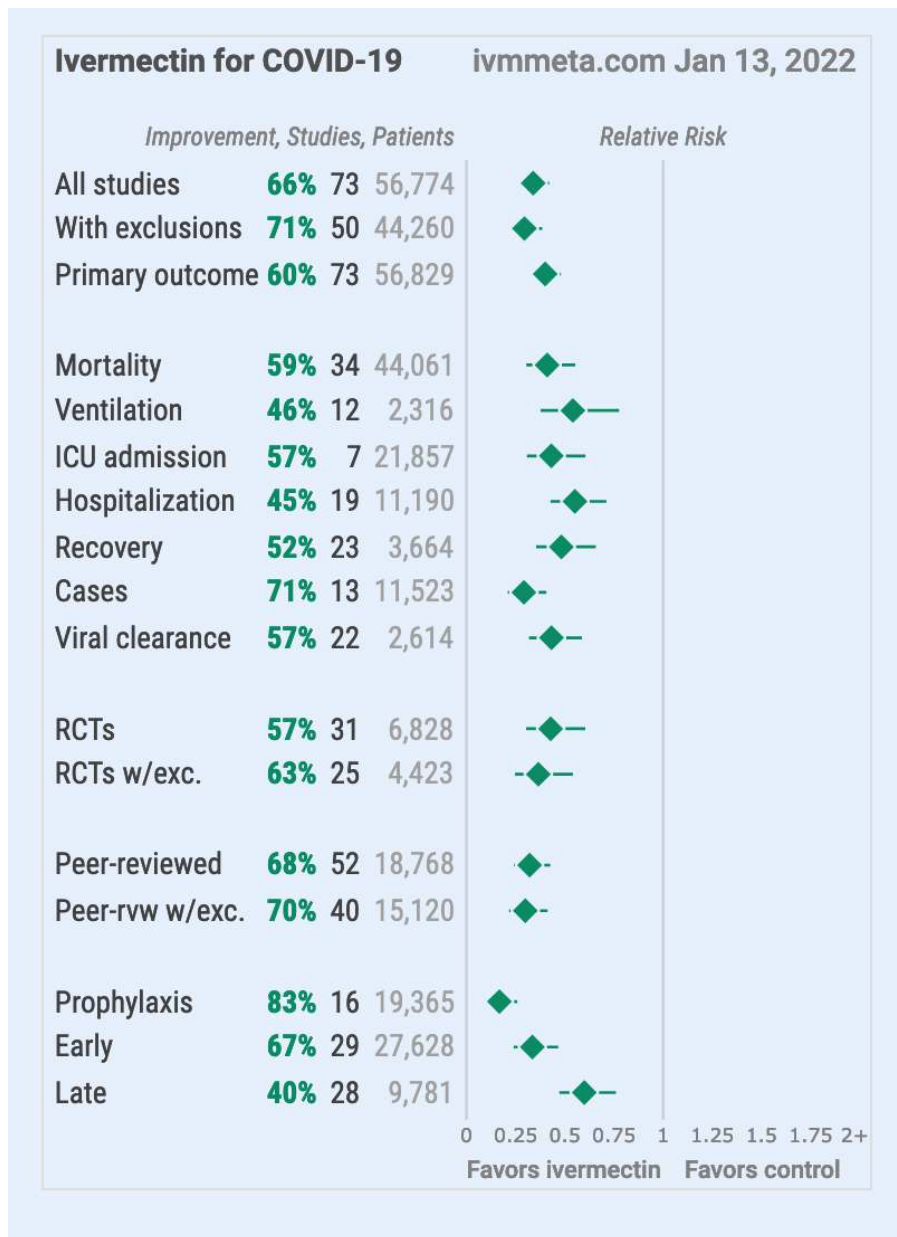
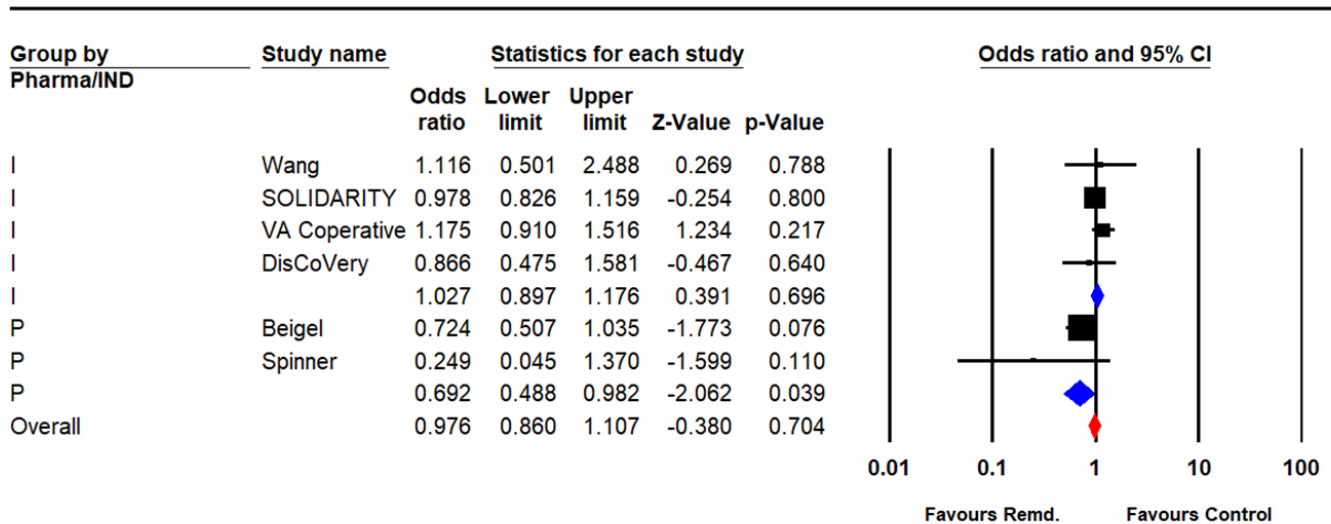


Table 5. A Regimen of Calcifediol* (a Single Dose) to Rapidly Raise Serum 25(OH)D above 50 ng/mL

Weight (lbs)	Weight (kgs)	Calcifediol (mg) [#]	Equivalent in IU	If calcifediol is not available, a bolus vitamin D ₃
15 – 21	7 – 10	0.1	16,000	20,000
22 – 30	10 – 14	0.15	24,000	35,000
31 – 40	15 – 18	0.2	32,000	50,000
41 – 50	19 – 23	0.3	48,000	60,000
51 – 60	24 – 27	0.4	64,000	75,000
61 – 70	28 – 32	0.5	80,000	100,000
71 – 85	33 – 39	0.6	96,000	150,000
86 – 100	40 – 45	0.7	112,000	200,000
101 – 150	46 – 68	0.8	128,000	250,000
151 – 200	69 – 90	1.0	160,000	300,000
201 – 300	91 – 136	1.5	240,000	400,000
>300	> 137	2.0	320,000	500,000

(From SJ Wimalawansa with permission).

Figure 9. Meta-Analysis of the Remdesivir RCTs Grouped by Independent Studies (I) and Those Done by Gilead™ (P)



Meta Analysis

5. MATH+ PROTOCOL (For Patients Admitted to the ICU) [369,370]

5.1 Core Components

- 1. Methylprednisolone** 80 mg loading dose followed by 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 6 hourly, then titrate down as appropriate. [321-333] Pulse methylprednisolone 500-1000 mg/day for 3 days (followed by taper) may be required. [331] We suggest that all patients admitted to the ICU have a chest CT scan on admission to allow risk stratification based on the extent of the disease; those with extensive disease should be initiated on high dose corticosteroids (see section below on severe COVID). As depicted in Table 2, methylprednisolone is the corticosteroid of choice. Observational and randomized studies have clearly demonstrated the superiority of methylprednisolone over low dose dexamethasone. [371,372] These clinical findings are supported by a genomic study.[227] Methylprednisolone should be weaned slowly over two weeks once oxygen is discontinued to prevent relapse/recurrence (20mg twice daily once of oxygen, then 20 mg/day for 5 days, then 10 mg/day for 5 days). While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/countries where it is not available the following (in order of preference) may be substituted for methylprednisolone (dose adjusted according to methylprednisolone dosages), 2) prednisolone, 3) prednisone, 4) hydrocortisone, and 5) LASTLY dexamethasone.
- 2. Ascorbic acid (Vitamin C)** 50 mg/kg (or 3000 mg) IV q 6 hourly for at least 7 days and/or until transferred out of ICU. [124,125,130,373-383]. *Mega-dose vitamin C* should be considered in severely ill patients, those with progressive respiratory failure and as salvage therapy: 25 g vitamin C in 200-500 cc saline over 4-6 hours every 12 hourly for 3-5 days, then 3g IV q 6 hourly for total of 7-10 days of treatment [384] (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. [385] 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.[384] Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport proteins and it is difficult to achieve adequate levels with PO administration. However, should IV Vitamin C not be available, it would be acceptable to administer PO vitamin C at a dose of 1g every 4–6 hours.
- 3. Anticoagulation:** The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a marginally increased mortality in ICU patients treated with full anti-coagulation (35.3% vs. 32.6%).[334] Critically ill COVID-19 patients frequently have impaired renal function and it is likely that in the absence of Xa monitoring patients were over-anticoagulated. However, full anti-coagulation should be continued on floor patients transitioned to the ICU who have normal renal function. In all other patients we would suggest intermediate dose enoxaparin i.e 60 mg/day (enhanced thromboprophylaxis) or 0.5 mg/kg q 12 hourly.[386] Full anticoagulation (enoxaparin or heparin) may be required in patients with increasing D-dimer or with thrombotic complications. Due to augmented renal clearance some patients may have reduced anti-Xa activity despite standard dosages of LMWH.[236] We therefore recommend monitoring anti-Xa activity aiming for an anti-Xa activity of 0.5 – 0.9 IU/ml. Heparin is suggested with CrCl < 15 ml/min. It should also be appreciated that vitamin C is a prerequisite for the synthesis of collagen and vitamin C deficiency

is classically associated with vascular bleeding.[124,125] This is relevant to COVID-19, as vitamin C levels are undetectable in severely ill COVID-19 patients and this may partly explain the increased risks of anticoagulation in ICU patients (not treated with vitamin C). [387-389] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [390]

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

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

5.2 Additional Treatment Components

4. Highly recommended: Ivermectin 0.6 – 0.8 mg/kg day orally for 5 days or until recovered [34,74-76,181,184-191,316-318,391-397]. A higher dose (up to 1.0 mg/kg) is suggested in patients with severe disease and/or those with delayed initiation of therapy. Note that ivermectin has potent antiviral and anti-inflammatory effects. As noted above clinical outcomes are superior with multiday as opposed to single day dosing. Furthermore, as indicated above, higher dosages and a longer treatment course are suggested with the Delta variant.
5. Nitazoxanide (NTZ) 600 mg BID for 7 days.[320] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
6. Melatonin 10 mg at night.[51-53]
7. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [398-403] Thiamine may play a role in dampening the cytokine storm. [399,404]
8. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe prothrombotic state and increasing the inflammatory response.[229,230,341,342] As the risk of significant bleeding is increased in patients receiving both ASA and heparin, ASA should therefore not be used in patients at high risk of bleeding. In addition (as noted below) patients should receive famotidine concurrently.
9. The anti-serotonin agent, cyproheptadine. Platelet activation results in the release of serotonin, which may contribute to the immune and vascular dysfunction associated with COVID-19. [215-219] Therefore, the serotonin receptor blocker cyproheptadine 4–8 mg PO q 6 hours should be considered.
10. Anti-androgen therapy (both men and women). Spironolactone 100 mg BID for 10 days. Second line: Dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. Finasteride 10 mg is an alternative (dutasteride cannot be crushed).[244] [405] **AVOID IN PREGNANCY.** [242,247] Bicalutamide 150 mg daily is also an option.
11. Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40 mg daily is an alternative.

5.3 Second Line Treatments

12. B complex vitamins.
13. Calcifediol [25-hydroxylated vitamin D; 25(OH)D]. Dosing as suggested in Table 5
14. Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed.
15. Atorvastatin 40- 80 mg/day (reduce dose to 40 mg if taken with ivermectin due to possible drug-drug interaction. Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[238-242] *Due to numerous drug-drug interactions simvastatin should be avoided.*
16. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [176] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [406-408]

5.4 Optional Treatments (and those of uncertain benefit)

17. *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [59-65].
18. *Optional:* JAK inhibitors ruxolitinib or baricitinib.
19. *Unclear benefit.* Losartan 50- 100 mg q day (reduce to 25 -50 mg with impaired renal function) or telmisartan 40-80 mg BID (reduce to 40 mg q day /BID with impaired renal function). [303,409,410]
20. *Unclear benefit.* Maraviroc 300 mg BID for 10 days. Maraviroc is a CCR5 antagonist. [291] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19.[288,411] Blocking the CCR5 receptor (CCR5R) repolarizes macrophages/monocytes and decreases the production of proinflammatory cytokines (see section on repolarizing macrophages/monocytes and section on Long-Covid).
21. *Not recommended:* The best information to date suggests that prophylactic azithromycin as well as doxycycline and quinolone antibiotics are of little benefit in patients with COVID-19.[312,412,413] Patients with COVID-19 are at an increased risk of developing bacterial superinfections and prophylactic antibiotics may increase the risk of infection with multi-resistant organisms.
22. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
23. *Not recommended.* Convalescent serum [414-419] nor monoclonal antibodies. [420] However, convalescent serum/ monoclonal antibodies may have a role in patients with hematologic malignancies.[421]
24. *Not recommended.* Colchicine (see above).
25. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [422-426] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [427] Tocilizumab may have of benefit in patients receiving an inadequate dose of corticosteroids.[428] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.
26. Broad-spectrum antibiotics added if complicating bacterial pneumonia is suspected based on procalcitonin levels and respiratory culture (no bronchoscopy). Due to the paradox of hyperinflammation 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. [429-431] Patients with non-

resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [432] Recommended first-line therapy for CAPA is either voriconazole or isavuconazole (beware drug-drug interactions). While low CD4 counts are typical of severe COVID-19 infection, PJP infections have not been reported; therefore PJP prophylaxis is not required.

27. Maintain *EUVOLEMIA* (this is not non-cardiogenic pulmonary edema). Due to the prolonged “symptomatic phase” with flu-like symptoms (6–8 days) patients may be volume depleted. Cautious rehydration with 500 ml boluses of Lactate Ringers may be warranted, ideally guided by non-invasive hemodynamic monitoring. Diuretics should be avoided unless the patient has obvious intravascular volume overload. Avoid hypovolemia.
28. Early norepinephrine for hypotension. It should however be appreciated that despite the cytokine storm, vasodilatory shock is distinctly uncommon in uncomplicated COVID-19 (when not complicated by bacterial sepsis). This appears to be due to the fact that TNF- α which is “necessary” for vasodilatory shock is only minimally elevated.
29. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible.*** Intubation is indicated in patients who have failed non-invasive ventilation and in those patients with excessive work of breathing. A subgroup of patients with COVID-19 deteriorates very rapidly. Intubation and mechanical ventilation may be required in these patients.
 - a. Accept “permissive hypoxemia” (keep O₂ Saturation > 84%); follow venous lactate and Central Venous O₂ saturations (ScvO₂) in patents with low arterial O₂ saturations
 - b. N/C 1–6 L/min
 - c. High Flow Nasal canula (HFNC) up to 60–80 L/min [433]
 - d. Trial of inhaled Flolan (epoprostenol)
 - e. Attempt proning (cooperative repositioning-proning) [434-437]
 - f. Intubation ... by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
 - g. Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cm H₂O.
 - h. Moderate sedation to prevent self-extubation
 - i. Trial of inhaled Flolan (epoprostenol)
 - j. Prone positioning.

There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no evidence to support this fear.[438,439] HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. HFNC is preferred over conventional oxygen therapy. [433] Intermittent CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

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

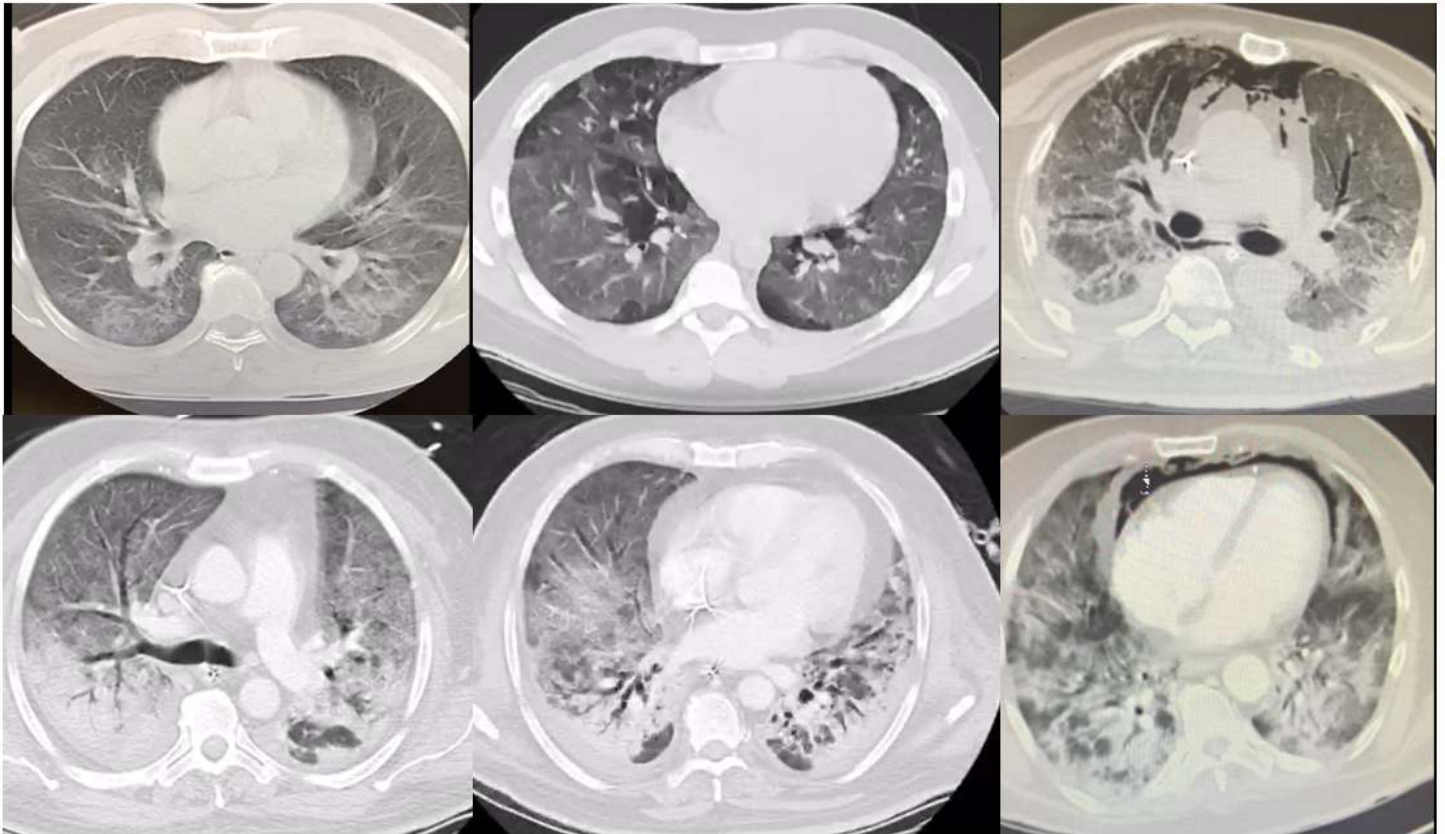


Table 6: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone - Number Need to Treat (NNT)

PUBLISHED RCT's/OCT's OF CORTICOSTEROID THERAPY IN COVID-19		ABSOLUTE DIFFERENCE IN MORTALITY	NUMBER NEEDED TO TREAT TO SAVE ONE LIFE
METHYLPREDNISONE – HOSPITAL PATIENTS (Edalatifard et al, Italy) 250mg methylprednisone daily x 3 days		5.9% vs. 42.9%	2.7
METHYLPREDNISONE – ICU PATIENTS (Confalonieri et al, Italy) 80mg methylprednisone daily x 8 days		7.2% vs. 23.3%	6.2
METHYLPREDNISONE- ARDS PATIENTS (OCT - Wu C et al- China) 1-2 mg/kg/day for 3-5 days		46.0% vs. 61.8%	6.3
METHYLPREDNISONE – HOSPITAL PATIENTS, (OCT - Fadel et al, USA) 0.5-1.0mg/kg/day x 3 days		13.6% vs. 26.3%	7.8
METHYLPREDNISONE - Pts on oxygen – (Fernandez-Cruz et al, Spain) 1mg/kg/day		13.9% vs. 23.9%	10.0
METHYLPREDNISONE VS. DEXAMETHASONE (Ranjbar et al, Iran) 2mg/kg/day MP vs. 6mg/day Dexamethasone		18.6% vs 37.5%	5.3
METHYLPREDNISONE VS. DEXAMETHASONE (OCT - Ko et al, USC) >= 1mg/kg/day MP for min. 3 days vs. 6mg/day Dex for min. 7 days	OVERALL	16.4% vs. 26.5%	10
	PTS ON MV	31% vs. 54%	4.3
HYDROCORTISONE -CAPE-COVID – ICU Patients (Dequin et al France) 200mg/day with taper over 14 days – stopped early		14.7% vs 27.4%	7.9
HYDROCORTISONE –REMAP-CAP – ICU Patients (Angus et al) 200 - 400 mg/day x 7 days – stopped early		28% vs 33% (NS)	20.0
DEXAMETHASONE – CODEX – ICU Patients (Tomazini et al) 20 mg x 5 days, 10 mg x 5 days		56.3% vs 61.5%	19.2
DEXAMETHASONE – RECOVERY (Hornsby et al) 6mg/day x 10 days	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4

6. An Approach to the Patient with Severe Life Threatening COVID-19 Organizing Pneumonia

The first task of the clinician is to determine the reversibility of the pulmonary disease. This is a critical assessment. Aggressive anti-inflammatory treatment is futile in patients with advanced fibrotic lung disease. The horse has already bolted and allowing the patient a “peaceful death” is the most compassionate and humane approach. The reversibility of the pulmonary disease is dependent on a number of factors superseded by a good deal of clinical judgement; these include:

- a) The length of time that has elapsed since the onset of symptoms. Early aggressive treatment is critical to prevent disease progression. With each day the disease becomes more difficult to reverse. The ‘traditional’ approach of supportive care alone is simply unacceptable.
- b) The level of inflammatory biomarkers particularly the CRP. In general the CRP tracks the level of pulmonary inflammation. [440] A high CRP is indicative of a hyper-inflammatory state and potentially reversible pulmonary inflammation.
- c) It is likely that advanced age is a moderating factor making the pulmonary disease less reversible.
- d) A chest CT is extremely helpful in determining the reversibility of disease. BEWARE this is not ARDS but organizing pneumonia. [441] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively (see Figure 10). [440,442-448] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19. [449,450] The changes in the CT follow a stereotypic progressive pattern:
 - I. Peripheral, patchy, predominantly basal ground glass opacification (GGO). GGO is defined an increase in density of lung with visualization of bronchial and vascular structures through it
 - II. Progressive widespread bilateral GGO
 - I. Crazy-paving (CGO with interlobular and intralobular septal thickening)
 - II. Air space consolidation (air bronchograms)
 - III. Dense airspace consolidation
 - IV. Coalescent consolidation
 - V. Segmental/subsegmental pulmonary vessel dilatation
 - VI. Bronchial wall thickening
 - VII. Linear opacities
 - VIII. Traction bronchiectasis
 - IX. Cavitation
 - X. Fibrotic changes with bullae and reticulation

GGO pattern is significantly more prevalent in early-phase disease compared with late-phase disease while crazy-paving and consolidation patterns are significantly more common in late-phase. [440] Therefore widespread GGO suggests reversibility while widespread consolidation with other features of more advanced disease suggest irreversible lung disease. However, when in doubt (borderline cases) a time-limited therapeutic trial of the aggressive “Full Monty” approach may be warranted.

7. The “FULL MONTY” for SEVERE COVID Pulmonary Disease

- I. Methylprednisolone 250-500 mg q 12 hourly for at least 3 days then titrate guided by clinical status and CRP.
- II. Ivermectin 1.0 mg/kg for 5 days
- III. Melatonin 10 mg PO at night
- IV. Enoxaparin 60 mg daily; critically ill patients usually have some degree of renal impairment and will require a renally adjusted lower dose. Patients with very high D-dimer and or thrombotic complications may require full anticoagulant doses of Lovenox. It may be prudent to monitor Xa levels aiming for 0.4-0.8 IU/ml (a somewhat lower anti-Xa).
- V. Vitamin C 3 g 6 hourly to 25g q 12 hourly
- VI. Cyproheptadine 4–8 mg PO q 6 hourly
- VII. Fluvoxamine 50- 100 mg BID or fluoxetine 20-40mg daily
- VIII. Spironolactone 100 mg BID
- IX. Atorvastatin 80 mg/day (reduce dose to 40mg if taken with ivermectin due to possible drug-drug interaction)
- X. Thiamine 200 mg q 12 hourly
- XI. NAC 1200 mg PO BID [272]
- XII. Finasteride 10 mg daily or dutasteride 2mg day 1 then 1mg daily or bicalutamide 150mg daily
- XIII. Omega-3 fatty acids 4g/day
- XIV. Famotidine 40 mg BID
- XV. Calcifediol (0.014 mg/kg) use as a single dose (see Table 5)
- XVI. Consider plasma exchange on admission to the ICU.

While it is unclear which of the above medications included in the “Severe Covid-19” cocktail contributes to improved outcomes, all of these drugs have been shown to be safe and independently to improve the outcome of patients with COVID-19. Ultimately it is irrelevant as to the contribution of each element as long as the patient improves and survives his/her ICU stay. We are in the midst of a pandemic caused by a virus causing devastating lung disease, and there is no place for “ivory tower medicine.”



8. Salvage Treatments

- High dose bolus corticosteroids; 500–1000 mg/day methylprednisolone for 3 days then taper. [329,331]
- Plasma exchange [451-457]. 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”.
- Calcifediol (0.014 mg/kg) use as a single dose (see Table 5)
- 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.[384,385] (also see <https://www.youtube.com/watch?v=Au-mp6RZjCQ>)
- In patients with a large dead-space ventilation i.e. high PaCO₂ 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.[458,459]
- 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”. [460-463]
- ECMO [464-466]. Unlike “typical ARDS”, COVID-19 patients may not progress into a resolution phase. Rather, patients with COVID-19 with unresolved inflammation may progress to a severe fibro-proliferative phase and ventilator dependency. ECMO in these patients would likely serve little purpose. ECMO however may improve survival in patients with severe single organ failure (lung) if initiated within 7 days of intubation. [467]
- Lung transplantation. [468]

9. Salvage treatments of unproven/no benefit

- Convalescent serum/monoclonal antibodies: Four RCTs failed to demonstrate a clinical benefit with the use of convalescent serum. [414-416,418,419] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[469] 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.[470] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [471]
- In patients hospitalized with severe COVID-19, Canakinumab, an anti-interleukin-1 β antibody failed to improve any outcome measure. [472]

- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [473-476] 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 [477,478] This treatment strategy appears to have an extremely limited role.

10. Treatment of Macrophage Activation Syndrome (MAS)

- Severe-COVID pneumonia/organizing pneumonia is in essence caused by the “pulmonary macrophage activation syndrome” and the distinction between severe COVID and MAS is unclear (see below). [9,441,479,480]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multisystem organ failure.[481]
- *“High dose corticosteroids.”* Methylprednisolone 500-1000 mg daily for three days and then wean according to Ferritin, CRP, AST/ALT. Ferritin should decrease by at least 15% before weaning corticosteroids.
- Consider plasma exchange.

11. Approach to the DELTA/P1 Variant

- Both the Delta and P1 variants are highly virulent strains of SARS-CoV-2. These variants replicate to achieve very high concentrations in the nasopharynx; hence they are much more transmissible and the time from exposure to symptom onset and to the pulmonary phase is much shorter. It is not uncommon for patients to be symptomatic for as little as 3 days prior to ICU admission.
- Early (day 1) outpatient treatment (MASK +) is critical to prevent progression to the more lethal pulmonary phase.
- ICU patients frequently present with very high levels of inflammatory markers (CRP, Ferritin, D-Dimer)
- The ‘Full Monty’ should be started on the first ICU Day.
- In those patients with very high inflammatory markers plasma exchange should be considered on admission.

12. Approach to the Omicron Variant

Omicron, the SARS-CoV-2 variant responsible for a cluster of cases in South Africa and that is now spreading around the world, is the most heavily mutated variant to emerge so far and carries mutations similar to changes seen in previous variants of concern associated with enhanced transmissibility and partial resistance to vaccine induced immunity. [13,482] In South Africa, Omicron has completely displaced the Delta variant, with Omicron being the major variant. [13,483] In total, the variant’s genome has around 50 mutations, including more than 30 in the spike protein. One of the omicron variant’s mutations leads to “S gene target failure” (or “S gene dropout”), meaning that one of several

areas of the gene that are targeted by PCR testing gives a false negative. Omicron is highly infectious, spreading rapidly among communities with neutralizing antibodies against SARS-CoV-2 acquired by natural infection or vaccination appearing to have limited protection. [18,19,482] In a case series of 785 cases from Denmark, 76% of patients were fully vaccinated. [16] Despite the apparent lack of efficacy of vaccination and monoclonal antibodies, antivirals directed at SARS-CoV-2 remain effective. [484] A high infectivity rate has been reported in large group gatherings. [16] While Omicron is highly infectious, it appears to cause much milder disease. Anosmia and ageusia are uncommon, which may distinguish Omicron from previous variants. Furthermore, Omicron appears less likely to cause pulmonary disease; this may be related to altered ACE-2 binding to pulmonary alveolar cells. [485] Nevertheless, the elderly and those with significant comorbidities may suffer severe disease.

At this time the prevention and early treatment for Omicron should not differ from that of the previous variants, i.e., the I-MASK+ protocol should be followed. Early treatment is critical to limit spread of the virus, and as this variant is highly infectious prophylaxis of close contacts is important. Similarly, it is likely that early treatment may limit the progression to long-COVID. Those infected with Omicron should be quarantined for up to 5 days. The optimal dose of ivermectin for early treatment is unclear, however, it is likely that a lower dose may suffice i.e. 0.3- 0.4 mg/kg. The Omicron variant uses an endosomal cell entry mechanism (where HCQ acts) making HCQ particularly useful for this variant. [486]

13. Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[487] A PCT is essential to rule out coexisting bacterial pneumonia.[488]
- As indicated above (corticosteroid section), a chest CT scan on admission to the ICU is very useful for risk stratification and for the initial corticosteroid dosing strategy. The Ichikado Score is a quantitative method to assess the extent of lung involvement on the CT scan.[449,489] Follow-up CXR, CT scan (if indicated) and chest ultrasound as clinically indicated.
- Daily: *CRP, Ferritin, D-Dimer and PCT*. CRP and Ferritin track disease severity closely (although ferritin tends to lag behind CRP). Early high CRP levels are closely associated with the degree of pulmonary involvement and the CT score. [490]
- 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. [491,492]
- ECHO as clinically indicated; Patients may develop a severe “septic” cardiomyopathy and/or COVID-19 myocarditis. [493,494]

14. Post ICU Management

- Enoxaparin 40–60 mg s/c daily
- Methylprednisolone 40 mg day, then wean slowly, follow CRP and oxygen requirements – wean off over two weeks once oxygen is discontinued to prevent relapse/recurrence
- Vitamin C 500 mg PO BID
- Melatonin 3–6 mg at night

- Vascepa, Lovaza or DHA/EPA 4g day
- Atorvastatin 40mg daily

15. Post Hospital Discharge Management

- Patients have an increased risk of thromboembolic events post-discharge. [495,496] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include: [497]
 - Increased D dimer (> 3 times ULN)
 - Increased CRP (> 2 times ULN) [498]
 - Age > 60
 - Prolonged immobilization
- Patients with unresolved pulmonary infiltrates and/or those who remain dyspneic and/or oxygen dependent should be discharged on a tapering course of corticosteroids (prednisone).
- Patients should continue to receive vitamin C, melatonin, omega-3 fatty acids and a statin. These agents may reduce this risk of developing the post-COVID syndrome.
- Nigella sativa and Kefir.
- Patients should be followed/monitored for developing the post-COVID/long hauler syndrome.

16. Pathophysiology of COVID-19

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

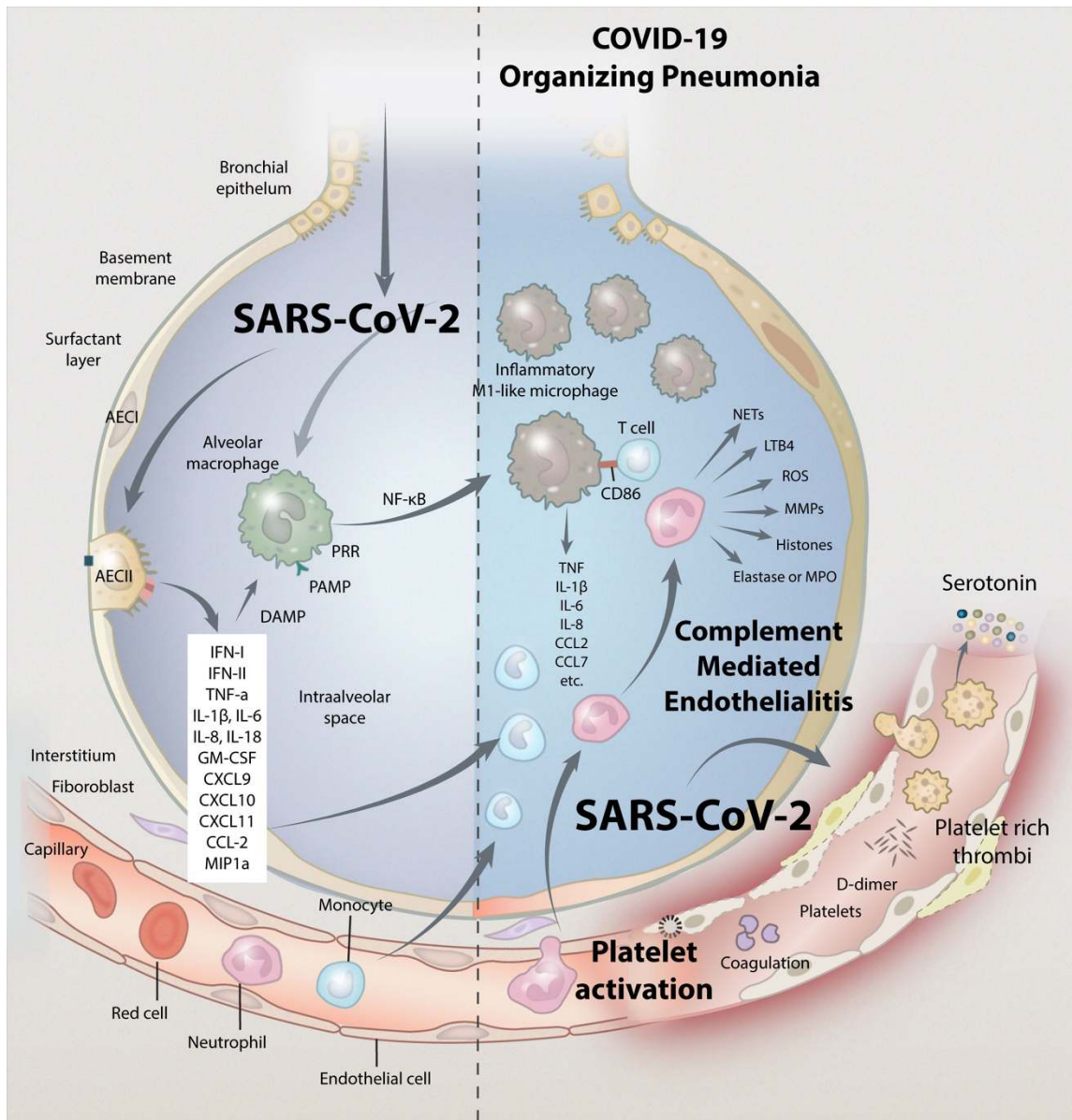
The pathophysiology of COVID-19

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

Based on clinical, proteomic, and genomic studies as well as autopsy data, severe COVID-19 disease can be considered to be the connection of three basic pathologic processes, namely a pulmonary macrophage activation syndrome with excess production of cytokines and chemokines and uncontrolled inflammation, a complement mediated endothelialitis together with a procoagulant state with a

thrombotic microangiopathy (see figure 11). In addition, platelet activation with the release of serotonin and the activation and degranulation of mast cells contributes to the hyper-inflammatory state. Autoantibodies have been demonstrated in a large number of hospitalized patients which adds to the end-organ damage and prothrombotic state. However, activated M1 macrophages appear to be the major driver of severe COVID-19 infection. Similarly, recent data suggests that the Long Haul Covid Syndrome (LHCS) results due to increased circulating levels of activated monocytes with ongoing cytokine production. [411] Interestingly, these monocytes contain high levels of the spike protein. [499] Both activated macrophages and activated monocytes express the same surface activation markers (CD14+, CD16+). This suggests that treatment aimed at repolarizing the macrophage/monocyte should have an important adjunctive role in the treatment of both acute COVID and the LHCS. Those interventions that have been demonstrated to repolarize macrophages/monocytes (from M1 to M2 phenotype) are listed below.

Figure 11. Pathogenetic Mechanism of Severe COVID-19 Disease



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

The Long Haul COVID Syndrome (LHCS) is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain and cognitive dysfunction. [500-512] Up to 80% of patients experience prolonged illness after Covid-19. LHCS is not only seen after the COVID infection, but it is being observed in some people that have received vaccines (likely due to monocyte/microglia activation by the spike protein from the vaccine). LHCS may persist for months after the acute infection and almost half of patients report reduced quality of life. Patients may suffer prolonged neuropsychological symptoms, including multiple domains of cognition. [509,513] A puzzling feature of the LHCS syndrome is that it is not predicted by initial disease severity; post-COVID-19 frequently affects mild-to-moderate cases and younger adults that did not require respiratory support or intensive care. [511]

The symptom set of LHCS is in the majority of the cases very similar to the chronic inflammatory response syndrome (CIRS)/ myalgic encephalomyelitis/chronic fatigue syndrome. [511] An important differentiating factor from CIRS is the observation that LHCS continues to improve on its own albeit slowly in the majority of cases. Another important observation is that LHCS includes more young people compared to severe COVID, which affects older people or persons with comorbidities. Furthermore, the similarity between the mast cell activation syndrome and LHCS has been observed, and many consider post-COVID to be a variant of the mast cell activation syndrome. [514]

The LHCS syndrome is highly heterogeneous and likely results from a variety of pathogenetic mechanisms. Furthermore, it is likely that delayed treatment (with ivermectin, etc.) in the early symptomatic phase will result in a high viral load which increase the risk and severity of LHCS. The following theories have been postulated to explain LHCS: [511]

1. Ongoing respiratory symptoms (SOB, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activated pulmonary macrophages).
2. Monocyte and microglia activation. Persistence of viral debris (? Spike protein) in monocytes and microglia results in an ongoing inflammatory response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments.
3. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[515] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [516] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [517] as well as severe cerebral vasoconstriction. [518] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirions" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[519].
4. An unmasking of mast cell activation syndrome (MCAS), or triggering of mast cell activation syndrome. Mast cells are present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for corticotropin releasing hormone.[520] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may

result in neurovascular inflammation.[520] The “brain-fog”, cognitive impairment and general fatigue reported in long-COVID may be due to mast cell related neurovascular inflammation.

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

1. Respiratory: shortness of breath, congestion, persistent cough, etc.
2. Neurological/psychiatric: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus/concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.
3. Musculoskeletal: myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life (ADL’s).
4. Cardiovascular: Palpitations, arrhythmias, Raynaud like syndrome, hypotension, and tachycardia on exertion.
5. Autonomic: Postural tachycardia syndrome (POTs), abnormal sweating.
6. Gastrointestinal disturbance: Anorexia, diarrhea, bloating, vomiting, nausea, etc.
7. Dermatologic: Itching, rashes, dermatographia
8. Mucus membranes: Running nose, sneezing, Burning and itchy eyes.

17.1 Approach to Treatment:

The treatment approach should be individualized according to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g. ivermectin, etc) during the acute symptomatic phase and adequate anti-inflammatory/macrophage repolarization therapy (e.g. corticosteroids, statins, omega-3 fatty acids, fluvoxamine, ivermectin, etc.) during the acute phase of COVID-19 are much more likely to develop the Post-COVID-19 Syndrome.

In patients with ongoing respiratory symptoms, chest imaging is suggested (preferably a chest CT scan). Those with unresolved pulmonary inflammation (organizing pneumonia with ground glass opacification) should be treated with a course of corticosteroids. Low-dose prednisolone/ methylprednisolone (10 mg/day) for six weeks is suggested. [521] However, the patients’ symptoms and CRP should be followed closely as a dose escalation may be required in those who respond poorly. An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. Pulmonary function testing demonstrates a restrictive type pattern with decreased residual volume and DLCO.[506] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [473-476] however additional data is required before this therapy can be more generally recommended. As discussed above, the serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. [364]

Similar to patients who have recovered from septic shock, [522] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the LHCS. This is

likely the consequence of monocyte activation syndrome and monocyte repolarization therapy is therefore indicated. Activated microglia may contribute to the neurological symptom's characteristic of LHCS. A cytokine panel may allow targeted anti-inflammatory therapy (Maraviroc in patients with high CCR5 levels). It should be noted that much like omega-3 fatty acids, corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4. [523]

Naltrexone is a well-known opioid antagonist used in chronic opiate abuse. Naltrexone is classically prescribed in daily doses of at least 50 mg taken orally. Paradoxically, low dose naltrexone (LDN) in a dose between 1 to 5 mg has been demonstrated to have anti-inflammatory, analgesic and neuromodulating properties. Specifically, LDN has been shown to reduce glial inflammatory response by modulating Toll-like receptor 4 signaling in addition to systemically upregulating endogenous opioid signaling by transient opioid-receptor blockade. [315,524] LDN typically in a dose of 4.5 mg has been used successfully to treat fibromyalgia, Crohn's disease, multiple sclerosis, and complex chronic pain syndromes as well as many chronic pain syndromes. [315,524] LDN may be particularly useful in the treatment of LHCS as it inhibits activated macrophages/monocytes and microglia. [524,525] Once activated, microglia produce inflammatory and excitatory factors that can cause sickness behaviors such as pain sensitivity, fatigue, cognitive disruption, sleep disorders, mood disorders, and general malaise; clinical features typical of those found with LHCS.

17.2 The I-RECOVER Protocol for the Treatment of “Long-haul COVID Syndrome”

Although numerous reports describe the epidemiology and clinical features of LHCS, [500-510] studies evaluating treatment options are glaringly sparse. [312] Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations. [526] In general, while the treatment of ‘Long COVID’ should be individualized, the following treatments may have a role in the treatment of this disorder. In addition, the I-RECOVER protocol may have a role in the treatment of post-vaccination syndrome. Patients with Long Covid should be managed by clinicians who have experience treating this troublesome disorder.

17.3 First Line Therapies

- 10-15 mg prednisone daily for 3 weeks. Taper to 10mg for three days, then 5 mg for three days and then stop.
- Ivermectin: 0.2 mg/kg body weight. Once daily for 1 week.
- Low dose naltrexone (LDN): Begin with 1 mg daily and increase to 4.5 mg as required. May take 2-3 months for full effect.
- Omega-3 fatty acids: Vascepa, Lovaza or DHA/EPA 4 g day. Omega-3 fatty acids play an important role in the resolution of inflammation by inducing resolvin production. [284,285]
- Vitamin D. The majority of those with post-COVID syndrome continue to have hypovitaminosis D. see tables 2 or 3 for vitamin D supplementation.

If symptoms do not improve after 1-2 weeks continue steroids, omega-3 fatty acids and Naltrexone and add second line medications.

17.4 Second Line Therapies

- Fluvoxamine (low dose) 25 mg once daily. Stop if the symptoms increase. Caution with the use of other antidepressants and psychiatric drugs. Taper and discontinue once symptoms improve.
- Atorvastatin: 20 -40 mg once daily. Caution in patients with Postural Orthostatic Tachycardia Syndrome (POTS); may exacerbate symptoms.

17.5 Third Line Therapy

- If InCellDx laboratory tests demonstrate high long hauler index despite above medications for 6-8 weeks, then consider Maraviroc 300 mg PO BID. Maraviroc is a C-C chemokine receptor type 5 (CCR5) antagonist. CCR5 receptors are expressed on macrophages and dendritic cells. CCR5 interacts with multiple ligands, notably the chemokines CCL3 (macrophage inflammatory protein-1), CCL4 (macrophage inflammatory protein-1), and CCL5 (RANTES). CCR5 and its ligands are overexpressed in COVID-19. [290,291,527] The activated CCR5 pathway may partly explain the persistence of activated monocytes in long-COVID. [411,499] Maraviroc is an expensive drug which has significant side effects and drug interactions.

17.6 Optional adjunctive therapies (in order of priority)

- Curcumin has anti-inflammatory and immunomodulating properties and has been demonstrated to repolarize macrophages. [108]
- *Nigella sativa* which like curcumin has anti-inflammatory and immunomodulating properties
- Vitamin C 500 mg BID (vitamin C inhibits histamine and repolarizes monocytes).[124]
- Melatonin 2- 8 mg at night (slow release/extended release) with attention to sleep hygiene. Increase dose from 1 mg as tolerated (may cause severe nightmares at high dosages)
- Kefir, probiotic yogurt and/or Bifidobacterium Probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome. Prolonged dysbiosis has been reported following COVID-19 infection. [528]
- Melatonin 2- 8 mg at night (slow release/extended release) with attention to sleep hygiene. Increase dose from 1 mg as tolerated (may cause severe nightmares at high dosages)
- Behavioral modification, mindfulness therapy [529] and psychological support may help improve survivors' overall well-being and mental health. [511]
- Luteolin 100-200 mg day or quercetin 250 mg day (or mixed flavonoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells,[520,530-533] and have been demonstrated to reduce neuroinflammation. [534]
- Famotidine 20-40 mg day (histamine-2 blocker for Mast Cell Activation syndrome). [514]
- H1 receptor blockers (for mast cell activation syndrome). Loratadine 10mg daily, Cetirizine 5-10mg daily, Fexofenadine 180mg daily.
- H2 receptor blockers (for mast cell activation syndrome). Famotidine 20 mg, or Nizatidine 150 mg – twice daily as tolerated.
- Montelukast 10 mg/day (for mast cell activation syndrome). Caution as may cause depression in some patients.
- Anti-androgen therapy. Spironolactone 50-100 mg BID and dutasteride 1mg daily.

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

- Corticosteroids [535]
- Statins [343,344]
- Omega-3 fatty acids [279-281]
- Melatonin [536]
- Vitamin C
- Anti-androgen therapy [537-539]
- Curcumin (turmeric) [108]

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

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

1. It is important to focus on the totality of the evidence and not just on RCTs (see figure 11). We are in the midst of a global pandemic and the use of cheap, effective, and safe repurposed drugs has and will continue to have a major role in the prevention and treatment of this disease.
2. Patients transition through a number of different phases (clinical stages). The treatment of each phase is distinct... this is critically important (see Figures 1 & 2).
3. Antiviral therapy is likely to be effective only during the viral replicative phase, whereas anti-inflammatory therapy is expected to be effective during the pulmonary phase and possibly the post-COVID-19 phase. While remdesivir is a non-specific antiviral agent that targets RNA viruses, it is likely that agents specifically designed to target SARS-CoV-2 will be developed.
4. The SARS-CoV-2 PCR remains positive for at least 2 weeks following detection of whole virus (by culture, See figure 3). Patients who progress to the pulmonary phase are usually PCR positive despite cessation of viral replication (and are therefore less likely to be infectious).
5. Due to the imperfect sensitivity of the PCR test, as many as 20% of patients who progress to the pulmonary phase will be PCR negative (even on repeat testing). At symptom onset PCR will be positive in approximately 60% of patients; maximal positivity rate is on day 8 (post infection) when 80% of patients will be positive (see Figure3). [540] COVID-19 is essentially a clinical diagnosis supported by laboratory tests.
6. Symptomatic patients are likely to be infectious during a narrow window starting 2–3 days before the onset of symptoms and to up to 6 days after the onset of symptoms (see Figure 3). [541]
7. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, SARS-CoV-2 variant, genetic heterogeneity mutations and polymorphisms, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[324,542-552] 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. [553]

8. The pulmonary phase is characterized by immune dysregulation, [515,545,554-567] a pulmonary microvascular injury (vasculopathy), [515,567-570] with activation of clotting and a procoagulant state together with the characteristics of an organizing pneumonia. [441,571]
9. Endothelial damage and an imbalance of both innate and adaptive immune responses, with aberrant macrophage activation, plays a central role in the pathogenesis of the severe COVID-19 Disease. [515]
10. As patients progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are two-fold.
 - a. Early treatment (of the pulmonary phase) is ESSENTIAL to a good outcome.
 - b. Treatment in the late pulmonary phase may require escalation of the dose of corticosteroids as well as the use of salvage methods (i.e., plasma exchange). However, patients who present in the late pulmonary phase may have progressed to the irreversible pulmonary fibroproliferative phase.
11. The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to “supportive care” alone. Furthermore, it is unlikely that there will be a single “silver bullet” to treat severe COVID-19 disease. Rather, patients will require treatment with multiple drugs/interventions that have synergistic and overlapping biological effects. Repurposed FDA approved drugs that are safe, inexpensive, and “readily” available are likely to have a major therapeutic effect on this disease. The impact of COVID-19 on middle- and low-income countries is enormous; these countries are not able to afford expensive proprietary “designer” molecules.
12. The radiographic and pathological findings of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [441,572,573]
13. THIS is NOT ARDS (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS. [574-576] The ground glass infiltrates are peripheral and patchy, [572] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with “typical ARDS”. [577] Extravascular lung water index (EVLWI) is normal or only slightly increased; this by definition excludes non-cardiogenic pulmonary edema (ARDS). Lung compliance is normal (this excludes ARDS). Patients are PEEP unresponsive. Treating patients as if they ARDS is an extremely dangerous approach. The hypoxia is due to an organizing pneumonia with severe ventilation/perfusion mismatch likely due to the microvascular narrowing, thrombosis and vasoplegia.
14. The core principles of the pulmonary phase (MATH+) is the use of anti-inflammatory agents to dampen the “cytokine storms” together with anticoagulation to limit the microvascular and macrovascular clotting and supplemental oxygen to help overcome the hypoxia.
15. Ivermectin has emerged as a highly effective drug for the prophylaxis and treatment of COVID-19. Ivermectin inhibits viral replication and has potent anti-inflammatory properties. Emerging clinical data (including RCTs) suggest that ivermectin may have an important clinical benefit across the spectrum of phases of the disease, i.e pre-exposure prophylaxis, post-exposure prophylaxis, during the symptomatic phase and during the pulmonary phase. [34,74-76,181,184-190,316-318,391-397,578] In the recommended dosages, ivermectin is remarkably safe and effective against SARS-CoV-2. However, as noted above, there is the potential for serious drug-drug interaction.

16. The pulmonary phase of COVID-19 is characterized by PROLONGED immune dysregulation that may last weeks or even months. The early and abrupt termination of anti-inflammatory agents will likely result in rebound inflammation. [579]
17. SARS-CoV-2, as compared to all other respiratory viruses, upregulates cytokines and chemokines while at the same time down regulating the expression of Interferon alpha (the hosts primary antiviral defense mechanism). [131,155] Low innate antiviral defenses and high pro-inflammatory mediators contribute to ongoing and progressive lung injury.
18. An unknown percentage of patients with COVID-19 present with “silent hypoxia” with a blunted respiratory response. This phenomenon may be related to involvement of chemoreceptors of the carotid bodies and/or brain stem dysfunction, [580,581] 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. [582] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[583,584] as well as viral replication [189,585]. Most importantly LWWH inhibits heparanase (HPSE).[586] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[586] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [587] 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. [375,380] Vitamin C protects the endothelium from oxidative injury. [124,588-590] Furthermore, vitamin C increases the expression of interferon-alpha [126] while corticosteroids (alone) decrease expression of this important protein. [591-594] 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. [326,595] 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),[596] genomic data specific for SARS-CoV-2,[227] and a long track record of successful use in inflammatory lung diseases (see Table 2).
22. It should be noted that animal studies have demonstrated that ivermectin has immunostimulatory effects.[597,598] For this reason patients taking ivermectin do not need to stop taking ivermectin when vaccinated. Indeed, ivermectin may boost the immune response to the vaccine.

And finally: “If what you are doing ain’t working, change what you are doing.”

Figure 12. Evaluating the Totality of Evidence



19. References

1. Horton, R. The Dawn of McScience. <https://www.nybooks.com/articles/2004/03/11/the-dawn-of-mcscience/>. 2004. The New York Review. 1-14-2022.
2. Angell M. The truth about drug companies: how they deceive us and what to do about it. New York: Random House; 2005.
3. Kennedy RF. The Real Anthony Fauci. Bill Gates, Big Pharma, and the Global War on Democracy and Public Health. New York, NY: Skyhorse Publishing; 2021.
4. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc* 2012; 87:982-90.
5. Peterson, D. J. Prescription of ivermectin or hydroxychloroquine as off-label medicines for the prevention and treatment of Covid-19. https://ago.nebraska.gov/sites/ago.nebraska.gov/files/docs/opinions/21-017_0.pdf. 2021. Office of the Attorney General, State of Nebraska. 1-14-2022.
6. Fatima S, Zaidi SS, Alsharidah AS et al. Possible prophylactic approach for SARS-CoV-2 infection by combination of melatonin, Vitamin C and Zinc in animals. *Frontiers in Veterinary Science* 2020; 7:585789.
7. Arslan B, Ergun NU, Topuz S et al. Synergistic effect of quercetin and vitamin C against COVID-19: Is a possible guard for front liners? *ssrn* 2020.
8. Ahmed AK, Albalawi YS, Shora HA et al. Effects of quadruple therapy: Zinc, Quercetin, Bromelain and Vitamin C on clinical outcomes of patients infected with COVID-19. *Rea Int Jou of End and Dia* 2020; 1:1005.
9. Marik P, Iglesias J, Varon J et al. A Scoping Review of the pathophysiology of COVID-19. *International Journal of Immunopathology and Pharmacology* 2021.
10. Leung K, Shum MMH, Leung GM et al. Early empirical assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *medRxiv* 2020.
11. Tegally H, Wilkinson E, Giovanetti M et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv* 2020.
12. Li B, Deng A, Li K et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 delta variant. *medRxiv* 2021.
13. He X, Hong W, Pan X et al. SARS-CoV-2 Omicron variant: Characteristics and prevention. *MedComm* 2021; 2:838-45.
14. Fratev F. The SARS-CoV-2 S1 spike mutation N501Y alters the protein interactions with both hACE2 and human derived antibody: A free energy of perturbation study. *bioRxiv* 2020.
15. Nonaka CK, Franco MM, Graf T et al. Genomic evidence of a SARS-CoV-2 reinfection case with E484K spike mutation in Brazil. *Preprints* 2021.
16. Espenhain L, Funk T, Overvad M et al. Epidemiological characterisation of the first 785 SARS-CoV-2 Omicron variant cases in Denmark, December 2021. *Euro Surveill* 2021; 26:2101146.
17. Hansen CH, Schelde AB, Mousten-Helm IR et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A danish cohort study. *medRxiv* 2022.
18. Jacobsen H, Strengert M, Maa H et al. Diminished neutralization responses towards SARS-CoV-2 Omicron Variant after mRNA or vector-based COVID-19 vaccinations. *medRxiv* 2021.
19. Cao Y, Wang J, Jian F et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature* 2021.
20. Hoffmann M, Kruger N, Schultz S et al. The omicron variant is highly resistant against antibody-mediated neutralization- implications for control of the COVID-19 pandemic. *Cell* 2021.
21. Jehi L, Ji X, Milinovich A et al. Individualizing risk prediction for positive COVID-19 testing. Results from 11,672 patients. *Chest* 2020; 158:1364-75.
22. DiPierro F, Derosa G, Maffioli P et al. Possible therapeutic effects of adjuvant Quercetin supplementation against early stage COVID-19 infection: A prospective, randomized, controlled, and open-label study. *International journal of general medicine* 2021; 14:2359-66.
23. Miranda-Massari JR, Toro AP, Loh D et al. The effects of vitamin C on the multiple pathological stages of COVID-19. *Life* 2021; 11:1341.
24. Holford P, Carr AC, Zawari M et al. Vitamin C intervention for Critical COVID-19: A pragmatic review of the current level of evidence. *Life* 2021; 11:1166.

25. Kory P, Meduri GU, Iglesias J et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. *ssrn* 2020.
26. Guy GP, Lee FC, sunshine G et al. Association of State-Issued mask mandates and allowing on premises restaurant dining with County-levels COVID-19 case and death growth rates-United States, March 1 - December 31, 2020. *MMWR* 2021; 70.
27. Guzzo CA, Furtek CI, Porras AG et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 2002; 42:1122-33.
28. Behera P, Patro BK, Singh AK et al. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study. *medRxiv* 2020.
29. Carvallo H, Hirsch RR, Alkis P et al. Study of the efficacy and safety of topical ivermectin + Iota-carrageenan in the prophylaxis against COVID-19 in health personnel. *Journal of Biomedical Research and Clinical Investigation* 2020; 2.
30. Kory P, Meduri GU, Iglesias J et al. Review of the emerging evidence supporting the use of Ivermectin in the prophylaxis and treatment of COVID-19. *Front Line Covid-19 Critical Care Alliance*. *osf io* 2020.
31. Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. *Int J Antimicrob Agents* 2020.
32. Morgenstern J, Redondo JN, Olavarria A et al. Retrospective cohort study of Ivermectin as a SARS-CoV-2 pre-exposure prophylaxis method in Healthcare Workers. *medRxiv* 2021.
33. Chahla RE, Medina Ruiz L, Mena T et al. Ivermectin reproposing for COVID-19 treatment outpatients in mild stage in primary health centers. *medRxiv* 2021.
34. Kircik LH, Del Rosso JQ, Layton AM et al. Over 25 years of clinical experience with Ivermectin: An overview of safety for an increasing number of indications. *J Drugs Dermatol* 2016; 15:325-32.
35. Aroke D, Tchouakam DN, Awungia AT et al. Ivermectin induced Steven-Johnsons syndrome: case report. *BMC Research Notes* 2017; 10:179.
36. Ngwasiri CA, Abanda MH, Aminde LN. Ivermectin-induced fixed drug eruption in an elderly Cameroonian: a case report. *Journal of Medical Case Reports* 2018; 12:254.
37. Veit O, Beck B, Steuerwald M et al. First case of ivermectin-induced severe hepatitis. *Trans R Soc Trop Med Hyg* 2021; 100:795-97.
38. Nicolas P, Maia MF, Bassat Q et al. Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob Health* 2020; 8:e92-e100.
39. Canga AG, Sahagun Prieto AM, Diez Liebana MJ et al. The pharmacokinetics and interactions of Ivermectin in humans-A mini-review. *The AAPS Journal* 2007; 10:42-46.
40. McCullough PA, Alexander PE, Armstrong R et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). *Reviews in Cardiovascular Medicine* 2020; 21:517-30.
41. Ladapo JA, McKinnon JE, McCullough PA et al. Randomized controlled trials of early ambulatory hydroxychloroquine in the prevention of COVID-19 infection, hospitalization, and death: Meta-analysis. *medRxiv* 2020.
42. McCullough PA, Kelly RJ, Ruocco G et al. Pathophysiological basis and rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) infection. *Am J Med* 2021; 134:16-22.
43. Risch HA. Early outpatient treatment of symptomatic, High-Risk Covid-19 patients that should be ramped-up immediately as key to the pandemic crisis. *Am J Epidemiol* 2020; 189:1218-26.
44. Colunga Biancatelli RM, Berrill M, Mohammed YH et al. Melatonin for the treatment of sepsis: the scientific rationale. *J Thorac Dis* 2020; 12 (Suppl 1):S54-S65.
45. Reiter RJ, Abreu-Gonzalez P, Marik PE et al. Therapeutic algorithm for use of melatonin in patients with COVID-19. *Front Med* 2020; 7:226.
46. Reiter RJ, Sharma R, Ma Q et al. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. *Medicine in Drug Discovery* 2020; 6:100044.
47. Zhang R, Wang X, Ni L et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci* 2020; 250:117583.
48. Kleszczynski K, Slominski AT, Steinbrink K et al. Clinical trials for use of melatonin to fight COVID-19 are urgently needed. *Nutrients* 2020; 12.
49. Coto-Montes A, Boga JA. ER stress and autophagy induced by SARS-CoV-2: The target for melatonin treatment. *Melatonin Res* 2020; 3:346-61.

50. Gandolfi JV, Di Bernardo AP, Chanes DA et al. The effects of melatonin supplementation on sleep quality and assessment of the serum melatonin in ICU patients: A randomized controlled trial. *Crit Care Med* 2020.
51. Castillo RR, Quizon GR, Juco MJ et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res* 2021; 3:297-310.
52. Ramiall V, Zucker J, Tatonetti N. Melatonin is significantly associated with survival of intubated COVID-19 patients. *medRxiv* 2021.
53. Farnoosh G, Akbaariqomi M, Badri T et al. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: A randomized, double-blind clinical trial. *medRxiv* 2021.
54. Farnoosh G, Akbaariqomi M, Badri T et al. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: A randomized, double-blind clinical trial. *Archives of Medical Research* 2021.
55. Darban M, Malek F, Memarian M et al. Efficacy of high dose vitamin C, melatonin and zinc in Iranian patients with acute respiratory syndrome due to Coronavirus infection: A pilot randomized trial. *Journal of Cellular & Molecular Anesthesia* 2021; 6:164-67.
56. Hasan ZT, AlAtrakji MQ, Mehuaiden AK. The effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. *International Journal of Infectious Diseases* 2022; 114:79-84.
57. Shneider A, Kudriavtsev A, Vakhusheva A. Can melatonin reduce the severity of COVID-19 pandemic. *medRxiv* 2020.
58. O'Brien MP, Forleo-Neto E, Musser BJ et al. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. *N Engl J Med* 2021.
59. Freedberg DE, Conigliaro J, Sobieszczyk ME et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *medRxiv* 2020.
60. Janowitz T, Baglenz E, Pattinson D et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. *Gut* 2020; 69:1592-97.
61. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. *Am J Gastroenterol* 2020.
62. Malone RW, Tisdall P, Fremont-Smith P et al. COVID-19: Famotidine, Histamine, Mast Cells, and mechanisms. *Research Square* 2020.
63. Sethia R, Prasad M, Mahapatra SJ et al. Efficacy of famotidine for COVID-19: A systematic review and meta-analysis. *medRxiv* 2020.
64. Shoaibi A, Fortin S, Weinstein R et al. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. *medRxiv* 2020.
65. Yeramaneni S, Doshi P, Sands K et al. Famotidine use is not associated with 30-day mortality: A coarsened exact match study in 7158 hospitalized COVID-19 patients from a large healthcare system. *medRxiv* 2020.
66. Almaro CV, Chey WD, Spiegel BM. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol* 2020.
67. Lee SW, Ha EK, Moon SY et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. *Gut* 2021; 70:76-84.
68. Munoz J, Ballester MR, Antonijoan RM et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18 mg tablet in healthy adult volunteers. *PLoS Neglected Tropical Diseases* 2018; 12:e0006020.
69. van schoor NM, Lips P. Worldwide vitamin D status. *Best Practice & Research Clinical Endocrinology & Metabolism* 2011; 25:671-80.
70. Lips P, de Jongh RT, van schoor NM. Trends in Vitamin D status around the world. *JBMR Plus* 2021; 5:e10585.
71. Baeke F, Takiishi T, Korf H et al. Vitamin D: modulator of the immune system. *Current Opinion in Pharmacology* 2010; 10:482-96.
72. Bartley J. Vitamin D: emerging roles in infection and immunity. *Expert Review of Antiinfective Therapy* 2010; 8:1359-69.
73. Kolls JK, Garry RF. Role of the T cell vitamin D receptor in severe COVID-19. *Nature Immunology* 2022; 23:3-10.

74. Gorial FI, Mashhadani S, Sayaly HM et al. Effectiveness of Ivermectin as add-on therapy in COVID-19 management (Pilot Trial). medRxiv 2020.
75. Khan MS, Khan MS, Debnath Cr et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. Archivos de Bronconeumologia 2020.
76. Rajter JC, Sherman MS, Fatteh N et al. ICON (Ivermectin in COvid Ninteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19. Chest 2020.
77. Niaee MS, Gheibl N, Namdar P et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Research Square 2020.
78. Elgazzar A, Hany B, Youssef SA et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. Research Square 2020.
79. Hashim HA, Maulood MF, Rasheed AM et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Bagdad, Iraq. medRxiv 2020.
80. Maghbooli Z, Sahraian MA, Ebrahimi M et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/ml reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PloS ONE 2020; 15:e0239799.
81. Grant WB, Lahore H, McDonnell SL et al. Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12:988.
82. Kaufman HW, Niles JK, Kroll MH et al. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D level. PloS ONE 2020; 15:e0239252.
83. Lau FH, Majumder R, Torabi R et al. Vitamin D insufficiency is prevalent in severe COVID-19. medRxiv 2020.
84. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection? Medicine in Drug Discovery 2020.
85. Rhodes JM, Subramanian S, Laird E et al. Editorial: Low population mortality from COVID-19 in countries south of 35 degrees North - supports vitamin D as a factor determining severity. Alimentary Pharmacology & Therapeutics 2020; (in press).
86. Dancer RC, Parekh D, Lax S et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015; 70:617-24.
87. Llie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020.
88. Daneshkhan A, Eshein A, Subramanian H. The role of vitamin D in suppressing cytokine storm of COVID-19 patients and associated mortality. medRxiv 2020.
89. Bergman P, Lindh AU, Bjorkhem-Bergman L et al. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. PloS ONE 2013; 8:e65835.
90. Carpagnano GE, Lecce V, Quaranta VN et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. J Endocrinol Invest 2020.
91. Israel A, Cicurel A, Feldhamer I et al. The link between vitamin D deficiency and Covid-19 in a large population. medRxiv 2020.
92. Radujkovic A, Hippchen T, Tiwari-Heckler S et al. Vitamin D deficiency and outcome of COVID-19 patients. Nutrients 2020; 12:2757.
93. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited. Aging Clin Exp Res 2020.
94. Annweiler C, Hanotte B, de L'Eprevier CG et al. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. Journal of Steroid Biochemistry & Molecular Biology 2020.
95. Moozhipurath RK, Kraft L, Skiera B. Evidence of protective role of Ultraviolet-B (UVB) radiation in reducing COVID-19 deaths. Nature Research 2020; 10:17705.
96. Cangiano B, Fatti LM, Danesi L et al. Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests. Aging 2020; 12.
97. De Smet D, De Smet K, Herroelen P et al. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. Am J Clin Pathol 2020.
98. Cozier YC, Castro-Webb N, Hochberg NS et al. Lower serum 25(OH) D levels associated with higher risk of COVID-19 infection in U.S. black women. PloS ONE 2021; 16:e0255132.
99. Loucera C, Pena-Chilet M, Esteban-Medina M et al. Real world evidence of calcifediol or vitamin D prescription and mortality rate of COVID-19 in a retrospective cohort of hospitalized Andalusian patients. Scientific Reports 2021; 11:23380.

100. Teshome A, Adane A, Girma B et al. The impact of Vitamin D level on COVID-19 infection: systematic review and meta-analysis. *Frontiers in Public Health* 2021; 9:624559.
101. Seven B, Gunduz O, Ozgu-Erdinc AS et al. Correlation between 25-hydroxy vitamin D levels and COVID-19 severity in pregnant women: a cross-sectional study. *Journal of Maternal-Fetal & Neonatal Medicine* 2021.
102. Murai IH, Fernandes AL, Sales LP et al. Effect of vitamin D3 supplementation vs placebo on hospital length of stay in patients with severe COVID-19: A multicenter, double-blind, randomized controlled trial. *JAMA* 2020.
103. Borsche L, Glauner B, von Mendel J. COVID-19 mortality risk correlates inversely with vitamin D3 status, and a mortality rate close to zero could theoretically be achieved at 50ng/ml 25(OH)D3: results of a systematic review and meta-analysis. *Nutrients* 2021; 13:3596.
104. Wimalawansa SJ. Effective and practical ways to overcome Vitamin D deficiency. *J Family Med Community Health* 2021; 8:1-8.
105. Reddy P, Edwards LR. Magnesium supplementation in vitamin D deficiency. *Am J Ther* 2019; 26:e124-e132.
106. Schwalfenberg GK. Vitamins K1 and K2: The emerging group of vitamins required for human health. *Journal of Nutrition and Metabolism* 2017; 2017:6254836.
107. Rattis BA, Ramos SG, Celes MR. Curcumin as a potential treatment for COVID-19. *Frontiers in Pharmacology* 2021; 21:675287.
108. Chai YS, Chen YQ, Lin SH et al. Curcumin regulates the differentiation of naive CD4+ T cells and activates IL-10 immune modulation against acute lung injury in mice. *Biomedicine and Pharmacotherapy* 2020; 125:109946.
109. Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C et al. Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. *Heliyon* 2021; 7:e06350.
110. Jena AB, Kanungo N, Nayak V et al. Catechin and curcumin interact with S protein of SARS-CoV2 and ACE2 of human cell membrane: insights from computational studies. *Scientific Reports* 2021; 11:2043.
111. Somi VK, Mehta A, Ratre YK et al. Curcumin, a traditional spice component, can hold promise against COVID-10? *Eur J Pharmacol* 2020; 886:173551.
112. Tahmasebi S, El-Esawi MA, Mahmoud ZH et al. Immunomodulatory effects of nanocurcumin on the Th17 cell responses in mild and severe COVID-19 patients. *J Cell Physiol* 2021; 236:5325-38.
113. Valizadeh H, Danshina S, Gencer MZ et al. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *International Immunopharmacology* 2020; 89:107088.
114. Al-Hatamleh MA, Hatmal MM, Sattat K et al. Antiviral and immunomodulatory effects of phytochemicals from honey against COVID-19: Potential mechanisms of action and future directions. *Molecules* 2020; 25:5017.
115. Hashem HE. *In Silico* approach of some selected honey constituents as SARS-CoV-2 main protease (COVID-19) inhibitors. *medRxiv* 2021.
116. Ashraf S, Ashraf S, Ashraf M et al. Honey and *Nigella sativa* against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial. *medRxiv* 2021.
117. Salim B, Noureddine M. Identification of compounds from *Nigella Sativa* as new potential inhibitors of 2019 Novel Coronavirus (COVID-10): Molecular docking study. *ChemRxiv* 2021.
118. Fakhar-e-Alam Kulyar M, Li R, Mehmood K et al. Potential influence of *Nigella sativa* (Black cumin) in reinforcing immune system: A hope to decelerate the COVID-19 pandemic. *Phytomedicine* 2021; 85:153277.
119. Khazdair MR, Ghafari S, Sadeghi M. Possible therapeutic effects of *Nigella sativa* and its thymoquinone on COVID-19. *Pharmaceutical Biology* 2021; 59:696-703.
120. Islam MN, Hossain KS, Sarker PP et al. Revisiting pharmacological potentials of *Nigella sativa* seed: A promising option for COVID-19 prevention and cure. *Phytotherapy Research* 2021; 35:1329-44.
121. Rahman MT. Potential benefits of combination of *Nigella sativa* and Zn supplements to treat COVID-19. *J Herbal Med* 2020; 23:100382.
122. Hannan MA. Black Cumin (*Nigella sativa* L.): A Comprehensive Review on Phytochemistry, Health Benefits, Molecular Pharmacology, and Safety. *Nutrients* 2021; 13.
123. Warner ME, Naranjo J, Pollard EM et al. Serotonergic medications, herbal supplements, and perioperative serotonin syndrome. *Can J Anaesth* 2017; 64:940-946.

124. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients* 2018; 10:1762.
125. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Therapeut* 2018; 189:63-70.
126. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. *Expert Rev Anti Infect Ther* 2020; 18:99-101.
127. Maggini S, Beveridge S, suter M. A combination of high-dose vitamin C plus zinc for the common cold. *Journal of International Medical Research* 2012; 40:28-42.
128. Colunga Biancatelli RM, Berrill M, Catravas JD et al. Quercetin and Vitamin C: experimental therapy for the prevention and treatment of SARS-CoV-2 via synergistic action. *Front Immunol* 2020.
129. Kyung Kim T, Lim HR, Byun JS. Vitamin C supplementaion reduces the odds of developing a common cold in Republic of Korea Army recruits: a randomised controlled trial. *BMJ Mil Health* 2020.
130. Hiedra R, Lo KB, Elbashesheh M et al. The use of IV vitamin C for patients with COVID-19: a case series. *Exp Rev Anti Infect Ther* 2020.
131. Khaerunnisa S. Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compuns by molecular docking study. *medRxiv* 2020.
132. Chen L, Li J, Luo C et al. Binding interaction of quercetin-3-B-galactoside and its synthetic derivatives with SARS-CoV 3CL: structure-activity relationship reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry Letters* 2006; 14:8295-306.
133. Nain Z, Rana HK, Lio P et al. Pathogenic profiling of COVID-19 and SARS-like viruses. *Briefings in Bioinformatics* 2020.
134. Yi L, Li Z, Yuan K et al. Small molecules blocking the entry of severe respiratory syndrome coronavirus into host cells. *J Virol* 2020; 78:11334-39.
135. Shakoor H, Feehan J, Dhaheri AS et al. Immune-boosting role of vitamins D,C,E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19. *Maturitas* 2020.
136. Calder PC. Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevenion & Health* 2020; 3.
137. Abian O, Ortega-Alarcon D, Jimenez-Alesanco A et al. Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. *International Journal of Biological Macromolecules* 2020; 164:1693-703.
138. Hemila H, Carr A, Chalker E. Vitamin C may increase the recovery rate of outpatient cases of SARS-CoV-2 infection by 70%: reanalysis of the COVID A to Z randomized clinical trial. *Research Square* 2021.
139. Chen L, Li J, Luo C et al. Binding interaction of quercetin-3-B-galactoside and its synthetic derivatives with SARS-CoV 3CLpro: Structure-activity relationship studies revela salient pharmacophore features. *Bioorganic & Medicinal Chemistry* 2020; 14:8295-306.
140. Ono K, Nakane H. Mechanisms of inhibition of various cellular DNA and RNA polymerases by several flavonoids. *J Biochem* 1990; 108:609-13.
141. Kaul TN, Middleton E, Pgra PL. Antiviral effects of flavonoids on human viruses. *J Med Virol* 1985; 15:71-79.
142. Shinozka K, Kikuchi Y, Nishino C et al. Inhibitory effect of flavonoids on DNA-dependent DNA and RNA polymerases. *Experientia* 1988; 44:882-85.
143. Martin JH, Crotty S, Warren P. Does an apple a day keep the doctor away because a phytoestrogen a day keeps the virus at bay? A review of the anti-viral properties of phytoestrogens. *Phytochemistry* 2007; 68:266-74.
144. Smith M, Smith JC. Repurposing therapeutics for COVID-19: Supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface. *ChemRxiv* 2020.
145. Leyva-Lopez N, Gutierrez-Grijalva EP, Ambriz-Perez D. Flavonoids as cytokine modulators: A possible therapy for inflammation-related diseases. *Int J Mol Sci* 2016; 17:921.
146. Nair MP, Kandaswami C, Mahajan S et al. The flavonoid, quercetin, differentially regulates Th-1 (INF) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. *Biochimica et Biophysica Acta* 2020; 1593:29-36.
147. Saeedi-Boroujeni A, Mahmoudian-Sani MR. Anti-inflammatory potential of Quercetin in COVID-19 treatment. *J Inflamm* 2021; 18:3.
148. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM et al. Zinc ionophore activity of Quercetin and Epigallocatechin-gallate:From Hepa 1-6 cells to a liposome model. *J Agric Food Chem* 2014; 62:8085-93.

149. Nieman DC, Simonson A, Sakaguchi CA et al. Acute Ingestion of a Mixed Flavonoid and Caffeine Supplement Increases Energy Expenditure and Fat Oxidation in Adult Women: A Randomized, Crossover Clinical Trial. *Nutrients* 2019; 11.
150. Nieman DC, Kay CD, Rathore AS et al. Increased Plasma Levels of Gut-Derived Phenolics Linked to Walking and Running Following Two Weeks of Flavonoid Supplementation. *Nutrients* 2018; 10.
151. Nieman DC, Ramamoorthy S, Kay CD et al. Influence of Ingesting a Flavonoid-Rich Supplement on the Metabolome and Concentration of Urine Phenolics in Overweight/Obese Women. *Journal of Proteome Research* 2017; 16:2924-35.
152. Cialdella-Kam L, Ghosh S, Meaney MP et al. Quercetin and Green Tea Extract Supplementation Downregulates Genes Related to Tissue Inflammatory Responses to a 12-Week High Fat-Diet in Mice. *Nutrients* 2017; 9.
153. Ohgitani E, Shin-Ya M, Ichitani M et al. Rapid inactivation in vitro of SARS-CoV-2 in saliva by black tea and green tea. *bioRxiv* 2021.
154. Giuliani C, Bucci I, Di Santo S et al. The flavonoid quercetin inhibits thyroid-restricted genes expression and thyroid function. *Food and Chemical Toxicology* 2014; 66:23-29.
155. de Souza dos Santos MC, Goncalves CF, Vaisman M et al. Impact of flavonoids on thyroid function. *Food and Chemical Toxicology* 2011; 49:2495-502.
156. Chandra AK, De N. Catechin induced modulation in the activities of thyroid hormone synthesizing enzymes leading to hypothyroidism. *Mol Cell Biochem* 2013; 374:37-48.
157. Pistollato F, Masias M, Agudo P et al. Effects of phytochemicals on thyroid function and their possible role in thyroid disease. *Ann N Y Acad Sci* 2019; 1433:3-9.
158. Sathyapalan T, Manuchehri AM, Thatcher NJ et al. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: A randomized, double-blind, crossover study. *J Clin Endocrinol Metab* 2020; 96:1422-49.
159. Tonstad S, Jaceldo-Siegl K, Messina M et al. The association between soya consumption and serum thyroid-stimulating hormone in the Adventist Health Study-2. *Public Health Nutr* 2016; 19:1464-70.
160. Colombo D, Lunardon L, Bellia G. Cyclosporine and herbal supplement interactions. *Journal of Toxicology* 2014; 2014:145325.
161. Vogel-Gonzalez M, Tallo-Parra M, Herrera-Fernandez V et al. Low zinc levels at admission associates with poor clinical outcomes in SARS-CoV-2 infection. *Nutrients* 2021; 13:562.
162. te Velthuis AJ, van den Worm SH, Sims AC et al. Zn²⁺ inhibits Coronavirus and Arterivirus RNA polymerase activity In Vitro and Zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010; 6:e1001176.
163. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. *Nutrients* 2017; 9.
164. Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *J Royal Soc Med Open* 2017; 8:1-7.
165. Hoeger J, Simon TP, Beeker T et al. Persistent low serum zinc is associated with recurrent sepsis in critically ill patients - A pilot study. *PLoS ONE* 2017; 12:e0176069.
166. Willis MS, Monaghan SA, Miller ML et al. Zinc-induced copper deficiency. A report of three cases initially recognized on bone marrow examination. *Am J Clin Pathol* 2005; 123:125-31.
167. Wu Y, Cheng X, Jiang G et al. Altered oral and gut microbiota and its association with SARS-CoV-2 viral load in COVID-19 patients during hospitalization. *npj Biofilms and Microbiomes* 2021; 7:61.
168. Hazan S, Stollman N, Bozkurt H et al. The missing microbes: Bifidobacterium and Faecalibacterium depletion and loss of microbiome diversity as potential susceptibility markers for SARS-CoV-2 infection and severity. *Clinical Gastroenterology & Hepatology* 2021.
169. Din AU, Mazhar M, Waseem M et al. SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotic role. *Biomedicine & Pharmacotherapy* 2021; 133:110947.
170. Yeoh YK, Zuo T, Lui GC et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021; 70:698-706.
171. Rosa DD, Dias MM, Grzeskowiak LM et al. Milk kefir: nutritional, microbiological and health benefits. *Nutrition Research Reviews* 2017; 30:82-96.
172. Kim DH, Jeong D, Kim H et al. Modern perspectives on the health benefits of kefir in next generation sequencing era: Improvement of the host gut microbiota. *Critical Reviews in Food Science and Nutrition* 2019; 59:1782-93.

173. Shakoor H, Freehan J, Mikkelsen K et al. Be well: A potential role for vitamin B in COVID-19. *Maturitas* 2020.
174. dos Santos LM. Can vitamin B12 be an adjuvant to COVID-19 treatment? *GSC Biological and Pharmaceutical Sciences* 2020; 11.
175. Kandeel M, Al-Nazawi M. Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. *Life Sci* 2020; 251:117627.
176. Tan CW, Ho LP, Kalimuddin S et al. Cohort study to evaluate effect of vitamin D, magnesium, and vitamin b12 in combination on severe outcome progression in older patients with coronavirus (COVID-19). *Nutrition* 2020; 80:111017.
177. Zhang P, Tsuchiya K, Kinoshita T et al. Vitamin B6 prevents IL-1B protein production by inhibiting NLRP3 inflammasome activation. *J Biol Chem* 2020; 291:24517-27.
178. Moreira A, Chorath K, Rajasekaran K et al. Demographic predictors of hospitalization and mortality in US children with COVID-19. *European Journal of Pediatrics* 2021; 180:1659-63.
179. Bhopal SS, Bagaria J, Olabi B et al. Children and young people remain at low risk of COVID-19 mortality. *Lancet Child-Adolescent* 2022; 5:e12-e13.
180. Browne NT, Snethen JA, Greenberg CS et al. When pandemics collide: The impact of COVID-19 on childhood obesity. *Journal of Pediatric Nursing* 2021; 56:90-98.
181. Hashim HA, Maulood MF, rasheed AM et al. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Bagdad, Iraq. *medRxiv* 2020.
182. Alam MT, Murshed R, Bhiuyan E et al. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. *Bangladesh Coll Phys Surg* 2020; 38:10-15.
183. Chowdhury AT, Shahabz M, Karim MR et al. A randomized trial of ivermectin-doxycycline and hydrochloroquine-azithromycin therapy on COVID-19 patients. *Research Square* 2020.
184. Chamie J. Real-World evidence: The case of Peru, casuality between Ivermectin and COVID-19 infection fatality rate. *ResearchGate* 2020.
185. Caly L, Druce JD, Catton MG et al. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020.
186. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. *In Vivo* 2020; 34:3023-26.
187. Maurya DK. A combination of Ivermectin and Doxycycline possibly blocks the viral entry and modulate the innate immune response in COVID-19 patients. *ChemRxiv* 2020.
188. Yang SN, Atkinson SC, Wang C et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. *Antiviral Res* 2020; 177:104760.
189. Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. *Preprints* 2020.
190. Swargiary A. Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from silico studies. *Research Square* 2020.
191. Kalfas S, Visvanathan K, Chan K et al. The therapeutic potential of ivermectin for COVID-19: A systematic review of mechanisms and evidence. *medRxiv* 2020.
192. Chamie-Quintero JJ, Hibberd JA, Scheim DE. Ivermectin for COVID-19 in Peru: 14-fold reduction in nationwide excess deaths, p=0.002 for effect by state, then 13-fold increase after ivermectin use restricted. *medRxiv* 2021.
193. Wehbe Z, Wehbe M, Iratni R et al. Repurposing Ivermectin for COVID-19: Molecular aspects and therapeutic possibilities. *Front Immunol* 2021; 12:663586.
194. Hazan S, Dave S, Gunaratne AW et al. Effectiveness of ivermectin-based multidrug therapy in severe hypoxic ambulatory COVID-19 patients. *medRxiv* 2021.
195. Bryant A, Lawrie TA, Dowswell T et al. Ivermectin for the prevention and treatment of COVID-19 infection: a systematic review and meta-analysis. *Lancet* 2021.
196. Hill A, Garratt A, Levi J et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. *Open Forum Infectious Diseases* 2021.
197. Rossignol JF, Bardin MC, Oaks JB et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. *medRxiv* 2021.
198. Cadegiani FA, Goren A, Wambier CG et al. Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly reduced symptoms compared to known outcomes in untreated patients. *New Microbes and New Infections* 2021; 43:100915.

199. Elalfy H, Besheer T, El-Mesery A et al. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. *J Med Virol* 2021; 93:3176-83.
200. Hong SK, Kim HJ, Song CS et al. Nitazoxanide suppresses IL-6 production in LPS-stimulated mouse macrophages and TG-injected mice. *International Immunopharmacology* 2012; 13:23-27.
201. Rossignol JF. Nitazoxanide: A first-in-class broad-spectrum antiviral agent. *Antiviral Res* 2014; 110:94-103.
202. Padmanabhan S, Padmanabhan K. The devil is in the dosing- targeting the interferon pathway by repositioning Nitazoxanide against COVID-19. *Research Square* 2021.
203. Cao J, Forrest CJ, Zhang X. A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Res* 2015; 114:1-10.
204. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *Journal of Infection and Public Health* 2016; 9:227-30.
205. Piacentini S, La Frazia S, Riccio A et al. Nitazoxanide inhibits paramyxovirus replication by targeting the Fusion protein folding: role of glycoprotein-specific thiol oxidoreductase ERp57. *Scientific Reports* 2018; 8:10425.
206. Merchant HA. CoViD-19: An early intervention therapeutic strategy to prevent developing a severe disease as an alternative approach to control the pandemic. *medRxiv* 2021.
207. da Silva JK, Figueirido PL, Byler KG et al. Essential oils as antiviral agents, potential of essential oils to treat SARS-CoV-2 infection: an In-Silico investigation. *Int J Mol Sci* 2020; 21:3426.
208. Winska K, Maczka W, Lyczko J et al. Essential oils as antimicrobial agents- Myths or real alternative. *Molecules* 2019; 24:2130.
209. Knezevic P, Aleksic V, Simin N et al. Antimicrobial activity of *Eucalyptus camaldulensis* essential oils and their interactions with conventional antimicrobial agents against multi-drug resistant *Acinetobacter baumannii*. *Journal of Ethnopharmacology* 2016; 178:125-36.
210. Reichling J, Schnitzler P, Suschke U et al. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties - an overview. *Forsch Komplementmed* 2009; 16:79-90.
211. Schnitzler P. Essential oils for the treatment of Herpes Simplex Virus infections. *Chemotherapy* 2019; 64:1-7.
212. Seet RC, Quek AM, Ooi DS et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: an open-label randomized trial. *Int J Infect Dis* 2021.
213. Vergara-Buenaventura A, Castro-ruiz C. Use of mouthwashes against COVID-19 in dentistry. *British Journal of Oral and Maxillofacial Surgery* 2020; 58:924-27.
214. Baxter AL, Schwartz KR, Johnson RW et al. Rapid initiation of nasal saline irrigation: hospitalizations in COVID-19 patients randomized to alkalization or povidone-iodine compared to a national dataset. *medRxiv* 2021.
215. Seneviratne CJ, Balan P, Ki KK et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: Randomized controlled trial in Singapore. *Infection* 2020; 49:305-11.
216. Frank S, Brown SM, Capriotti JA et al. In vitro efficacy of a povidone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. *JAMA Otolaryngol Head Neck Surg* 2020; 146:1054-58.
217. Burton MJ, Clarkson JE, Goulao B et al. Antimicrobial mouthwashes (gargling) and nasal sprays to protect healthcare workers when undertaking aerosol-generating procedures (AGPs) on patients without suspected or confirmed COVID-19 infection (Review). *Cochrane Database of Syst Rev* 2020; 9:CD013628.
218. Meister TL, Briggemann Y, Todt D et al. Virucidal efficacy of different oral rinses against severe acute respiratory syndrome coronavirus 2. *J Infect Dis* 2020; 222:1289-92.
219. Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. *Dermatology* 2002; 204 (suppl 1):37-41.
220. Teng F, He T, Huang S et al. Cetylpyridinium chloride mouth rinses alleviate experimental gingivitis by inhibiting dental plaque maturation. *Journal of Oral Science* 2016; 8:182-90.
221. Rosing CK, Cavagni J, Gaio EJ et al. Efficacy of two mouthwashes with cetylpyridinium chloride: a controlled randomized clinical trial. *Braz Oral res* 2017; 31:e47.
222. Green A, Roberts G, Tobery T et al. In vitro assessment of the virucidal activity of four mouthwashes containing Cetylpyridinium Chloride, ethanol, zinc and a mix of enzymes and proteins against human coronavirus. *bioRxiv* 2021.
223. Choudhury IM, Shabnam N, Ahsan T et al. Effect of 1% povidone iodine mouthwash/gargle, nasal and eye drop in COVID-19 patient. *Bioresearch Communications* 2021; 7.

224. Ader AW, Paul TL, Reinhardt W et al. Effect of mouth rinsing with two polyvinylpyrrolidone-iodine mixtures on iodine absorption and thyroid function. *J Clin Endocrinol Metab* 2021; 66:632-35.
225. Bianconi V, Violi F, Fallarino F et al. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? *Drugs* 2020.
226. Muller C, Karl N, Ziebuhr J et al. D,L-lysine acetylsalicylate + glycine impairs coronavirus replication. *J Antivir Antiretrovir* 2020.
227. Draghici S, Nguyen TM, Sonna LA et al. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2020.
228. Varatharajah N. COVID-19 CLOT: What is it? Why in the lungs? Extracellular histone, "auto-activation" of prothrombin, emperipolesis, megakaryocytes, "self-association" of Von Willebrand factor and beyond. *Preprints* 2020.
229. Cloutier N, Allaey S, Marcoux G et al. Platelets release pathogenic serotonin and return to circulation after immune complex-mediated sequestration. *PNAS* 2018;E1550-E1559.
230. Hottz ED, Azevedo-Quintanilha Ig, Palhinha L et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood* 2020; 136:1330-1341.
231. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. *N Engl J Med* 2019; 381:2529-40.
232. Amrein K, Martucci G, McNALLY JD. When not to use meta-analysis: Analysing the meta-analysis on vitamin D in critical care. *Clin Nutr* 2017; 36:1729-30.
233. Wessel, L. "its a nightmare". How Brazilian scientists became ensnared in chloroquine politics. Researchers accused of killing patients after using a high dose to treat coronavirus infections. <https://www.science.org/content/article/it-s-nightmare-how-brazilian-scientists-became-ensnared-chloroquine-politics> . 2020. *Science*. 10-20-0021.
234. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home: Potential pitfalls and practical guidance. *Ann Thorac Med* 2020.
235. Jouffroy R, Jost D, Prunet B. Prehospital pulse oximetry: a red flag for early detection of silent hypoxemia in COVID-19 patients. *Crit Care* 2020; 24:313.
236. Lucas JM, Heinlein C, Kim T et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov* 2020; 4:1310-1325.
237. Marik PE, DePerrior SE, Ahmad Q et al. Gender-based disparities in COVID-19 patient outcomes. *Journal of Investigative Medicine* 2021; 69:814-18.
238. Liadet L, Szabo C. Blocking mineralocorticoid receptor with spironolactone may have a wide range of therapeutic actions in severe COVID-19 disease. *Crit Care* 2020; 24:318.
239. Kotfis K, Lechowicz K, Drozdal S et al. COVID-19-The potential beneficial therapeutic effects of spironolactone during SARS-CoV-2 infection. *Pharmaceuticals* 2021; 14:71.
240. Cadebiani FA, Wambier CG, Goren A. Spironolactone: An anti-androgenic and anti-hypertensive drug that may provide protection against the novel Coronavirus (SARS-CoV-2) induced acute respiratory distress syndrome (ARDS) in COVID-19. *Frontiers in Medicine* 2020; 7:453.
241. Cadebiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARS-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS). *Medical Hypotheses* 2020; 143:110112.
242. Cadebiani FA, McCoy J, Zimmerman A et al. Efficacy of proxalutamide in hospitalized COVID-19 patients: A randomized, double-blind, placebo-controlled, parallel-design clinical trial. *medRxiv* 2021.
243. Wambier CG, de Pina Almeida Prado Junior B, Pereira CS et al. Brazilian blood donation eligibility criteria for dermatologic patients. *An Bras Dermatol* 2021; 87:590-595.
244. Zarehoseinzade E, Allami A, Ahmadi M et al. Finasteride in hospitalized adult males with COVID-19: A risk factor for severity of the disease or an adjunct treatment: A randomized controlled clinical trial. *Medical Journal of the Islamic Republic of Iran* 2021; 35:30.
245. Samuel RM, Majd H, Richter MN et al. Androgen signaling regulates SARS-CoV-2 receptor levels and is associated with severe COVID-19 symptoms in men. *Cell Stem Cell* 2020; 27:876-89.
246. Cadebiani FA, McCoy J, Wambier CG et al. Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to remission in males with COVID-19: A randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV Trial- Biochemical). *Cureus* 2021.
247. McCoy J, Goren A, Cadebiani FA et al. Proxalutamide reduces the rates of hospitalization for COVID-19 male outpatients: A randomized double-blinded placebo-controlled trial. *Front Med* 2021; 8:668698.

248. Wambier CG, Lin EM, Cadegiani FA et al. Accelerated viral clearance and symptom resolution in symptomatic COVID-19 outpatients treated with antiandrogens. medRxiv 2021.
249. Cadegiani FA, Goren A, Wambier CG et al. An open-label prospective observational study of antiandrogen and non-antiandrogen early pharmacological approaches in females with mild-to-moderate COVID-19. The PreAndroCoV Female trial. medRxiv 2021.
250. McCoy J, Cadegiani FA, Wambler CG et al. 5-alpha-reductase inhibitors are associated with reduced frequency of COVID-19 symptoms in males with androgenic alopecia. JEADV 2021; 35:e243-e246.
251. Goren A, Wambler CG, Herrera S et al. Anti-androgens may protect against severe COVID-19 outcomes: results form a prospective cohort of 77 hospitalized men. JEADV 2021; 35:e13-e15.
252. van Zuuren EJ, Fedorowicz Z, Schoones J. Interventions for female pattern hair loss (Review). Cochrane Database of Syst Rev 2016; 5:CD007628.
253. Seale LR, Eglini AN, McMichael AJ. Side effects related to 5 alpha-reductase inhibitor treatment of hair loss in women: A review. J Drugs Dermatol 2016; 15:414-19.
254. Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. A randomized clinical trial. JAMA 2020.
255. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of COVID-19. Open Forum Infectious Diseases 2021.
256. Hamed MG, Hagaga RS. The possible immunoregulatory and anti-inflammatory effects of selective serotonin reuptake inhibitors in coronavirus disease patients. Medical Hypotheses 2020; 144:110140.
257. Hoertel N, Sanchez-Rico M, Vernet R et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. Molecular Psychiatry 2021.
258. Zimering MB, Razzaki T, Tsang T et al. Inverse association between serotonin 2A receptor antagonist medication use and mortality in severe COVID-19 infection. Endocrinol Diabetes Metab J 2020; 4:1-5.
259. Reis G, Moreira-Silva EA, Silva DC et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomized, platform clinical trial. Lancet Glob Health 2021.
260. Calusic M, Marcec R, Luksa L et al. Safety and efficacy of fluvoxamine in COVID-19 ICU patients: an open label, prospective cohort trial with matched controls. Br J Clin Pharmacol 2021.
261. Lee TC, Vigod S, Hanula R et al. Fluvoxamine for outpatient COVID-19 to prevent hospitalization: A systematic review and meta-analysis. medRxiv 2021.
262. Sukhatme VP, Reiersen AM, Vayttaden SJ et al. Fluvoxamine: A review of its mechanism of action and its role in COVID-19. Frontiers in Pharmacology 2021; 12:652688.
263. Hartter S, Wang X, Weigmann H et al. Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. J Clin Psychopharmacology 2021; 21:167-74.
264. Maurer-Spurej E, Pittendreigh C, Solomons K. The influence of selective serotonin reuptake inhibitors on human platelet serotonin. Thromb Haemost 2004; 91:119-28.
265. Bismuth-Evenzal Y, Gonopolsky Y, Gurwitz D et al. Decreased serotonin content and reduced agonist-induced aggregation in platelets of chronically medicated with SSRI drugs. Journal of Affective Disorders 2012; 136:99-103.
266. Javors MA, Houston JP, Tekell JL et al. Reduction of platelet serotonin content in depressed patients treated with either paroxetine or desipramine. International Journal of Neuropsychopharmacology 2000; 3:229-35.
267. Hoertel N. Do the selective serotonin reuptake inhibitor antidepressants fluoxetine and fluvoxamine reduce mortality among patients with COVID-19? JAMA Network Open 2021; 4:e2136510.
268. Oskotsky T, Maric I, Tang A et al. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. JAMA Network Open 2021; 4:e2133090.
269. Ishima T, Fujita Y, Hashimoto K. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. Eur J Pharmacol 2014; 727:167-73.
270. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J 2020.
271. Shi Z, Puyo CA. N-Acetylcysteine to combat COVID-19: an evidence review. Therapeutics and Clinical Risk Management 2020; 16:1047-55.

272. Assimakopoulos SF, Aretha D, Kominos D et al. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. *Infectious Diseases* 2021; 53:847-54.
273. Kumar P, Osahon O, Vides DB et al. Severe glutathione deficiency, oxidative stress and oxidant damage in adults hospitalized with COVID-19: implications for GlyNac (Glycine and N-acetylcysteine) supplementation. *Antioxidants* 2022; 11.
274. Altay O, Arif M, Li X et al. Combined metabolic activators accelerates recovery in mild-to-moderate COVID-19. *Adv Sci* 2021;202101222.
275. Weinreich DM, Sivapalasingam S, Norton T et al. REGEN-CoV antibody cocktail clinical outcomes study in Covid-19 outpatients. *N Engl J Med* 2021.
276. Verderese JP, Stepanova M, Lam B et al. Neutralizing monoclonal antibody treatment reduces hospitalization for mild and moderate coronavirus disease 2019 (COVID-19): A real-world experience. *Clin Infect Dis* 2021.
277. Kreuzberger N, Hirsch C, Chai KL et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane Database of Syst Rev* 2021;CD013825.
278. Gupta A, Gonzalez-Rojas Y, oya J et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody Sotrovimab. *N Engl J Med* 2021; 385:1941-50.
279. Gutierrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. *Int J Mol Sci* 2019; 20:5028.
280. Titos E, Rius B, Gonzalez-Periz A et al. Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. *J Immunol* 2021; 187:5408-18.
281. Yoshihara T, Shimada K, Fukao K et al. Omega 3 polyunsaturated fatty acids suppress the development of aortic aneurysms through the inhibition of macrophage-mediated inflammation. *Circ J* 2015; 79:1470-1478.
282. Hammock BD, Wang W, Gilligan MM et al. Eicosanoids. The overlooked storm in Coronavirus Disease 2019 (COVID-19)? *Am J Pathol* 2020.
283. Das UN. Can bioactive lipids inactivate coronavirus (COVID-19)? *Arch Med Res* 2020; 51:282-86.
284. Lee CR, Zeldin DC. Resolvin infectious inflammation by targeting the host response. *N Engl J Med* 2015; 373:2183-85.
285. Serhan CN. Novel pro-resolving lipid mediators in inflammation are leads for resolution physiology. *Nature* 2014; 510:92-101.
286. Law HK, Cheng CY, Ng HY et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. *Blood* 2005; 105:2366-74.
287. Baranova A, Cao H, Zhang F. Unraveling risk genes of COVID-19 by multi-omics integrative analysis. *Frontiers in Medicine* 2021.
288. Li S, Jiang L, Li X et al. Clinical and pathological investigation of patients with severe COVID-19. *JCI Insight* 2020; 5:e138070.
289. Yang B, Fulcher JA, Ahn J et al. Clinical characteristics and outcomes of COVID-19 patients receiving compassionate use Leronlimab. *Clin Infect Dis* 2021.
290. Patterson BK, seethamraju H, Dhody K et al. Disruption of the CCL5/RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. *medRxiv* 2020.
291. Patterson BK, seethamraju H, Dhody K et al. CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and decreases SARS-CoV2 RNA in plasma by day 14. *International Journal of Infectious Diseases* 2021; 103:25-32.
292. Gulick RM, Fatkenheuer G, Burnside R et al. Five-year safety evaluation of Maraviroc in HIV-1-infected treatment-experienced patients. *J Acquir Immune Defic Syndr* 2014; 65:78-81.
293. Ayoub A, Alston S, Goodrich J et al. Hepatic safety and tolerability in the maraviroc clinical development program. *AIDS* 2010; 24:2743-55.
294. Giaquinto C, Mawela MP, Chokephaibutkit K et al. Pharmacokinetics, safety and efficacy of Maraviroc in treatment-experienced pediatric patients infected with CCR5=tropic HIV-1. *Pediatr Infect Dis* 2018; 37:459-65.
295. Idelsis Esquivel-Moynelo I, Perez-Escribano J, Duncan-Roberts Y et al. Effect of combination of interferon alpha-2b and interferon-gamma or interferon alpha 2b alone for elimination of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. *medRxiv* 2020.

296. Davoudi-Monfarad E, Rahmani H, Khalili H et al. Efficacy and safety of interferon B-1a in treatment of severe COVID-19: A randomized clinical trial. medRxiv 2020.
297. Wang N, Zhan Y, Zhu L et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host & Microbe 2020; ePub.
298. Meng Z, Wang T, Chen L et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent COVID-19 in medical staff in an epidemic area. medRxiv 2020.
299. Feld JJ, Kandel C, Biondi MJ et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Resp Med 2021.
300. Berg K, Bolt G, Andersen H et al. Zinc potentiates the antiviral action of human IFN-alpha tenfold. J Interferon Cytokine Res 2001; 21:471-74.
301. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. J Interferon Cytokine Res 1997; 17:469-72.
302. Puskarich MA, Ingraham NE, Merck LH et al. Effect of losartan on hospitalized patients with COVID-19-induced lung injury: A randomized clinical trial. medRxiv 2021.
303. Duarte M, Pelorosso F, Nicolosi L et al. Telmisartan for treatment of COVID-19 patients: an open multicenter randomized clinical trial. EClinicalMedicine 2021; 37:100962.
304. Yu LM, Bafadhel M, Doeward J et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. Lancet 2021; 398:843-55.
305. Ramakrishnan S, Nicolau DV, Langford B et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Resp Med 2021.
306. Schultze A, Walker AJ, MacKenna B et al. Inhaled corticosteroids use and the risk of COVID-19 related death among 966,461 patients with COPD or asthma: An OpenSAFELY analysis. medRxiv 2020.
307. Aveyard P, Gao M, Lindson N et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. Lancet Resp Med 2021.
308. Clemency BM, Varughese R, Morse CG et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19. A randomized clinical trial. JAMA Intern Med 2021.
309. Tardif JC, Bouabdallaoui N, L'Allier PL et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. Lancet Resp Med 2021.
310. Finkelstein Y, Aks SE, Hutson JR et al. Colchicine poisoning: the dark side of an ancient drug. Clinical Toxicology 2010; 48:407-14.
311. Effect of Dexamethasone in hospitalized patients with COVID-19-Preliminary report. N Engl J Med 2020.
312. Azithromycin in hospitalized patients with COVID-19 (RECOVERY) a randomised, controlled, open-label, platform trial. medRxiv 2020.
313. Rosenthal N, Zhun Cao Z, Gundrum J et al. Risk factors associated with in-hospital mortality in a US National Sample of patients with COVID-19. JAMA Network Open 2020; 3:e2029058.
314. Butler CC, Yu LM, Dorward J et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet Resp Med 2021.
315. Toljan K, Vrooman B. Low-dose naltrexone (LDN) - Review of therapeutic utilization. Med Sci 2018; 6:82.
316. Zhang X, Song Y, Ci X et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res 2008; 57:524-29.
317. Ci X, Li H, Yu Q et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen activated protein kinase pathway. Fundamental & Clinical Pharmacology 2009; 23:449-55.
318. DiNicolantonio JJ, Barroso-Arranda J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart 2020; 7:e001350.
319. DiNicolantonio JJ, Barroso-Aranda J, McCarty MF. Anti-inflammatory activity of ivermectin in late-stage COVID-19 may reflect activation of systemic glycine receptors. Open Heart 2021; 8:e001655.
320. Blum VF, Cimerman S, Huneter JR et al. Nitazoxanide superiority to placebo to treat moderate COVID-19 - A pilot prove of concept randomized double-blind clinical trial. EClinicalMedicine 2021; 37:100981.
321. Villar J, Confalonieri M, Pastores SM et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome (ARDS) caused by COVID-19. Crit Care Expl 2020; 2:e0111.
322. Fadel R, Morrison AR, Vahia A et al. Early course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020; 71:2114-20.

323. Chroboczek T, Lacoste M, Wackenheim C et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRxiv 2020.
324. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020.
325. Cruz AF, Ruiz-Antoran B, Gomez AM et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. medRxiv 2020.
326. Liu J, Zheng X, Huang Y et al. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol 2020.
327. Meduri GU, Bridges L, Shih MC et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016; 42:829-40.
328. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. JAMA 2020.
329. Ruiz-Irastorza G, Pijoan JI, Bereciatu E et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. medRxiv 2020.
330. Tomazini BM, Maia IS, Cavalcanti AB et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. The CoDEX randomized clinical trial. JAMA 2020; 324:1307-16.
331. Edalatfard M, Akhtari M, Salehi M et al. Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020.
332. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA 2020.
333. Dequin PF, Heming N, Meziani F et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. A randomized Clinical trial. JAMA 2020.
334. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021; 389:790-802.
335. Heaney RP, Armas LA, Shary JR et al. 25-hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr 2008; 87:1738-42.
336. Castillo ME, Costa LM, Barrios JM et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol 2020; 203:105751.
337. Loucera C, Pena-Chilet M, Esteban-Medina M et al. Real world evidence of calcifediol use and mortality rate of COVID-19 hospitalized in a large cohort of 16,401 Adalusian patients. medRxiv 2021.
338. Nogues X, Overjero D, Pineda-Moncus M et al. Calcifediol treatment and COVID-19-related outcomes. medRxiv 2021.
339. Henriquez MS, de Tejada Romero MJ. Cholecalciferol or calcifediol in the management of vitamin D deficiency. Nutrients 2020; 12:1617.
340. Elamir YM, Amir H, Lim S et al. A randomized pilot study using calcitriol in hospitalized patients. Bone 2022; 154:116175.
341. Barrett TJ, Lee AH, Xia Y et al. Platelet and vascular biomarkers associate with thrombosis and death in coronavirus disease. Circulation Research 2020; 127:945-47.
342. Zhang S, Liu Y, Wang X et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. Journal of hematology & oncology 2020; 13:120.
343. Kauerova S, Bartuskova H, Muffova B et al. Statins directly influence the polarization of adipose tissue macrophages: A role in chronic inflammation. Biomedicines 2021; 9:211.
344. van der Meij E, Koning GG, Vriens PW et al. A clinical evaluation of statin pleiotrophy: Statins selectively and dose-dependently reduce vascular inflammation. PloS ONE 2013; 8:e53882.
345. Calfee CS, Delucchi KL, Sinha P et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Resp Med 2018; 6:691-98.
346. Zhang XJ, Qin JJ, Cheng X et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metabolism 2020.

347. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA et al. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 2020; 24:429.
348. Gupta A, Madhavan MV, Poterucha TJ et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Research Square* 2020.
349. Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. *Am J Cardiol* 2020.
350. Tan WY, Young BE, Lye DC et al. Statin use is associated with lower disease severity in COVID-19 infection. *Nature Research* 2020.
351. Spinelli FR, Conti F, Gadina M. HiJAKing SARS-COV-2? The potential role of JAK inhibitors in the management of COVID-19. *Sci Immunol* 2020; 5:eabc5367.
352. Chen CX, Wang JJ, Li H et al. JAK-inhibitors for coronavirus disease-2019 (COVID): a meta-analysis. *Leukemia* 2021.
353. Marconi VC, Ramanan AV, de Bono S et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Resp Med* 2021.
354. Jalali F, Rezaie S, Rola P et al. COVID-19 pathophysiology: Are platelets and serotonin hiding in plain sight? *ssrn* 2021.
355. Lin OA, Karim ZA, Vemana HP et al. The antidepressant 5-HT_{2a} receptor antagonists Pizotifen and cyproheptadine inhibit serotonin-enhanced platelet function. *PLoS ONE* 2014; 9:e87026.
356. Zaid Y, Guessous F, Puhm F et al. Platelet reactivity to thrombin differs between patients with COVID-19 and those with ARDS unrelated to COVID-19. *Blood Advances* 2021; 5:635-39.
357. Zaid Y, Puhm F, Allaey I et al. Platelets can associate with SARS-CoV-2 RNA and are hyperactivated in COVID-19. *Circ Res* 2020; 127:1404-18.
358. Dawson C, Christensen CW, Rickaby DA et al. Lung damage and pulmonary uptake of serotonin in intact dogs. *J Appl Physiol* 1985; 58:1761-66.
359. MacLean MR, Herve P, Eddahibi S et al. 5-hydroxytryptamine and the pulmonary circulation: receptors, transporters and the relevance to pulmonary arterial hypertension. *Br J Pharmacol* 2000; 131:161-68.
360. Blackshear JL, Orlandi C, Hollenberg NK. Constrictive effect of serotonin on visible renal arteries: a pharmacangiographic study in anesthetized dogs. *J Cardiovasc Pharmacol* 1991; 17:68-73.
361. Watchorn J, Hang DY, Joslin J et al. Critically ill COVID-19 patients with acute kidney injury have reduced renal blood flow and perfusion despite preserved cardiac function: A case-control study using contrast enhanced ultrasound. *Lancet Resp Med* 2021.
362. McGoon MD, Vanhoutte PM. Aggregating platelets contract isolated canine pulmonary arteries by releasing 5-hydroxytryptamine. *J Clin Invest* 1984; 74:823-33.
363. Almqvist P, Skudder P, Kuenzig M et al. Effect of cyproheptadine on endotoxin-induced pulmonary platelet trapping. *Am Surg* 1984; 50:503-5.
364. Skurikhin EG, Andreeva TV, Khnelevskaya ES et al. Effect of antiserotonin drug on the development of lung fibrosis and blood system reactions after intratracheal administration of bleomycin. *Bull Exp Biol Med* 2012; 152:519-23.
365. Doaei S, Gholami S, Rastgoo S et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med* 2021; 19:128.
366. Pan H, Peto R, Karim QA et al. Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial. *medrx* 2020.
367. Ohl ME, Miller DR, Lund BC et al. Association of remdesivir treatment with survival and length of hospital stay among US veterans hospitalized with COVID-19. *JAMA Network Open* 2021; 4:e2114741.
368. Ader F, Hites M, Poissy J et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis* 2021.
369. Marik PE, Kory P, Varon J et al. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. *Exp Rev Anti Infect Ther* 2020.
370. Kory P, Meduri GU, Iglesias J et al. Clinical and scientific rationale for the "MATH+" hospital treatment protocol for COVID-19. *J Intensive Care Med* 2020.

371. Ranjbar K, Shahriarad R, erfani A et al. Methylprednisolone or dexamethasone, which one is the superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. *BMC Infect Dis* 2021; 21:337.
372. Ko JJ, Wu C, Mehta N et al. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. *medRxiv* 2021.
373. Fowler AA, Truwit JD, Hite D et al. Vitamin C Infusion for Treatment In Sepsis-Induced Acute Lung Injury-CITRIS-ALI: A Randomized, Placebo Controlled Clinical Trial. *JAMA* 2018; 322:1261-70.
374. Marik PE, Khangoora V, Rivera R et al. Hydrocortisone, Vitamin C and Thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; 151:1229-38.
375. Barabutis N, Khangoora V, Marik PE et al. Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest* 2017; 152:954-62.
376. Cheng RZ. Can early and high-dose vitamin C prevent and treat coronavirus disease 2019 (COVID-19). *Medicine in Drug Discovery* 2020.
377. Wang Y, Lin H, Lin BW et al. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care* 2019; 9:58.
378. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. *PharmaNutrition* 2020; 12:100190.
379. Iglesias J, Vassallo AV, Patel V et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. *Chest* 2020; 158:164-73.
380. de Melo AF, Homem-de-Mello M. High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection. *Crit Care* 2020; 24:500.
381. Zhang J, Rao X, Li Y et al. High-dose vitamin C infusion for the treatment of critically ill COVID-19. *Research Square* 2020.
382. Kumari P, Dembra S, Dembra P et al. The role of vitamin C as adjuvant therapy in COVID-19. *Cureus* 2020; 12:e11779.
383. Al Sulaiman K, Al Juhani O, Badreldin HA et al. Adjunctive therapy with ascorbic in critically ill patients with COVID-19: A multicenter propensity score matched study. *Crit Care* 2021.
384. Lankadeva YR, Peiris RM, Okazaki N et al. Reversal of the pathophysiological responses to Gram-negative sepsis by megadose Vitamin C. *Crit Care Med* 2020.
385. Zhang J, Rao X, Li Y et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Ann Intensive Care* 2020.
386. Lavinio A, Ercole A, Battaglini D et al. Safety profile of enhanced thromboprophylaxis strategies for critically ill COVID-19 patients during the first wave of the pandemic: observational report from 28 European intensive care units. *Crit Care* 2021; 25:155.
387. Patterson G, Isales CM, Fulzele S. Low level of vitamin C and dysregulation of vitamin C transporter might be involved in the severity of COVID-19 infection. *Aging and Disease* 2020; 12.
388. Tomassa-Irriguible TM, Lielsa-Berrocal L. COVID-19: Up to 87% critically ill patients had low vitamin C values. *Research Square* 2020.
389. Arvinte C, Singh M, Marik PE. Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American Community Hospital Intensive Care Unit in May 2020. A pilot study. *Medicine in Drug Discovery* 2020; 8:100064.
390. Lopes RD, Furtado RH, Bronhara B et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet* 2021; 397:2253-63.
391. Murshed MR, Bhiuyan E, Saber S et al. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. *Bangladesh Coll Phys Surg* 2020; 38:10-15.
392. Jans DA, Wagstaff KM. Ivermectin as a broad-spectrum host directed anti-viral: The real deal. *Cells* 2020; 9:2100.
393. Sharun K, Dhama K, Patel SK et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Ann Clin Microbiol Antimicrob* 2020; 19:23.
394. Peralta EG, Fimia-Duarte R, Cardenas JW et al. Ivermectin, a drug to be considered for the prevention and treatment of SARS-CoV-2. Brief literature review. *EC Veterinary Science* 2020; 5:25-29.
395. Al-Jassim KB, Jawad AA, Al-Masoudi EA et al. Histopathological and biochemical effects of ivermectin on kidney functions, lung and the ameliorative effects of vitamin C in rabbits. *Bas J Vet Res* 2016; 14:110-124.

396. Mudatsir M, Yufika A, Nainu F et al. Antiviral activity of ivermectin against SARS-CoV-2: an old-fashioned dog with a new trick- Literature review. *Sci Pharm* 2020; 88:36.
397. Carvallo H, Hirsch R, Farinella ME. Safety and efficacy of the combined use of Ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. *medRxiv* 2020.
398. Menezes RR, Godin AM, Rodrigues FF et al. Thiamine and riboflavin inhibit production of cytokines and increase the anti-inflammatory activity of a corticosteroid in a chronic model of inflammation induced by complete Freund's adjuvant. *Pharmacological Reports* 2020; 69:1036-43.
399. Vatsalya V, Li F, Frimodig J et al. Therapeutic prospects for Th-17 cell immune storm syndrome and neurological symptoms in COVID-19: Thiamine efficacy and safety, In-vitro evidence and pharmacokinetic profile. *medRxiv* 2020.
400. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! *J Thorac Dis* 2016; 8:1062-66.
401. Moskowitz A, Donnino MW. Thiamine (vitamin B1) in septic shock: a targeted therapy. *J Thorac Dis* 2020; 12 (suppl 1):S78-S83.
402. Woolum JA, Abner EL, Kelly A et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med* 2018; 46:1747-52.
403. Marik PE. Thiamine: An essential component of the metabolic resuscitation protocol. *Crit Care Med* 2018; 46:1869-70.
404. Al Sulaiman K, Aljuhani O, Al Dossari M et al. Evaluation of thiamine as adjunctive therapy in COVID-19 critically ill patients: A multicenter propensity score matched study. *Research Square* 2021.
405. Chen L, Jiang X, Huang L et al. Bioequivalence of a single 10-mg dose of finasteride 5-mg oral disintegrating tablets and standard tablets in healthy adult male Han Chinese volunteers: A randomized sequence, open-label, two-way crossover study. *Clinical Therapeutics* 2009; 31:2242-48.
406. Lee CY, Jan WC, Tsai PS et al. Magnesium sulfate mitigates acute lung injury in endotoxemia rats. *J Trauma* 2011; 70:1177-85.
407. Salem M, Kasinski N, Munoz R et al. Progressive magnesium deficiency increases mortality from endotoxin challenge: Protective effects of acute magnesium replacement therapy [abstract]. *Crit Care Med* 1995;A260.
408. Jiang P. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? A systematic review and meta-analysis. *Shock* 2019; 47:288-95.
409. Rothlin RP, Vetulli HM, Duarte M et al. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. *Drug Dev Res* 2020; 81:768-70.
410. Nejat R, Sadr AS, Freitas BT et al. Losartan inhibits SARS-CoV-2 replication in vitro. *J Pharm Pharm Sci* 2021; 24:390-399.
411. Patterson BK, Guevara-Coto J, Yogendra R et al. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. *Front Immunol* 2021.
412. Oldenburg CE, Doan T. Azithromycin for severe COVID-19. *Lancet* 2020.
413. Futado RH, Berwanger O, Fonseca HA et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised trial. *Lancet* 2020.
414. Agarwal A, Mukherjee A, Kumar G et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; 371:m3939.
415. Simonovich VA, Pratz LD, Scibona P et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med* 2020.
416. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E et al. Convalescent plasma for COVID-19: A multicenter, randomized clinical trial. *medRxiv* 2020.
417. Balcells ME, Rojas L, Le Corre N et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. *PLOS Med* 2021; 18:e1003415.
418. Janiaud P, Axfors C, Schmitt AM et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19. A systematic review and meta-analysis. *JAMA* 2021.
419. Li L, Zhang W, Hu Y et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. A randomized clinical trial. *JAMA* 2020; 324:460-470.
420. Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? *Filaria Jurnal* 2003; 3 (Suppl I):S8.

421. Thompson MA, Henderson JP, Shah PK et al. Convalescent plasma and improved survival in patients with hematologic malignancies and COVID-19. medRxiv 2021.
422. Rosas IO, Brau N, Waters M et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv 2020.
423. Hermine O, Mariette X, Tharaux PL et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized Clinical Trial. JAMA Intern Med 2020.
424. Stone JH, Frigault MJ, Sterling-Boyd NJ et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020.
425. Salvarani C, Dolci G, Massari M et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. A randomized clinical trial. JAMA Intern Med 2020.
426. Salama C, Han J, Yau L et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2020.
427. Jeffreys L, Pennington SH, Duggan J et al. Remdesivir-Ivermectin combination displays synergistic interactions with improved in vitro antiviral activity against SARS-CoV-2. bioRxiv 2020.
428. Gordon AC, Mouncey PR, Rowan KM et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19 - Preliminary report. medRxiv 2021.
429. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020.
430. Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clinical Microbiology & Infection 2021; 27:9-11.
431. Le Balc'h P, Pinceaux K, Pronier C et al. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care 2020; 24:530.
432. Koehler P, Bassetti M, Chen SC et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021.
433. Ospina-Tascon GA, Calderon-Tapia LE, Garcia AF et al. Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19. A randomized clinical trial. JAMA 2021; 326:2161-71.
434. Xu Q, Wang T, Quin X et al. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19; a case series. Crit Care 2020; 24:250.
435. Elharrar X, Trigui Y, Dois AM et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA 2020.
436. Reddy MP, Subramaniam A, Afroz A et al. Prone positioning of nonintubated patients with Coronavirus Disease 2019- A systematic review and meta-analysis. Crit Care Med 2021.
437. Xin Y, Martin K, Morais CC et al. Diminishing efficacy of prone positioning with late application in evolving lung injury. Crit Care Med 2021.
438. Haymet A, Bassi GL, Fraser JF. Airborne spread of SARS-CoV-2 while using high-flow nasal cannula oxygen therapy: myth or reality. Intensive Care Med 2020; 46:2248-51.
439. Winslow RL, Zhou J, Windle EF et al. SARS-CoV-2 environmental contamination from hospitalized patients with COVID-19 receiving aerosol-generating procedures. Thorax 2021.
440. Francone M, Lafrate F, Masci GM et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. European Radiology 2020; 30:6808-17.
441. Kory P, Kanne JP. SARS-CoV-2 organizing pneumonia: "Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?". BMJ Open Resp Res 2020; 7:e000724.
442. Parry AH, Wani AH, Shah NN et al. Chest CT features of coronavirus disease-19 (COVID-19) pneumonia: which findings on initial CT can predict an adverse short-term outcome? BJR Open 2020; 2:20200016.
443. Zhang J, Meng G, Li W et al. Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respiratory Research 2020; 21:180.
444. Yang R, Li X, Liu H et al. Chest CT severity score: An imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging 2020; 2:e2000047.
445. Li K, Wu J, Wu F et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative Radiology 2020; 55:1-5.
446. Pan F, Ye T, Sun P et al. Time course of lung changes at Chest CT during recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2021; 295:715-21.
447. Ding X, Xu J, Zhou J et al. Chest CT findings of COVID-19 pneumonia by duration of symptoms. European Journal of Radiology 2020; 127:109009.

448. Bernheim A, Mei X, Huang M et al. Chest CT findings in Coronavirus disease 2019 (COVID-19): relationship to duration of infection. *Radiology* 2020; 295:685-91.
449. Ichikado K, Suga M, Muranka H et al. Prediction of prognosis for acute respiratory distress syndrome with thin-section CT: Validation in 44 cases. *Radiology* 2006; 238:321-29.
450. Ichikado K, Suga M, Muller NL et al. Acute interstitial pneumonia. Comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *Am J Respir Crit Care Med* 2002; 165:1551-56.
451. Keith P, Day M, Perkins L et al. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit Care* 2020.
452. Keith P, Wells AH, Hodges J et al. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: A single center experience. *Crit Care* 2020; 24:518.
453. Busund R, Koukline V, Utrobin U et al. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. *Intensive Care Med* 2002; 28:1434-39.
454. Morath C, Weigand MA, Zeier M et al. Plasma exchange in critically ill COVID-19 patients. *Crit Care* 2020; 24:481.
455. Khamis F, Al-Zakwani I, Al Hashmi S et al. Therapeutic plasma exchange in adults with severe COVID-19 infection. *Int J Infect Dis* 2020.
456. Fernandez J, Gratacos-Gines J, Olivas P et al. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. *Crit Care Med* 2020.
457. Gucyetmez B, Atalan HK, Sertdemir I et al. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. *Crit Care* 2020; 24:492.
458. Poor HD, Ventetuolo CE, Tolbert T et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *medRxiv* 2020.
459. Wang J, Najizadeh N, Moore EE et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost* 2020.
460. Abou-Arab O, Huette P, Debouvries F et al. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. *Crit Care* 2020; 24:645.
461. Bagate F, Tuffet S, Masi P et al. Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. *Ann Intensive Care* 2020.
462. Caplan M, Goutay J, Bignon A et al. Almitrine infusion in severe acute respiratory syndrome coronavirus-2 induced acute respiratory distress syndrome: A single-center observational study. *Crit Care Med* 2020.
463. Payen D. Coronavirus disease 2019 acute respiratory failure: Almitrine drug resuscitation or resuscitating patients by almitrine? *Crit Care Med* 2020.
464. Henry MB, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care* 2020; 58:27-28.
465. Abrams D, Lorusso R, Vincent JL et al. ECMO during the COVID-19 pandemic: when is it unjustified. *Crit Care* 2020; 24:507.
466. Supady A, Taccone FS, Lepper PM et al. Survival after extracorporeal membrane oxygenation in severe COVID-19 ARDS: results from an international multicenter registry. *Crit Care Med* 2021; 25:90.
467. Barbaro RP, MacLaren G, Boonstra PS et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020.
468. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Resp Med* 2021; 8:944-46.
469. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2020.
470. Cerutti A, Chen K, Chorny A. Immunoglobulin responses at the mucosal interface. *Annu Rev Immunol* 2011; 29:273-93.
471. Jacobs JJ. Neutralizing antibodies mediate virus-immune pathology of COVID-19. *Med Hypotheses* 2020; 143:109884.
472. Caricchio R, Abbate A, Gordeev I et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19. A randomized clinical trial. *JAMA* 2021.
473. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. *Medical Hypotheses* 2020; 144:11005.

474. Saba A, Vaidya PJ, Chavhan VB et al. Combined pirfenidone, azithromycin and prednisolone in post-H1N1 ARDS pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35:85-90.
475. Spagnolo P, Balestro E, Aliberti S et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Resp Med* 2020; 8:750-752.
476. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antibirotic therapy. *Lancet Resp Med* 2020; 8:807-15.
477. Brouwer WP, Duran S, Kuijper M et al. Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. *Crit Care* 2019; 23:317.
478. Villa G, Romagnoli S, De Rosa S et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. *Crit Care* 2020; 24:605.
479. Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. *Inflammation Regeneration* 2020; 40:19.
480. Opoka-Winiarska V, Grywalska E, Rolinski J. Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? *BMC Medicine* 2020; 18:214.
481. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. *BMC Medicine* 2017; 15:172.
482. Torjesen I. COVID-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ* 2021; 375:n2943.
483. Wolter N, Jassat W, Walaza S et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. *medRxiv* 2021.
484. Dabrowska A, Szczepanski A, Botwina P et al. Efficacy of antiviral drugs against the omicron variant of SARS-CoV-2. *bioRxiv* 2021.
485. Glocker MO, Opuni KF, Thiesen HJ. Compared with SARS-CoV2 wild type S pike protein, the SARS-CoV-2 omicron's receptor binding motif has adopted a more SARS-CoV1 and or bat/civet-like structure. *bioRxiv* 2021.
486. Willett BJ, Grove J, MacLean OA et al. The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism. *medRxiv* 2021.
487. Ahmad Q, DePerrior SE, Dodani S et al. Role of inflammatory biomarkers in the prediction of ICU admission and mortality in patients with COVID-19. *Medical Research Archives* 2020; 8:1-10.
488. Marik PE, Stephenson E. The ability of procalcitonin, lactate, white blood cell count and neutrophil-lymphocyte count ratio to predict blood stream infection. Analysis of a large database. *J Crit Care* 2020; 60:135-39.
489. Ichikado K, Muranaka H, Gushima Y et al. Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study. *BMJ Open* 2012; 2:e000545.
490. Tan C, Huang Y, Shi F et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol* 2020; 92:856-62.
491. Howell AP, Parrett JL, Malcom DR. Impact of high-dose intravenous vitamin C for treatment of sepsis on point-of-care blood glucose readings. *J Diabetes Sci Technol* 2019.
492. Stephenson E, Hooper MH, Marik PE. Vitamin C and Point of Care glucose measurements: A retrospective, Observational study [Abstract]. *Chest* 2018; 154 (suppl.):255a.
493. Hekimian G, Kerneis M, Zeitouni M et al. COVID-19 acute myocarditis and multisystem inflammatory syndrome in Adult Intensive and cardiac Care Units. *Chest* 2020.
494. Ma KL, Liu ZH, Cao CF et al. COVID-19 myocarditis and severity factors: An adult cohort study. *medRxiv* 2020.
495. Brosnahan SB, Bhatt A, Berger JS et al. COVID-19 pneumonia hospitalizations followed by re-presentation for presumed thrombotic event. *Chest* 2020.
496. Gianni D, allen SL, Tsang J et al. Post-discharge thromboembolic outcomes and mortality of hospitalized COVID-19 patients: The CORE-19 registry. *Blood* 2021.
497. Spyropoulos AC, Lipardi C, Xu J et al. Modified IMPROVE VTE Risk Score and elevated D-Dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open* 2020; 4:e59-e65.

498. Kunutsor SK, Seidu S, Blom AW et al. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. *Eur J Epidemiol* 2017; 32:657-67.
499. Patterson BK, Francisco EB, Yogendra R et al. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in post-acute sequelae of COVID-19 (PASC) up to 15 months post-infection. *bioRxiv* 2021.
500. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020.
501. Prescott HC, Girard TD. Recovery from Severe COVID-19. Leveraging the lessons of survival from sepsis. *JAMA* 2020.
502. Greenhalgh T, Knight M, A'Court C et al. Management of post-acute Covid-19 in primary care. *BMJ* 2020.
503. Chopra V, Flanders SA, O'Malley M. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann Intern Med* 2020.
504. Mandal S, Barnett J, Brill SE et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalization for COVID-19. *Thorax* 2020.
505. Michelen M, Manoharan L, Elkheir N et al. Characterising long-term covid-19: a rapid living systematic review. *medRxiv* 2020.
506. Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021.
507. Logue JK, Franko NM, McCulloch DJ et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Network Open* 2021; 4:e210830.
508. Janiri D, Carfi A, Kotzalidis GD et al. Posttraumatic stress disorder in patients after severe COVID-19 infection. *JAMA Psychiatry* 2021.
509. Voruz P, Allali G, Benzakour L et al. Long COVID neuropsychological deficits after severe, moderate or mild infection. *medRxiv* 2021.
510. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021.
511. Yong SJ. Long-haul COVID-19: Putative pathophysiology, risk factors, and treatments. *medRxiv* 2020.
512. Bek LM, Berentschot JC, Huijts S et al. Symptoms persisting after hospitalization for COVID-19: 12 month interim results of the COFLOW study. *medRxiv* 2021.
513. Taquet M, Geddes JR, Husain M et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021.
514. Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis* 2020.
515. Bryce C, Grimes Z, Pujadas E et al. Pathophysiology of SARS-CoV-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. *The Mount Sinai COVID-19 autopsy experience. medRxiv* 2020.
516. Lu Y, Li X, Geng D et al. Cerebral micro-structural changes in COVID-19 patients - An MRI-based 3-month follow-up study. *EClinicalMedicine* 2020.
517. Franke C, Ferse C, Kreye J et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain, Behavior, and Immunity* 2021.
518. Sirous R, Taghvaei R, Hellinger JC et al. COVID-19-associated encephalopathy with fulminant cerebral vasoconstriction: CT and MRI findings. *Radiology Case Reports* 2020; 15:2208-12.
519. Magro CM, Mulvey JJ, Laurence J et al. Docked severe acute respiratory syndrome coronavirus 2 proteins within the cutaneous and subcutaneous microvasculature and their role in the pathogenesis of severe coronavirus disease 2019. *Human Pathology* 2020; 106:106-16.
520. Theoharides TT, Cholevas C, Polyzoidis K et al. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. *Biofactors* 2021; 47:232-41.
521. Dhooria S, Chaudhary S, Sehgal IS et al. High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (COLDSTER). *Eur Respir J* 2021.
522. Riche F. Protracted immune disorders at one year after ICU discharge in patients with septic shock. *Crit Care* 2018; 22:42.
523. Andreakos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. *Allergy* 2020.
524. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol* 2014; 33:451-59.

525. Liu SL, Li YH, Shi GY et al. A novel inhibitory effect of naloxone on macrophage activation and atherosclerosis formation in mice. *J Am Coll Cardiol* 2006; 48:1871-79.
526. COVID-19 rapid guideline: managing the long-term effects of COVID-19. www.nice.org.uk/guidance/ng188 . 2020. National Institute for Health and Care Excellence. 4-26-2021.
527. Cuesta-Llavona E, Gomez J, Albaiceta GM et al. Variant-genetic and transcript-expression analysis showed a role for the chemokine-receptor CCR5 in COVID-19 severity. *International Immunopharmacology* 2021; 98:107825.
528. Chen Y, Gu S, Chen Y et al. Six-month follow-up of gut microbiota richness in patients with COVID-19. *Gut* 2021.
529. Sanabria-Mazo JP, Montero-Marin J, Feliu-Soler A et al. Mindfulness-based program plus amygdala and insula retraining (MAIR) for the treatment of women with fibromyalgia: A pilot randomized controlled trial. *J Clin Med* 2020; 9:3246.
530. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. *Biofactors* 2020; 46:306-8.
531. Bawazeer MA, Theoharides TC. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF- κ B, inhibited by methoxyluteolin. *Eur J Pharmacol* 2019; 865:172760.
532. Weng Z, Patel AB, Panagiotidou S et al. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J Allergy Clin Immunol* 2015; 135:1044-52.
533. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. *J Pharmacol Exp Ther* 2017; 361:462-71.
534. Calis Z, Mogulkoc R, Baltaci AK. The roles of flavonols/flavonoids in neurodegeneration and neuroinflammation. *Mini Rev Med Chem* 2020; 20:1475-88.
535. Luvanda M, Posch W, Vosper J et al. Dexamethasone promotes *Aspergillus fumigatus* growth in macrophages by triggering M2 repolarization via targeting PKM2. *J Fungi* 2021; 7:70.
536. Reiter RJ, Sharma R, Ma Q et al. Plasticity of glucose metabolism in activated immune cells: advantages for melatonin inhibition of COVID-19 disease. *Melatonin Res* 2020; 3:362-79.
537. Ma WH, Zhang XG, Guo LL et al. Androgen receptor inhibition alleviated inflammation in experimental autoimmune myocarditis by increasing autophagy in macrophages. *European Review for Medical & Pharmacological Sciences* 2021; 25:3762-71.
538. Becerra-Diaz M, Strickland AB, Keselman A et al. Androgen and androgen receptor as enhancers of M2 macrophage polarization in allergic lung inflammation. *J Immunol* 2018; 201:2923-33.
539. Ma W, Zhang J, Guo L et al. Suppressed androgen receptor expression promotes M2 macrophage reprogramming through the STAT3/SOCS3 pathway. *EXCLI Journal* 2019; 18:21-29.
540. Kurcicka L, Lauer SA, Laeyendecker O et al. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med* 2020; 173:262-67.
541. Cheng HY, Jian SW, Liu DP et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med* 2020; 180:1156-63.
542. Zhao J, Yang Y, Huang H et al. Relationship between ABO blood group and the COVID-19 susceptibility. *medRxiv* 2020.
543. Banerjee A, Pasea L, Harris S et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020; 395:1715-25.
544. Goren A, Vamo-Galvan S, Wambier CG et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain- A potential clue to the role of androgens in COVID-19 severity. *J Cosmetic Dermatol* 2020.
545. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497-506.
546. Guan W, Ni Z, Hu Y et al. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med* 2020.
547. von der Thusen J, van der Eerden M. Histopathology and genetic susceptibility in COVID-19 pneumonia. *Eur J Clin Invest* 2020.
548. Sweeney TE, Liesenfeld O, Wacker J et al. Validation of inflammopathic, adaptive, and coagulopathic sepsis endotypes in Coronavirus disease 2019. *Crit Care Med* 2020.

549. Tartof SY, Qian L, Hong V et al. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. *Ann Intern Med* 2020.
550. Pujadas E, Chaudhry F, McBride R et al. SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Resp Med* 2020.
551. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. *Science* 2020; 369.
552. Zhang Q, Bastard P, Liu Z et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020.
553. Li MY, Li L, Zhang Y et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infectious Diseases of Poverty* 2020; 9:45.
554. Zhou Y, Fu B, Zheng X et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev* 2020; 7:998-1002.
555. Blanco-Melo D, Nilsson-Payant BE, Liu WC et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020; 181:1036-45.
556. Giamarellou-Bouboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host & Microbe* 2020.
557. McGonagle D, Sharif K, O'Regan A et al. The role of cytokines including interleukin-6 in COVID-19 induces pneumonia and macrophage activation syndrome-like disease. *Autoimmunity Reviews* 2020; 19:102537.
558. Zhou F, Yu T, Du R et al. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020.
559. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. *J Microbiol Immunol Infect* 2020.
560. Giamarellou-Bourboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *medRxiv* 2020.
561. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395:1033-34.
562. Qin C, Zhou L, Hu Z et al. Dysregulation of the immune response in patients with COVID-19 in Wuhan, China. *Lancet Infect Dis* 2020.
563. Zhang C, Wu Z, Li JW et al. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonists Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020.
564. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. *J Infection* 2020.
565. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020.
566. Tay MZ, Poh CM, Renia L et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews* 2020; 20:363-74.
567. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med* 2020; 46:1105-8.
568. Teuwen LA, Geldhof V, Pasut A et al. COVID-19: the vasculature unleashed. *Nature Reviews* 2020.
569. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020.
570. Ackermann M, Verleden SE, Kuehnel M et al. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. *N Engl J Med* 2020; 383:120-128.
571. Torrealba JR, Fisher S, Kanne JP et al. Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. *Human Pathology* 2018; 71:30-40.
572. Kanne JP, Little BP, Chung JH et al. Essentials for radiologists on COVID-19: an Update-Radiology Scientific Expert Panel. *Radiology* 2020.
573. Copin MC, Parmentier E, Duburcq T et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection [letter]. *Intensive Care Med* 2020.
574. Gattinoni L, Chiumello D, Caironi P et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensive Care Med* 2020; 46:1099-102.
575. Chiumello D, Cressoni M, Gattinoni L. Covid-19 does not lead to a "typical" Acute Respiratory Distress syndrome. *Lancet* 2020.
576. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020; 24:154.
577. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005; 31:776-84.
578. Patel AN, Desai SS, Grainger DW et al. Usefulness of ivermectin in COVID-19 illness. *medRxiv* 2020.

579. Jeronimo CM, Farias ME, Almeida FF et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020.
580. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med* 2020.
581. Schurink B, Roos E, Radonic T et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 2020.
582. Buijssers B, Yanginlar C, Maciej-Hulme ML et al. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine* 2020.
583. Kim SY, Jin W, Sood A et al. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. *Antiviral Res* 2020; 181:104873.
584. Clausen TM, Sandoval DR, Spliid CB et al. SARS-CoV-2 infection depends on cellular heparan sulphate and ACE2. *bioRxiv* 2020.
585. Kwon PS, Oh H, Kwon SJ et al. Sulphated polysaccharides effectively inhibit SARS-CoV-2 in vitro. *Cell Discovery* 2020; 6:50.
586. Huang X, Han S, Liu X et al. Both UFH and NAH alleviate shedding of endothelial glycocalyx and coagulopathy in LPS-induced sepsis. *Exp Thera Med* 2020; 19:913-22.
587. Buijssers B, Yanginlar C, de Nooijer A et al. Increased plasma heparanase activity in COVID-19 patients. *medRxiv* 2020.
588. May JM, Qu ZC. Ascorbic acid prevents oxidant-induced increases in endothelial permeability. *Biofactors* 2011; 37:46-50.
589. Utoguchi N, Ikeda K, Saeki K et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. *Journal of Cellular Physiology* 1995; 163:393-99.
590. Han M, Pendem S, Teh SL et al. Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. *Free Radic Biol Med* 2010; 48:128-35.
591. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci* 2004; 1024:138-46.
592. Shodell M, Siegal FP. Corticosteroids depress INF-alpha-producing plasmacytoid dendritic cells in human blood. *J Allergy Clin Immunol* 2001; 108:446-48.
593. Thomas BJ, Porritt RA, Hertzog PJ et al. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. *Scientific Reports* 2014; 4:7176.
594. Singanayagam A, Glanville N, Girkin JL et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nature Communications* 2018; 9:2229.
595. Salton F, Confalonieri P, Santus P et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. *medRxiv* 2020.
596. Braude AC, Rebeck AS. Prednisone and methylprednisolone disposition in the lung. *Lancet* 1983;995-97.
597. Sajid MS, Iqbal Z, Muhammad G et al. Effects of ivermectin on the cellular and humoral immune responses of rabbits. *Life Sci* 2007; 80:1966-70.
598. Blakley BR, Rousseaux CG. Effect of ivermectin on the immune response in mice. *Am J Vet Res* 1991; 52:593-95.