# APPENDIX TO AMICUS BRIEF OF NON-PARTY AMICUS FRONT LINE COVID-19 CRITICAL CARE ALLIANCE

MATH+®

COVID HOSPITAL TREATMENT

# A GUIDE TO MANAGING THE HOSPITALIZED COVID-19 PATIENT

September 6, 2022

FLCCC ALLIANCE

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

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## Disclaimer

The information in this document is our recommended approach to COVID-19 in the hospitalized patient, based on the best (and most recent) literature. It is provided as guidance to healthcare providers worldwide on the prevention and early treatment of COVID-19. Our guidance should only be used by medical professionals in formulating their approach to COVID-19. Patients should always consult with their provider before starting any medical treatment. As this is a highly dynamic topic, we will update these guidelines as new information emerges. Please ensure you are using the latest version of this protocol.

To read more about the safety of the vitamins and nutraceuticals listed on the FLCCC protocols during pregnancy, please review this document.

## 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. [1] In fact, 30 percent of all prescriptions are for off-label uses, written by American doctors exercising their medical judgment.

Many states — including Nebraska, Tennessee, and Missouri — have asserted the right of physicians to prescribe, and pharmacists to dispense, off-label drugs such as ivermectin and hydroxychloroquine for the treatment of COVID-19. For example, Nebraska's Attorney General, Doug Peterson, released a legal opinion in October 2021 saying he did not see data to justify legal action against healthcare professionals who prescribe ivermectin or hydroxychloroquine. [2] In May 2022, Tennessee approved a standing order allowing ivermectin to be dispensed over the counter.

## Overview of MATH+ and Key Concepts

As the pandemic has played out over the last two years, more than six million patients have died worldwide. Most countries across the globe have limited resources to manage this humanitarian crisis. The FLCCC physicians developed the **MATH+ protocol** to provide guidance for the treatment of the pulmonary phase of this devastating disease with the goal of reducing hospital mortality. We are now realizing the relentless malpractice of deliberately withholding effective early COVID treatments and forcing the use of toxic remdesivir in hospitalized patients may have unnecessarily killed up to 800,000 Americans. [3]

The core principle of 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.

COVID is an extraordinarily complex, yet treatable, disease; many of its mysteries are still unravelling. However, a few concepts are key to its management.

It is critically important to recognize that infection with SARS-CoV-2, the virus that causes COVID-19, progresses through stages. Treatment approaches are therefore highly stage-specific (see Figures 2-4 and Table 1). Antiviral therapy is likely to be effective only during the viral replicative phase. Anti-inflammatory therapy is expected to be effective during the pulmonary phase and possibly the post-COVID phase.

While there is no "magic bullet" for COVID-19, several therapeutic agents have shown great promise for the treatment of this disease. These include ivermectin, Vitamin D, quercetin, melatonin, fluvoxamine, spironolactone, corticosteroids, curcumin (turmeric), *Nigella sativa* and anti-androgen therapy. A growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [4-6] In the midst of a global pandemic, the use of cheap, effective, and safe repurposed drugs has and will continue to have a major role to play. We must focus on the totality of evidence, and not just on randomized controlled trials (RCTs) (see Figure 1).

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 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. [7-29] In the recommended dosages, ivermectin is remarkably safe and effective against SARS-CoV-2. However, as noted below, there is the potential for serious drug-drug interaction.

COVID-19 is essentially a clinical diagnosis supported by laboratory tests. At symptom onset, a PCR test 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 Figure 4). [30] A PCR test remains positive for at least two weeks. Patients who progress to the pulmonary phase are usually PCR-positive, despite cessation of viral replication (and are therefore less likely to be infectious). However, 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).

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 4). [31]

COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, virus variant, genetic heterogeneity mutations and polymorphisms, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and comorbidities. [32-43] 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. [44]

The pulmonary phase is characterized by prolonged immune dysregulation, [35;45-59] a pulmonary microvascular injury (vasculopathy), [58-62] with activation of clotting and a procoagulant state together with the characteristics of an organizing pneumonia. [63;64] Immune dysregulation may last weeks or even months. The early and abrupt termination of anti-inflammatory agents will likely result in rebound inflammation. [65]

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. [59]

The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to "supportive care" alone. As patients progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are two-fold:

- Early treatment of the pulmonary phase is ESSENTIAL to a good outcome.
- 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.

The radiographic and pathological findings of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [63;66;67] The initial pulmonary phase neither looks like, smells like nor is ARDS. [68-70] The ground glass infiltrates are peripheral and patchy, [66] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS". [71] 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.

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.

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, [72;73] and necessitates pulse oximetry in symptomatic patients managed at home.

It should be recognized that Low Molecular Weight Heparin (LWMH) has non-anticoagulant properties that are likely beneficial in patients with COVID-19; these include anti-inflammatory effects and inhibition of histones. [74] In addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry, [75;76] as well as viral replication [11;77]. Most importantly LWWH inhibits heparanase (HPSE). [78] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis. [78] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [79] 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).

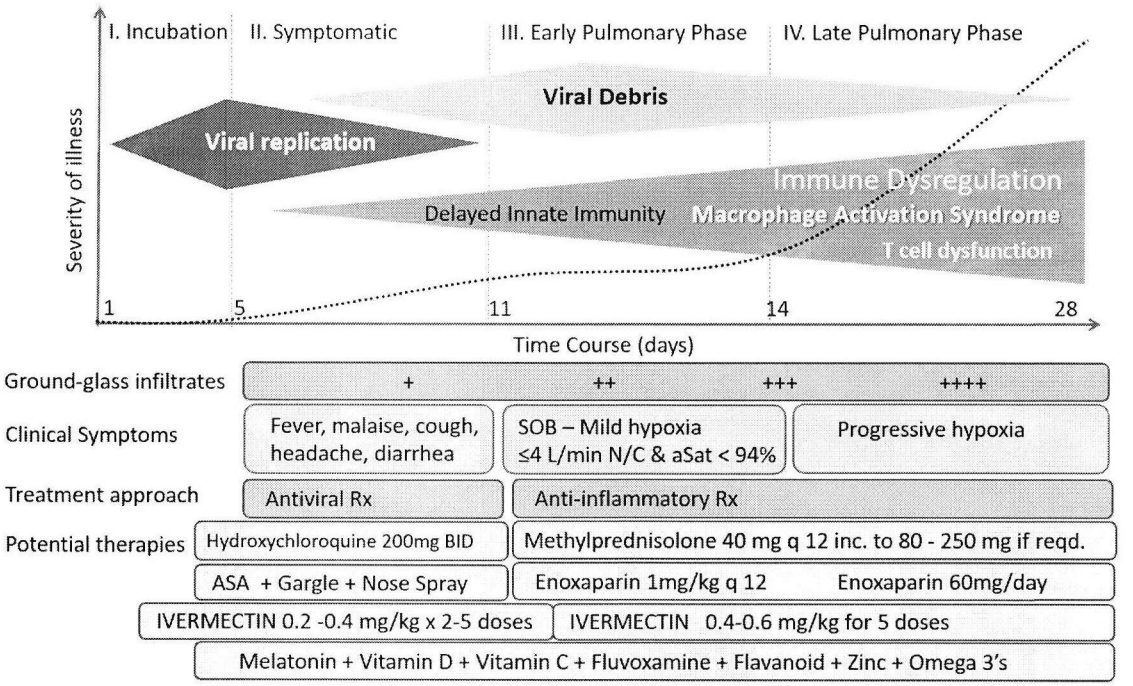
The combination of steroids and ascorbic acid (Vitamin C) is essential. Both have powerful synergistic anti-inflammatory actions. [80;81] Vitamin C protects the endothelium from oxidative injury. [82-85] Furthermore, Vitamin C Increases the expression of interferon-alpha [86] while corticosteroids (alone) decrease expression of this important protein. [87-90] 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. [91;92] It is likely that LMWH acts synergistically with corticosteroids and Vitamin C to protect the endothelium and treat the endothelialitis of severe COVID-19 disease.

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), [93] genomic data specific for SARS-CoV-2, [94] and a long track record of successful use in inflammatory lung diseases (see Table 1).

**Figure 1. Evaluating the Totality of Evidence**

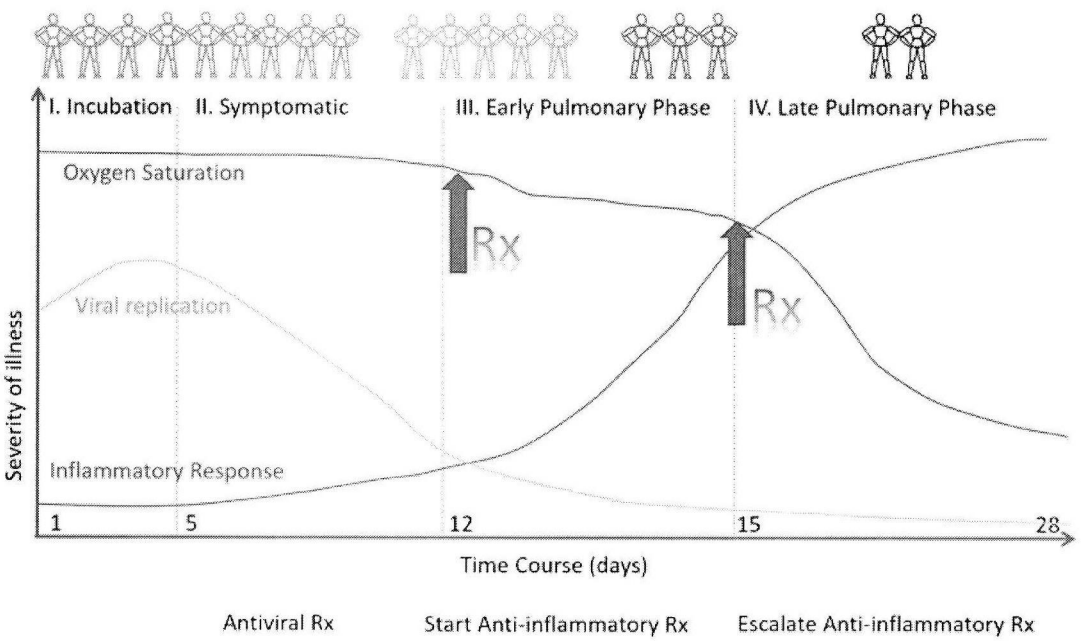

Source: FLCCC

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




Source: FLCCC

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




Source: FLCCC

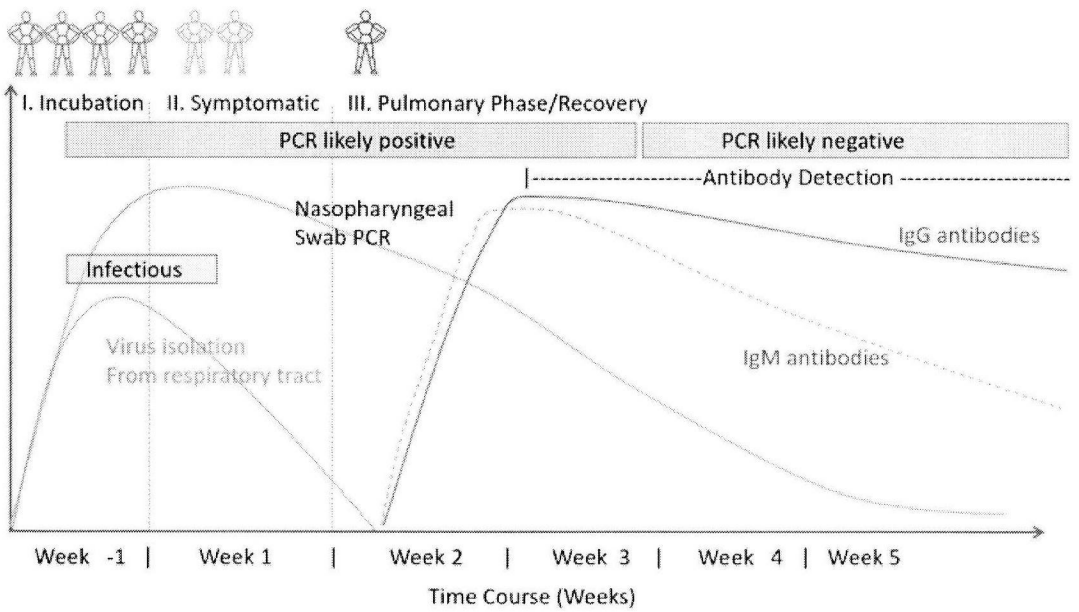
**Note:** Viral replication in Figures 2 and 3 are typical for the original Wuhan SARS-CoV-2 virus (Alpha strain). The time course of Omicron BA.4 and BA.5 appears to be contracted/shortened compared to the Wuhan (Alpha) strain.

THIS IS A STEROID-RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL.

Not too early. Not too late.

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




Source: FLCCC

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

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

Source: FLCCC

** 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.

**Table 2. Drug Interactions with Ivermectin**

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

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

Source: Medscape

# Mildly Symptomatic Patients (On hospital floor/ward)

## First Line Therapies (in order of priority)

**Ivermectin, low molecular weight heparin (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.

- **Ivermectin** 0.4–0.6 mg/kg daily for 5 days or until symptoms resolve (see Figure 4). A higher dose may be required when treatment is delayed and in patients with more severe disease. [7-12;15-18;20;29;95-102]. Ivermectin retains full efficacy against the Omicron variants (as best we know). Ivermectin is best taken with a meal or just following a meal for greater absorption. It should be noted that ivermectin has potent anti-inflammatory properties apart from its antiviral properties. [13;14;23;103] Ivermectin is a remarkably safe drug with minimal adverse reactions (almost all minor). [29] However, potential drug-drug interactions should be reviewed before prescribing ivermectin (see Table 2). Note that ivermectin should not be administered with quercetin.
- **Methylprednisolone** 80 mg bolus dose followed by 40 mg every 12 hours (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 every 12 hours in patients with progressive symptoms and increasing c-reactive protein (CRP). There is now overwhelming and irrefutable evidence that corticosteroids reduce the risk of death in patients in the pulmonary phase of COVID-19, i.e., those requiring supplemental oxygen or higher levels of support. [37;91;104-114] **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. While methylprednisolone is the corticosteroid of choice, in regions/countries where it is not available the following (in order of preference) may be substituted for methylprednisolone (dose adjusted according to methylprednisolone dosages): prednisolone; prednisone; hydrocortisone; and, LASTLY, dexamethasone.
- **Enoxaparin** 1 mg/kg every 12 hours (see dosage adjustments and Xa monitoring below). The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a significant reduction of the primary endpoint (composite of organ support days and hospital mortality) regardless of D-dimer levels. [115]
- **Vitamin C** 500–1000 mg every 6 hours.
- **Quercetin** 250–500 mg twice daily (if available). Note that ivermectin should not be administered with quercetin.
- **Zinc** 75–100 mg/day.
- **Melatonin** 6 mg at night. [116-122]
- **Fluvoxamine** 50 mg twice daily. Fluoxetine 20-40 mg daily is an alternative. [123-126] NOTE: Some individuals who are prescribed fluvoxamine experience acute anxiety,

which needs to be carefully monitored for and treated by the prescribing clinician to prevent rare escalation to suicidal or violent behavior.

## Second Line and Optional Treatments

- **Nitazoxanide (NTZ)** 600 mg twice daily for 7 days. [127] NTZ is considered an alternative to ivermectin, or 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 United States.
- **Vitamin D3/Calcifediol**. For patients hospitalized with COVID-19, the dosing scheme listed in Table 3 is suggested. Vitamin D3 requires hydroxylation in the liver to become 25(OH)D, causing a lag of about 3 to 4 days. [128] This may explain the lack of benefit of Vitamin D3 in patients hospitalized with severe COVID-19. [129] Calcifediol is already 25-hydroxylated, and thus, it bypasses the liver and become available in the circulation within four hours of administration. Among other benefits, it permits boosting the immune system and improving the functions of other systems within a day. Orally administered, a single dose of calcifediol raises serum 25(OH)D concentration within four hours. Therefore, calcifediol is particularly useful in acute infections like COVID-19, and in sepsis. [130-134] The single oral calcifediol dose is calculated as 0.014 mg/kg body weight. To be most effective, a loading dose of Vitamin D3 should be administered with or within the first week of administration of calcifediol. We recommend against the use of **calcitriol** [1,25(OH)2D], which has minimal effect on immune cells. Moreover, the effective dose (ED50) and toxic level overlap at the dose currently suggested for COVID-19. [135]
- **Aspirin/Acetylsalicylic acid (ASA)** 325 mg daily — if not contraindicated. Moderate to severe COVID infection results in profound platelet activation, contributing to the pro-thrombotic state and increasing the inflammatory response. [136-139]
- **B complex** vitamins.
- **N-acetyl cysteine (NAC)** 600-1200 mg by mouth twice daily. [140-144]
- **Anti-androgen therapy** (both men and women). Spironolactone 100 mg twice daily for 10 days. Second line anti-androgen: Dutasteride 2 mg day 1, followed by 1 mg for 10 days. AVOID IN PREGNANCY. [145-147]
- *Optional:* **Famotidine** 40 mg twice daily (20–40 mg/day in renal impairment). [148-154] Famotidine may be useful for its protective effect on gastric mucosa, as well as its antiviral and histamine-blocking properties.
- *Optional:* The anti-serotonin agent, **cyproheptadine** 4–8 mg by mouth every 6 hours should be considered in patients with more severe disease. [155;156] Patients with COVID-19 have increased circulating levels of serotonin, which is likely the result of increased platelet activation and decreased removal by the pulmonary circulation due to an extensive microcirculatory vasculopathy. [155;157-159] 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. [160-163] Furthermore, serotonin itself enhances platelet

aggregation, creating a propagating immuno-thrombotic cycle. [164] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [165]

- *Optional*: **Vascepa** (Ethyl eicosapentaenoic acid) 4 g daily or Lovaza (EPA/DHA) 4 g daily; alternative DHA/EPA 4 g daily. [166] Vascepa and Lovaza tablets **must be swallowed** and cannot be crushed, dissolved, or chewed.
- *Optional:* **JAK inhibitors** ruxolitinib or baricitinib. JAK inhibitors target JAK1, JAK2, JAK3, and whose inhibition downregulates the JAK/STAT signaling pathway decreasing cytokine concentrations. [167] These drugs have been shown to decrease the use of mechanical ventilation and the risk of death. [168;169] 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.
- *Not recommended:* **Remdesivir.** The SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup. [170] The VA study showed no mortality benefit with remdesivir and a longer length of hospital stay. [171] Most recently, the DisCoVeRy trial reported no outcome benefit from remdesivir. [172] 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 6).
- Not recommended: **Colchicine**. Recruitment to the colchicine arm of the RECOVERY trial has been closed as no mortality benefit was noted (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. [173]

NOTE: Transfer patients to ICU as early as possible if respiratory symptoms worsen, oxygen requirements increase, or arterial desaturation emerges.

## Table 3. A Single-Dose Regimen of Calcifediol to Rapidly Raise Serum 25(OH)D above 50 ng/mL

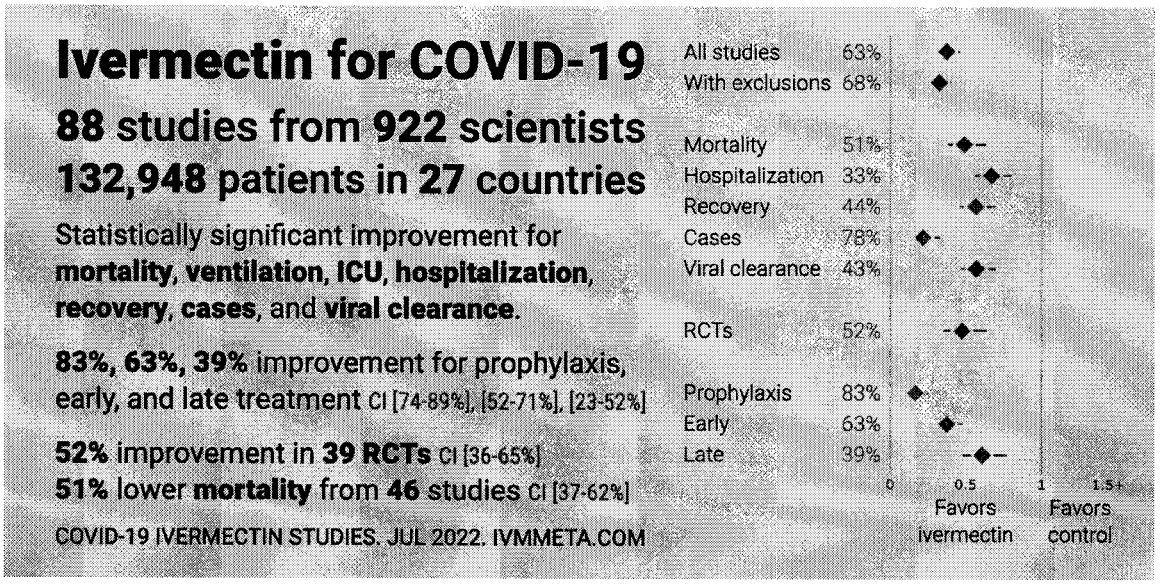
Using a regimen of calcifediol * to rapidly raise serum 25(OH)D concentration above 50 ng/mL (125 nmol/L) in medical emergencies (i.e., to raise serum levels within four hours). ** A single body weight based, oral dose is calculated: 0.014 mg/kg body weight.

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

Source: Nutrients'—Special Issue: "Vitamin D—Calcifediol and COVID" [174]

* Calcifediol [partially activated vitamin D3, 25(OH)D]. ** Use the earliest possible in person with COVID-19, sepsis, Kawasaki disease, multisystem inflammatory syndrome, acute respiratory distress syndrome, burns, and vitamin D deficiency in early pregnancy and other clinical emergencies. # Measurement (or the concentration) of serum 25(OH)D is unnecessary. ## If calcifediol is unavailable, the equivalent dose of vitamin D is administered, as illustrated in Table 2, preferably in divided doses over three to five days. Irrespective of the regimen used, daily or weekly follow-up maintenance vitamin D dose is necessary as described in the text.

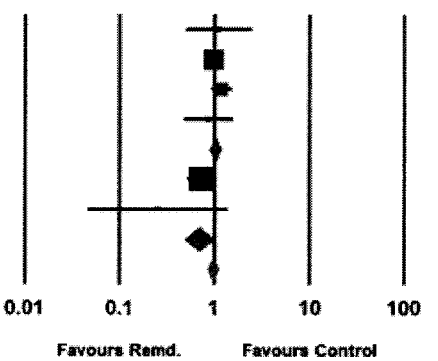
**Figure 5. Ivermectin for COVID-19: Real-time meta-analysis of 88 studies**




Source: c19ivermectin.com

**Figure 6. Meta-Analysis of the Remdesivir RCTs Grouped by Independent Studies (I) and Those Done by Gilead™ (P)**

| Group by Pharma/IND | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| I | Wang | 1.116 | 0.501 | 2.488 | 0.269 | 0.788 |
| I | SOLIDARITY | 0.978 | 0.826 | 1.159 | -0.254 | 0.800 |
| I | VA Coperative | 1.175 | 0.910 | 1.516 | 1.234 | 0.217 |
| I | DisCoVery | 0.866 | 0.475 | 1.581 | -0.467 | 0.640 |
| I | | 1.027 | 0.897 | 1.176 | 0.391 | 0.696 |
| P | Beigel | 0.724 | 0.507 | 1.035 | -1.773 | 0.076 |
| P | Spinner | 0.249 | 0.045 | 1.370 | -1.599 | 0.110 |
| P | | 0.692 | 0.488 | 0.982 | -2.062 | 0.039 |
| Overall | | 0.976 | 0.860 | 1.107 | -0.380 | 0.704 |




Meta Analysis

# Treatment for Patients Admitted to ICU

## First line treatments

- ***Methylprednisolone*** 80 mg loading dose followed by 40 mg every 12 hours for at least 7 days and until transferred out of ICU. In patients with an increasing C-reactive protein (CRP) or worsening clinical status increase the dose to 80 mg every 6 hours, then titrate down as appropriate. [37;91;104-114] Pulse methylprednisolone 500-1000 mg/day for 3 days (followed by taper) may be required. [112] 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 4, methylprednisolone is the corticosteroid of choice. Observational and randomized studies have clearly demonstrated the superiority of methylprednisolone over low dose dexamethasone. [175;176] These clinical findings are supported by a genomic study. [94] Methylprednisolone should be weaned slowly over two weeks once oxygen is discontinued to prevent relapse/recurrence (20 mg twice daily 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.
- ***Ascorbic acid (Vitamin C)*** 50 mg/kg (or 3000 mg) IV every 6 hours for at least 7 days and/or until transferred out of ICU. [80;81;85;177-187]. *High-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 hours for 3-5 days, then 3 g IV every 6 hours for total of 7-10 days of treatment. [188] High-dose Vitamin C appears safe in patients with acute renal failure and end-stage renal disease. In patients with chronic renal failure, a dose of 12.5 g every 12 hours may be suitable. [189] In the study by Lankadeva et al, high-dose Vitamin C increased renal cortical blood flow and renal cortical pO2; oxalate crystals were not detected. [188] Note caution with POC glucose testing. 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 1 g every 4–6 hours.
- ***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%). [115] 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 every 12 hours. [190] 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. [85;179] 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). [191-193] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [194]

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.

## Additional Treatment Components

- *Highly recommended*: **Ivermectin** 0.6 mg/kg day orally for 5 days or until recovered [7-20;22-29;195]. 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.
- **Nitazoxanide** (NTZ) 600 mg twice daily for 7 days. [127] NTZ should 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.
- **Melatonin** 10 mg at night. [117-119]
- **Thiamine** 200 mg IV every 12 hours for 3-5 days, then 200 mg daily [196-201] Thiamine may play a role in dampening the cytokine storm. [197;202]
- **Aspirin/Acetylsalicylic acid** (ASA) 325 mg daily. COVID infection results in profound platelet activation contributing to the severe pro-thrombotic state and increasing the inflammatory response. [136-139] As the risk of significant bleeding is increased in patients receiving both ASA and heparin, ASA should not be used in patients at high risk of bleeding. In addition (as noted below) patients should receive famotidine concurrently.
- 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 by mouth every 6 hours should be considered.
- **Anti-androgen therapy** (both men and women). Spironolactone 100 mg twice daily for 10 days. Second line: Dutasteride 2 mg day 1, followed by 1 mg for 10 days. Finasteride 10 mg is an alternative (dutasteride cannot be crushed). [203;204] **AVOID IN PREGNANCY**. [145;146] Bicalutamide 150 mg daily is also an option.

- **Fluvoxamine** 50 mg twice daily. Fluoxetine 20-40 mg daily is an alternative. NOTE: Some individuals who are prescribed fluvoxamine experience acute anxiety, which needs to be carefully monitored for and treated by the prescribing clinician to prevent rare escalation to suicidal or violent behavior.

## Second Line Treatments

- **B complex vitamins.**
- **Calcifediol** [25-hydroxylated vitamin D; 25(OH)D]. Dosing as suggested in Table 3.
- **Vascepa** (Ethyl eicosapentaenoic acid) 4 g daily or Lovaza (EPA/DHA) 4 g daily; alternative DHA/EPA 4 g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed.
- **Magnesium** 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [205] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [206-208]

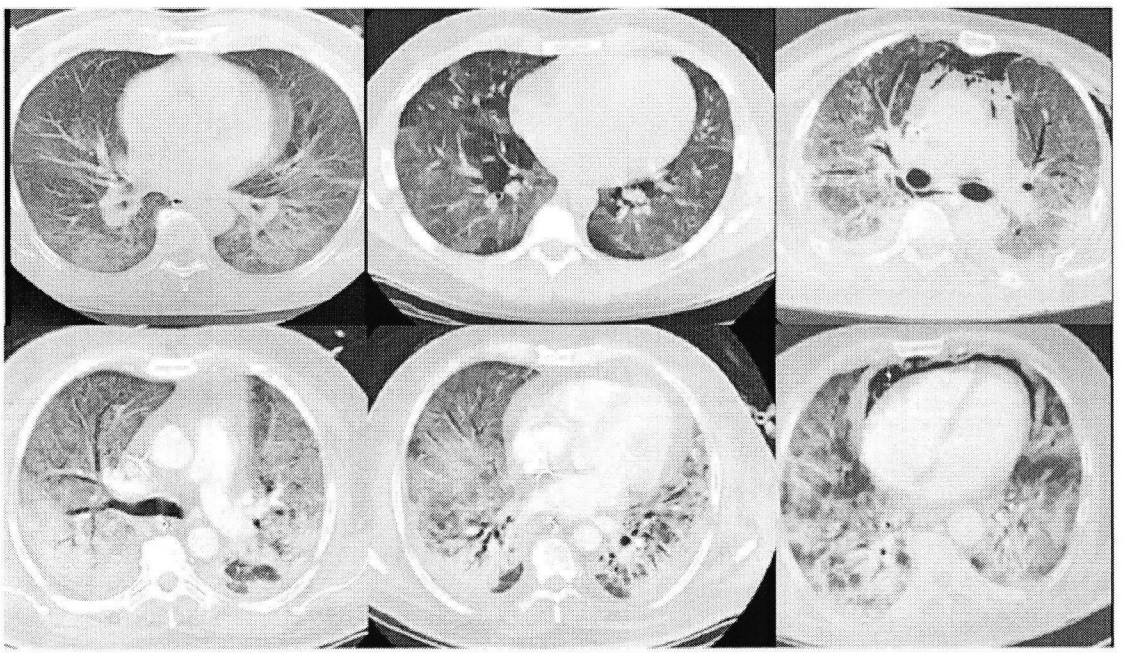
## Optional Treatments (and those of uncertain benefit)

- *Optional:* **Famotidine** 40 mg twice daily (20–40 mg/day in renal impairment). [148-154]
- *Optional:* **JAK inhibitors** ruxolitinib or baricitinib.
- *Optional:* **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
- *Unclear benefit*. **Losartan** 50-100 mg/day (reduce to 25-50 mg with impaired renal function) or telmisartan 40-80 mg twice daily (reduce to 40 mg/day or twice daily with impaired renal function). [209-211]
- *Unclear benefit.* **Maraviroc** 300 mg twice daily for 10 days. Maraviroc is a CCR5 antagonist. [212] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19. [213;214] Blocking the CCR5 receptor (CCR5R) repolarizes macrophages/monocytes and decreases the production of proinflammatory cytokines.
- *Not recommended:* **Remdesivir**. This drug has no benefit at this stage of the disease.
- *Not recommended.* **Convalescent serum** [215-220] nor **monoclonal antibodies**. [221] However, convalescent serum/monoclonal antibodies may have a role in patients with hematologic malignancies. [222] The role of bebtetovimab requires further evaluation. [223]
- *Not recommended.* **Colchicine** (see above).
- *Not recommended.* **Tocilizumab**. Five RCTs have now failed to demonstrate a clinical benefit from tocilizumab. [224-228] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [229] Tocilizumab may have benefit in patients receiving an inadequate dose of corticosteroids. [230] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.

- **Broad-spectrum antibiotics** added if complicating bacterial pneumonia is suspected based on procalcitonin levels and respiratory culture (no bronchoscopy). Due to the paradox of hyper-inflammation and immune suppression (a major decrease of HLA-DR on CD14 monocytes, T cell dysfunction and decreased CD4 and CD8 counts) secondary bacterial and fungal infections (Candida and Aspergillus species) and viral reactivation is not uncommon. [231-233] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [234] 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.
- 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.
- 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.
- 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 $O_2$ saturations ($ScvO_2$) in patents with low arterial $O_2$ saturations
    b. N/C 1–6 L/min
    c. High Flow Nasal canula (HFNC) up to 60–80 L/min [235]
    d. Trial of inhaled Flolan (epoprostenol)
    e. Attempt proning (cooperative repositioning-proning) [236-239]
    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 $H_2O$.
    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. [240;241] HFNC is a better option for the patient and the healthcare system than intubation and mechanical ventilation. HFNC is preferred over conventional oxygen therapy. [235] Intermittent CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

**Figure 7. "Typical" Progression of Chest CT Findings**



Source: FLCCC

**Table 4: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone - Number Needed to Treat**

| 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 |
| METHLPREDNISONE – 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 at 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 |
| DEXAMATHASONE – RECO VERY (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 |

Source: FLCCC

## Patients 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. [242] 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. [63] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively (see Figure 7). [242-249] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19. [250;251] 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. [242] 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.

## The "FULL MONTY" for Severe COVID Pulmonary Disease

I. Methylprednisolone 250-500 mg every 12 hours for at least 3 days, then titrate guided by clinical status and CRP

II. Ivermectin 1 mg/kg for 5 days

III. Melatonin 10 mg by mouth 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 every 6 hours to 25 g every 12 hours

VI. Cyproheptadine 4–8 mg by mouth every 6 hours

VII. Fluvoxamine 50-100 mg twice daily or fluoxetine 20-40 mg daily

VIII. Spironolactone 100 mg twice daily

IX. Thiamine 200 mg every 12 hours

X. NAC 1200 mg by mouth twice daily [142]

XI. Finasteride 10 mg daily or dutasteride 2 mg day 1 then 1 mg daily or bicalutamide 150 mg daily

XII. Omega-3 fatty acids 4 g/day

XIII. Famotidine 40 mg twice daily

XIV. Calcifediol (0.014 mg/kg) use as a single dose (see Table 3)

XV. Consider plasma exchange on admission to the ICU

All 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. In the midst of a pandemic caused by a virus resulting in devastating lung disease, there is no place for "ivory tower medicine."

# Salvage Treatments

- High dose bolus corticosteroids: 500–1000 mg/day methylprednisolone for 3 days then taper. [110;112]
- Plasma exchange [252-258]. 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 3).
- Mega-dose Vitamin C should be considered in severely ill patients and as salvage therapy: 25 g Vitamin C in 200-500 cc saline over 4-6 hours, 12 hourly for 3-5 days, then 3g IV 6 hourly for total of 7-10 days of treatment. [188;189]
- In patients with a large dead-space ventilation (i.e., high $PaCO_2$ despite adequate minute ventilation) consider "Half-dose rTPA" to improve pulmonary microvascular blood flow; 25 mg of tPA over 2 hours followed by a 25 mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation. [259;260]
- 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". [261-264]
- ECMO [265-267]. 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. [268]
- Lung transplantation. [269]

## Salvage Treatments of Unproven/No Benefit

- Convalescent serum/monoclonal antibodies: Four RCTs failed to demonstrate a clinical benefit with the use of convalescent serum. [215-217;219;220] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[270] 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 (i.e., pulmonary phase). In addition, IgG is a large protein that penetrates tissues poorly, and is unlikely to achieve submucosal concentrations required for mucosal immunity. [271] Lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [272]

- In patients with progressive fibrosis, the combination of anti-fibrotic therapy with corticosteroids should be considered. [273-276] 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 [277;278] This treatment strategy appears to have an extremely limited role.

# Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers. [279] A PCT is essential to rule out coexisting bacterial pneumonia. [280]
- 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. [250;281] 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. [282]
- 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. [283;284]
- ECHO as clinically indicated; Patients may develop a severe "septic" cardiomyopathy and/or COVID-19 myocarditis. [285;286]

## 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

## Post Hospital Discharge Management

Patients have an increased risk of thromboembolic events post-discharge. [287;288] Extended thromboprophylaxis (with a DOAC) should be considered in high-risk patients. Risk factors include: [289]

i. Increased D dimer (> 3 times ULN)

ii. Increased CRP (> 2 times ULN) [290]

iii. Age > 60

iv. Prolonged immobilization

   a. 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).

   b. Patients should continue to receive Vitamin C, melatonin, Omega-3 fatty acids and a statin. These agents may reduce this risk of developing long COVID.

   c. *Nigella sativa* and Kefir.

   d. Patients should be followed/monitored for developing long COVID.

# References


1. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc 2012; 87:982-990.
2. Peterson DJ. 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 [cited 2022 Jan. 14];
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. Fatima S, Zaidi SS, Alsharidah AS, Alijaser FS, Banu N. Possible prophylactic approach for SARS-CoV-2 infection by combination of melatonin, Vitamin C and Zinc in animals. Fronteirs in Veterinary Science 2020; 7:585789.
5. Arslan B, Ergun NU, Topuz S, Semerci SY, Suner N. Synergistic effect of quercetin and vitamin C against COVID-19: Is a possible guard for front liners? ssrn 2020.
6. Ahmed AK, Albalawi YS, Shora HA, Abelseed HK, Al-Kattan AN. 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.
7. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020.
8. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. In Vivo 2020; 34:3023-3026.
9. 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.
10. Yang SN, Atkinson SC, Wang C, Lee A. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. Antiviral Res 2020; 177:104760.
11. Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. Preprints 2020.
12. 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.
13. Zhang X, Song Y, Ci X, An N, Ju Y. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res 2008; 57:524-529.
14. Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N 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; 23:449-455.
15. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. ICON (Ivermectin in COvid Ninteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19. Chest 2020.
16. Gorial FI, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM. Effectiveness of Ivermectin as add-on therapy in COVID-19 management (Pilot Trial). medRxiv 2020.
17. Khan MS, Khan MS, Debnath Cr, Nath PN, Mahtab MA. Ivermectin treatment may improve the prognosis of patients with COVID-19. Archivos de Bronconeumologia 2020.

18. Hashim HA, Maulood MF, rasheed AM, Fatak DF, Kabah KK. Controlled randomized clinical triaal on using Ivermectin with Doxycycline for treating COVID-19 patients in Bagdad, Iraq. medRxiv 2020.
19. Murshed MR, Bhiuyan E, Saber S, Alam RF, Robin RF. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. Bangladesh Coll Phys Surg 2020; 38:10-15.
20. Chamie J. Real-World evidence: The case of Peru, casuality between Ivermectin and COVID-19 infection fatality rate. ResearchGate 2020.
21. Patel AN, Desai SS, Grainger DW, Mehra MR. Usefulness of ivermectin in COVID-19 illness. medRxiv 2020.
22. Jans DA, Wagstaff KM. Ivermectin as a broad-spectrum host directed anti-viral: The real deal. Cells 2020; 9:2100.
23. 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.
24. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob 2020; 19:23.
25. Peralta EG, Fimia-Duarte R, Cardenas JW, Dominguez DV, Segura RB. 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.
26. Al-Jassim KB, Jawad AA, Al-Masoudi EA, Majeed SK. 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.
27. Mudatsir M, Yufika A, Nainu F, Frediansyah A, Megawati D. Antiviral activity of ivermectin against SARS-CoV-2: an old-fashioned dog with a new trick- Literature review. Sci Pharm 2020; 88:36.
28. Carvallo H, Hirsch R, Farinella ME. Safety and efficacy of the combined use of Ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. medRxiv 2020.
29. Kircik LH, Del Rosso JQ, Layton AM, schauber J. Over 25 years of clinical experience with Ivermectin: An overview of safety for an increasing number of indications. J Drugs Dermatol 2016; 15:325-332.
30. Kurcicka L, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polmerase chain reacion-based SARS-CoV-2 tests by time since exposure. Ann Intern Med 2020; 173:262-267.
31. Cheng HY, Jian SW, Liu DP, Huang WT, Lin HH. Contact tracing assessment of COVI-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med 2020; 180:1156-1163.
32. Zhao J, Yang Y, Huang H, Li D, Gu D. Relationship between ABO blood group and the COVID-19 susceptibility. medRxiv 2020.
33. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet 2020; 395:1715-1725.
34. Goren A, Vamo-Galvan S, Wambier CG, McCoy J. 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.
35. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China. Lancet 2020; 395:497-506.

36. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020.
37. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan,China. JAMA Intern Med 2020.
38. von der Thusen J, van der Eerden M. Histopathology and genetic susceptibility in COVID-19 pneumonia. Eur J Clin Invest 2020.
39. Sweeney TE, Liesenfeld O, Wacker J, He YD, rawling D, Remmel M. Validation of inflammopathic, adaptive, and coagulopathic sepsis endotypes in Coronavirus disease 2019. Crit Care Med 2020.
40. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. Ann Intern Med 2020.
41. Pujadas E, Chaudhry F, McBride R, Richter F, Zhao S. SARS-CoV-2 viral load predictes COVID-19 mortality. Lancet Resp Med 2020.
42. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. Science 2020; 369.
43. Zhang Q, Bastard P, Liu Z, Le Pen J, Chen J, Korol C. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020.
44. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious Diseases of Poverty 2020; 9:45.
45. Zhou Y, Fu B, Zheng X, Wang D, Zhao C. Pathogenic T cellls and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev 2020; 7:998-1002.
46. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020; 181:1036-1045.
47. Giamarellos-Bouboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host & Microbe 2020.
48. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induces pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews 2020; 19:102537.
49. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
50. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. J Microbiol Immunol Infect 2020.
51. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. medRxiv 2020.
52. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395:1033-1034.
53. Qin C, Zhou L, Hu Z, Zhang S. Dysregulation of the immune response in patiens with COID-19 in Wuhan, China. Lancet Infect Dis 2020.
54. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonsit Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020.
55. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. J Infection 2020.

56. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020.
57. Tay MZ, Poh CM, Renia L, MacAry PA. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews 2020; 20:363-374.
58. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020; 46:1105-1108.
59. Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R et al. Pathopysiology 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.
60. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nature Reviews 2020.
61. Varga Z, Flammer AJ, Steiger P, Habrecker M, Andermatt R, Zinkernagel AS. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020.
62. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N Engl J Med 2020; 383:120-128.
63. 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.
64. Torrealba JR, Fisher S, Kanne JP, Butt YM, Glazer C, Kershaw C. Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. Human Pathology 2018; 71:30-40.
65. Jeronimo CM, Farias ME, Almeida FF, Sampaio VS, Alexandre MA, Melo GC. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A ramdomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020.
66. Kanne JP, Little BP, Chung JH, Elicker BM. Essentials for radiologists on COVID-19: an Update-Radiology Scientific Expert Panel. Radiology 2020.
67. Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D. Time to consider histologic pattern of lung injury to treat critically ill patietns with COVID-19 infection [letter]. Intensive Care Med 2020.
68. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med 2020; 46:1099-1102.
69. Chiumello D, Cressoni M, Gattinoni L. Covid-19 does not lead to a "typical" Acute Respiratory Distress syndrome. Lancet 2020.
70. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020; 24:154.
71. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med 2005; 31(6):776-784.
72. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med 2020.
73. Schurink B, Roos E, Radonic T, Barbe E, Bouman CS. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 2020.

74. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine 2020.
75. Kim SY, Jin W, Sood A, Montgomery DW, Grant OC, Fuster MM. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. Antiviral Res 2020; 181:104873.
76. Clausen TM, Sandoval DR, Spliid CB, PiHl J, Painter CD, Thacker BE et al. SARS-CoV-2 infection depends on cellular heparan sulphate and ACE2. bioRxiv 2020.
77. Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K et al. Sulphated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discovery 2020; 6:50.
78. Huang X, Han S, Liu x, Wang T, Xu H. Both UFH and NAH alleviate shedding of endothelial glycocalyx and coagulopathy in LPS-induced sepsis. Exp Thera Med 2020; 19:913-922.
79. Buijsers B, Yanginlar C, de Nooijer A, Grondman I, Jonkman I, Rother N. Increased plasma heparanase activity in COVID-19 patients. medRxiv 2020.
80. Barabutis N, Khangoora V, Marik PE, Catravas JD. Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. Chest 2017; 152:954-962.
81. 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.
82. May JM, Qu ZC. Ascorbic acid prevents oxidant-induced increases in endothelial permeability. Biofactors 2011; 37:46-50.
83. Utoguchi N, Ikeda K, Saeki K, Oka N, Mizuguchi H, Kubo K et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. Journal of Cellular Physiology 1995; 163(2):393-399.
84. Han M, Pendem S, Teh SL, Sukumaran DK, Wu F, Wilson JX. Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. Free Radic Biol Med 2010; 48:128-135.
85. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. Nutrients 2018; 10:1762.
86. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Rev Anti Infect Ther 2020; 18:99-101.
87. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci 2004; 1024:138-146.
88. Shodell M, Siegal FP. Corticosteroids depress INF-alpha-producing plasmacytoid dentritic cells in human blood. J Allergy Clin Immunol 2001; 108:446-448.
89. Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. Scientific Reports 2014; 4:7176.
90. Singanayagam A, Glanville N, Girkin JL, Ching YM, Marcellini A. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nature Communications 2018; 9:2229.
91. Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol 2020.
92. Salton F, Confalonieri P, Santus P, Harari S, Scala R, Lanini S et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv 2020.
93. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet 1983;995-997.

94. Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, Fadel R et al. COVID-19: disease pathways and gene expression chnages predict methylprednisolone can improve outcome in severe cases. Bioinformatics 2020.
95. Niaee MS, Gheibl N, Namdar P, Allami A, Javadi A. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. Research Square 2020.
96. Alam MT, Murshed R, Bhiuyan E, Saber S, Alam RF, Robin RC. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. Bangladesh Coll Phys Surg 2020; 38:10-15.
97. Chowdhury AT, Shahabz M, Karim MR, Islam J, Guo D, He D. A randomized trial of ivermectin-doxycycline and hydrochloroquine-azithromycin therapy on COVID-19 patients. Research Square 2020.
98. Kory P, Meduri GU, Iglesias J, Varon J, Berkowitz K, Wagshul F et al. Review of the emerging evidencce supporting the use of Ivermectin in the prophylaxis and treatment of COVID-19. Front Line Covid-19 Critical Care Alliance. osf io 2020.
99. 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.
100. Hazan S, Dave S, Gunaratne AW, Dolai S, Clancy RL, McCullough PA et al. Effectiveness of ivermectin-based multidrug therrapy in severe hypoxic ambulatory COVID-19 patients. medRxiv 2021.
101. Bryant A, Lawrie TA, Dowswell T, Fordham E, Mitchell S, Hill SR et al. Ivermectin for the prevention and treatment of COVID-19 infection: a systematic review and meta-analysis. Lancet 2021.
102. Hill A, Garratt A, Levi J, Falconer J, Ellis L, McCann K et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infectious Diseases 2021.
103. 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.
104. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid tratment in the acute respiratory distress syndrome (ARDS) caused by COVID-19. Crit Care Expl 2020; 2:e0111.
105. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudry Z, Bhargava P et al. Early course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020; 71:2114-2120.
106. Chroboczek T, Lacoste M, Wackenheim C, Challan-Belval T, Amar B, Boisson T. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRxiv 2020.
107. Cruz AF, Ruiz-Antoran B, Gomez AM, Lopez AS. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. medRxiv 2020.
108. Meduri GU, Bridges L, Shih MC, Marik PE, Siemienluk RA, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outomces: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016; 42:829-840.
109. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. JAMA 2020.

110. Ruiz-Irastorza G, Pijoan JI, Bereciatua E, Dunder S, Dominguez J, Garcia-Escudero P. 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.
111. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC. Effect of dexamethasone on days alive and ventilaor-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. The CoDEX randomized clinical trial. JAMA 2020; 324:1307-1316.
112. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S. Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020.
113. 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.
114. Dequin PF, Heming N, Meziani F, Plantefeve G, Voiriot G. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. A randomized Clinical trial. JAMA 2020.
115. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021; 389:790-802.
116. Gandolfi JV, Di Bernardo AP, Chanes DA, Martin DF, Joles VB, Amendola CP 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.
117. Castillo RR, Quizon GR, Juco MJ, Roman AD, de Leon DG, Punzalan FE 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.
118. Ramiall V, Zucker J, Tatonetti N. Melatonin is significantly associated with survival of intubated COVID-19 patients. medRxiv 2021.
119. Farnoosh G, Akbaariqomi M, Badri T, Bagheri M, Izadi M. 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.
120. 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.
121. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, rezaie E. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patietns with COVID-19: A randomized, double-blind clinical trial. Archives of Medical Research 2021.
122. Darban M, Malek F, Memarian M, Gohari A, Kiani A, Emadi A. Efficacy of high dose vitamin C, melatonin and zinc in Iranian patients with acute respiratory sydrome due to Coronavirus infection: A pilot randomized trial. Journal of Cellular & Molecular Anesthesia 2021; 6:164-167.
123. Calusic M, Marcec R, Luksa L, Jurkovic I, Kovac N, Likic R. Safety and efficacy of fluvoxamine in COVID-19 ICU patients: an open label, prospective cohort trial with matched controls. Br J Clin Pharmacol 2021.
124. Reis G, Moreira-Silva EA, Silva DC, Thabane L, Guyatt GH, Mills EJ. 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.
125. Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: A review of its mechanism of action and its role in COVID-19. Fronteirs in Pharmacology 2021; 12:652688.
126. Oskotsky T, Maric I, Tang A, Oskotsky B, Wong RJ, Sirota M. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. JAMA Network Open 2021; 4:e2133090.
127. Blum VF, Cimerman S, Huneter JR, Tierno P, Lacerda A, Soeiro A. Nitazoxanide superioroty to placebo to treat moderate COVID-19 - A pilot prove of concept randomized double-blind clinical trial. EClinicalMedicine 2021; 37:100981.
128. Heaney RP, Armas LA, Shary JR, Bell NH, Binkley N, Hollis BW. 25-hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr 2008; 87:1738-1742.
129. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF. Effect of vitamin D3 supplementaion vs placebo on hospital length of stay in patients with severe COVID-19: A multicenter, double-blind, randomized controlled trial. JAMA 2020.
130. Castillo ME, Costa LM, Barrios JM, Diaz JF, Miranda JL, Bouillon R 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.
131. Loucera C, Pena-Chilet M, Esteban-Medina M, Villegas R, Lopez-Miranda J. Real world evidence of calcifediol use and mortality rate of COVID-19 hospitalized in a large cohort of 16,401 Adalusian patients. medRxiv 2021.
132. Nogues X, Overjero D, Pineda-Moncus M, Bouillon R. Calcifediol treatment and COVId-19-related outcomes. medRxiv 2021.
133. Loucera C, Pena-Chilet M, Esteban-Medina M, Villegas R, Tunez I. 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.
134. Henriquez MS, de Tejada Romero MJ. Cholecalciferol or calcifediol in the management of vitamin D deficiency. Nutrients 2020; 12:1617.
135. Elamir YM, Amir H, Lim S, Rana Y, Lopez CG, Omar A. A randomized pilot study using calcitriol in hospitalized patients. Bone 2022; 154:116175.
136. Hottz ED, Azevedo-Quintanilha Ig, Palhinha L, Teixeira L, Barreto EA. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020; 136:1330-1341.
137. Barrett TJ, Lee AH, Xia Y, Lin LH, Black M, Cotzia P. Platelet and vascular biomarkers associate with thrombosis and death in coronavirus disease. Circulation Research 2020; 127:945-947.
138. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. Journal of hematology & oncology 2020; 13:120.
139. Cloutier N, Allaeys I, Marcoux G, Machius KR, Mailhot B. Platelets release pathogenic serotonin and return to circulation after immune complex-mediated sequestration. PNAS 2018;E1550-E1559.
140. 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.

141. Shi Z, Puyo CA. N-Acetylcysteine to combat COVID-19: an evidence review. Therapeutics and Clinical Risk Management 2020; 16:1047-1055.
142. Assimakopoulos SF, Aretha D, Kominos D, Dimitropoulou D, Lagadinou M. 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(11):847-854.
143. Kumar P, Osahon O, Vides DB, Hanania N, Minard CG. Severe glutathione deficiency, oxidative stress and oxidant damage in adults hospitalized with COVID-19: implications for GlyNac (Glycine and N-acetylcysteine) supplementaion. Antioxidants 2022; 11(50).
144. Izquierdo JL, Soriano JB, Gonzalez Y, Lumbreras S. Use of N-Acetylcysteine at high doses as an oral treatment for patients with COVID-19. Science Progress 2022; 105.
145. McCoy J, Goren A, Cadegiani FA, Vano-Galvan S, Kovacevic M, Situm M 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.
146. Cadegiani FA, McCoy J, Zimerman A, Mirza FN, Barros RN. Efficacy of proxalutamide in hospitalized COVID-19 patients: A randomized, double-blind, placebo-controlled, parallel-design clinical trial. medRxiv 2021.
147. Cadegiani FA, McCoy J, Wambier CG, Goren A. 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.
148. Freedberg DE, Conigliaro J, Sobieszczyk ME, Markowitz DD. Famotidine use is associated with impoved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. medRxiv 2020.
149. Janowitz T, Baglenz E, Pattinson D, Wang TC, Conigliaro J. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. Gut 2020; 69:1592-1597.
150. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. Am J Gastroenterol 2020.
151. Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang XP, White KM. COVID-19: Famotidine, Histamine, Mast Cells, and mechanisms. Research Square 2020.
152. Sethia R, Prasad M, Mahapatra SJ, Nischal N, Soneja M. Efficacy of famotidine for COVID-19: A systematic review and meta-analysis. medRxiv 2020.
153. Shoaibi A, Fortin S, Weinstein R, Berlin JA. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. medRxiv 2020.
154. Yeramaneni S, Doshi P, Sands K, Cooper M, Kurbegov D, Fromell G. 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.
155. Jalali F, Rezaie S, Rola P, Kyle-Sidell C. COVID-19 pathophysiology: Are platelets and serotonin hiding in plain sight? ssrn 2021.
156. Lin OA, Karim ZA, Vemana HP, Espinosa EV, Khasawneh FT. The antidepressant 5-HT2a receptor antagonists Pizotifen and cyproheptadine inhibit serotonin-enhanced platelet function. PloS ONE 2014; 9:e87026.
157. Zaid Y, Guessous F, Puhm F, Elhamdani W, Chentoufi L, Morris AC. Platelet reactivity to thrombin differs between patients with COVID-19 and those with ARDS unrelated to COVID-19. Blood Advances 2021; 5:635-639.

158. Zaid Y, Puhm F, Allaeys I, Naya A, Oudghiri M. Platelets can associate with SARS-CoV-2 RNA and are hyperactivated in COVID-19. Circ Res 2020; 127:1404-1418.
159. Dawson C, Christensen CW, Rickaby DA, Linehan JH, Johnston MR. Lung damage and pulmonary uptake of serotonin in intact dogs. J Appl Physiol 1985; 58:1761-1766.
160. MacLean MR, Herve P, Eddahibi S, Adnot S. 5-hydroxytryptamine and the pulmonary circulation: receptors, transporters and the relevance to pulmonary arterial hypertension. Br J Pharmacol 2000; 131:161-168.
161. Blackshear JL, Orlandi C, Hollenberg NK. Constrictive effect of serotonin on visible renal arteries: a pharmacoangiographic study in anesthetized dogs. J Cardiovasc Pharmacol 1991; 17:68-73.
162. Watchorn J, Hang DY, Joslin J, Bramham K, Hutchings SD. 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.
163. McGoon MD, Vanhoutte PM. Aggregating platelets contract isolated canine pulmonary arteries by releasing 5-hydroxytryptamine. J Clin Invest 1984; 74:823-833.
164. Almqvist P, Skudder P, Kuenzig M, Schwartz SI. Effect of cyproheptadine on endotoxin-induced pulmonary platelet trapping. Am Surg 1984; 50:503-505.
165. Skurikhin EG, Andreeva TV, Khnelevskaya ES, Ermolaeva LA, Pershina OV, Krupin VA. Effect of antiserotonin drug on the development of lung fibrosis and blood system reactions after intratracheal administration of bleomycin. Bull Exp Biol Med 2012; 152:519-523.
166. Doaei S, Gholami S, Rastgoo S, Bourbour F, Ghorat F, Joola P. 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.
167. Spinelli FR, Conti F, Gadina M. HiJAKing SARS-C0V-2? The potential role of JAK inhibitors in the management of COVID-19. Sci Immunol 2020; 5:eabc5367.
168. Chen CX, Wang JJ, Li H, Yuan LT, Gale RP. JAK-inhibitors for coronavirus disease-2019 (COVID): a meta-analysis. Leukemia 2021.
169. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V. Efficacy and safety of baricitinib for the treament of hospitalized adults with COVID-19 (COV-BARRIER): a randomised, double-blind,parallel-group, placebo-controlled phase 3 trial. Lancet Resp Med 2021.
170. Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM. Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial. medrx 2020.
171. Ohl ME, Miller DR, Lund BC, Kobayashi T, Miell KR. Association of remdesivir treatment with survival and length of hospital stay among US veterans hospitalized with COVID-19. JAMA Network Open 2021; 4:e2114741.
172. Ader F, Hites M, Poissy J, Belhadi D, Diallo A, Staub T. 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.
173. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Pollak U. Colchicine poisoning: the dark side of an acient drug. Clinical Toxicology 2010; 48:407-414.
174. Wimalawansa SJ. Rapidly increasing serum 25(OD)D boosts immune system, against infections - Sepsis and COVID-19. Nutrients 2022; 14:2997.

175. Ranjbar K, Shahriarad R, erfani A, Khodamoradi Z, Saadi MH. 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.
176. Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. medRxiv 2021.
177. Fowler AA, Truwit JD, Hite D, Morris PE, DeWilde C, Priday A et al. Vitamin C Infusion for TReatment In Sepsis-Induced Acute Lung Injury- CITRIS-ALI: A Randomized, Placebo Controlled Clinical Trial. JAMA 2018; 322:1261-1270.
178. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C and Thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. Chest 2017; 151:1229-1238.
179. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacol Therapeut 2018; 189:63-70.
180. Cheng RZ. Can early and high-dose vitamin C prevent and treat coronavirus disease 2019 (COVID-19). Medicine in Drug Discovery 2020.
181. Wang Y, Lin H, Lin BW, Lin JD. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. Ann Intensive Care 2019; 9:58.
182. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. PharmaNutrition 2020; 12:100190.
183. Iglesias J, Vassallo AV, Patel V, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. Chest 2020; 158:164-173.
184. Hiedra R, Lo KB, Elbashabsheh M, Gul F, Wright RM. The use of IV vitamin C for patients with COVID-19: a case series. Exp Rev Anti Infect Ther 2020.
185. Zhang J, Rao X, Li Y, Zhu Y, Liu G, Guo G et al. High-dose vitamin C infusion for the treatment of critically ill COVID-19. Research Square 2020.
186. Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020; 12:e11779.
187. Al Sulaiman K, Al Juhani O, Badreldin HA, Salah KB, Alharbi A, Arabi YM. Adjunctive therapy with ascorbic in critically ill patients with COVID-19: A multicenter propensity score matched study. Crit Care 2021.
188. Lankadeva YR, Peiris RM, Okazaki N, Birchall IE, Doenom A, Evans RG et al. Reversal of the pathophysiological responses to Gram-negative sepsis by megadose Vitamin C. Crit Care Med 2020.
189. Zhang J, Rao X, Li Y, Zhu Y, Liu G, Guo G et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intenisve Care 2020.
190. Lavinio A, Ercole A, Battaglini D, Magnoni S, Badenes R, Thomas W 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.
191. 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.
192. Tomassa-Irriguible TM, Lielsa-Berrocal L. COVID-19: Up to 87% critically ill patients had low vitamin C values. Research Square 2020.

193. 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.
194. Lopes RD, Furtado RH, Bronhara B, Damiani LP, Barbosa LM. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentraion (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet 2021; 397:2253-2263.
195. Kalfas S, Visvanathan K, Chan K, Drago J. The therapeutic potential of ivermectin for COVID-19: A systematic review of mechanisms and evidence. medRxiv 2020.
196. Menezes RR, Godin AM, Rodrigues FF, Coura GM, Melo IS, Brito AM. 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; 69:1036-1043.
197. Vatsalya V, Li F, Frimodig J, Gala KS, Srivastava S, Kong M. 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.
198. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! J Thorac Dis 2016; 8:1062-1066.
199. Moskowitz A, Donnino MW. Thiamine (vitamin B1) in septic shock: a targeted therapy. J Thorac Dis 2020; 12 (suppl 1):S78-S83.
200. Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, Morris PE, Flannery AH. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Crit Care Med 2018; 46:1747-1752.
201. Marik PE. Thiamine: An essential component of the metabolic resuscitation protocol. Crit Care Med 2018; 46:1869-1870.
202. Al Sulaiman K, Aljuhani O, Al Dossari M, Alshahrani A, Alharbi A. Evaluation of thiamine as adjunctive therapy in COVID-19 critically ill patients: A multicenter propensity score matched study. Research Square 2021.
203. Zarehoseinzade E, Allami A, Ahmadi M, Bijani B. 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.
204. Chen L, Jiang X, Huang L, Lan K, Wang H, Hu 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; 31:2242-2248.
205. Tan CW, Ho LP, Kalimuddin S, Cherng BP, Teh YE. 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.
206. Lee CY, Jan WC, Tsai PS, Huang CJ. Magnesium sulfate mitigates acute lung injury in endotoxemia rats. J Trauma 2011; 70:1177-1185.
207. Salem M, Kasinski N, Munoz R, Chernow B. Progressive magnesium deficiency inceases mortality from endotoxin challenge:Protective effects of acute magnesium replacement therapy [abstract]. Crit Care Med 1995;A260.
208. Jiang P. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? A systematic review and meta-analysis. Shock 2019; 47:288-295.

209. Duarte M, Pelorosso F, Nicolosi L, Salgado V, Vetulli H. Telmisartan for treatment of COVID-19 patients: an open multicenter randomized clinical trial. EClinicalMedicine 2021; 37:100962.
210. Rothlin RP, Vetulli HM, Duarte M, Pelorosso FG. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. Drug Dev Res 2020; 81:768-770.
211. Nejat R, Sadr AS, Freitas BT, Murray J, Pegan SD. Losartan inhibits SARS-CoV-2 replication in vitro. J Pharm Pharm Sci 2021; 24:390-399.
212. Patterson BK, seethamraju H, Dhody K, Corley MJ, Kazempour K, Lalezari J et al. CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and deceases SARS-CoV2 RNA in plasma by day 14. International Journal of Infectious Diseases 2021; 103:25-32.
213. Patterson BK, Guevara-Coto J, Yogendra R, Francisco E, Long E, Pise A. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. Front Immunol 2021.
214. Li S, Jiang L, Li X, Lin F, Wang Y, Li B. Clinical and pathological investigation of patients with severe COVID-19. JCI Insight 2020; 5:e138070.
215. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnager T. 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.
216. Simonovich VA, Pratx LD, Scibona P, Beruto MV, Vallone MG. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med 2020.
217. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, Ruiz-Antoran B, de Molina RM. Convalescent plasma for COVID-19: A multicenter, randomized clinical trial. medRxiv 2020.
218. Balcells ME, Rojas L, Le Corre N, Ceballos ME, Ferres M, Chang M. 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.
219. Janiaud P, Axfors C, Schmitt AM, Glory V, Moher D. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19. A systematic review and meta-analysis. JAMA 2021.
220. Li L, Zhang W, Hu Y, Tong X, Zeng S, Yang J. 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.
221. Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? Filaria Jurnal 2003; 3 (Suppl I):S8.
222. Thompson MA, Henderson JP, Shah PK, Rubenstein SM, Joyner MJ, Flora DB. Convalescent plasma and improved survival in patients with hematologic malignancies and COVID-19. medRxiv 2021.
223. Westendorf K, Zentelis S, Wang L, Foster D, Wiggin M, Lovett E. LY-CoV1404 (bebtelovimab) potently neuralizes SARS-CoV-2 variants. bioRxiv 2022.
224. Rosas IO, Brau N, Waters M, Go R, Hunter BD, Bhagani S et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv 2020.
225. Hermine O, Mariette X, Tharaux PL, Resche-Rignon M, Porcher R. 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.

226. Stone JH, Frigault MJ, Sterling-Boyd NJ, Fernandes AD, Harvey FL. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020.
227. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. A randomized clinical trial. JAMA Intern Med 2020.
228. Salama C, Han J, Yau L, Reiss WG, Kramer B. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2020.
229. Jeffreys L, Pennington SH, Duggan J, Breen A, Jinks J. Remdesivir-Ivermectin combination displays synergistic interactions with improved in vitro antiviral activity against SARS-CoV-2. bioRxiv 2020.
230. Gordon AC, Mouncey PR, Rowan KM, Nichol AD, Arabi YM, Annane D. Interleukin-6 receptor antagonists in critically ill patients with COVID-19 - Preliminary report. medRxiv 2021.
231. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020.
232. Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clinical Microbiology & Infection 2021; 27:9-11.
233. Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care 2020; 24:530.
234. Koehler P, Bassetti M, Chen SC, Colombo AL, Perfect JR. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021.
235. Ospina-Tascon GA, Calderon-Tapia LE, Garcia AF, Zarama V, Vargas MP, Vaaron J. 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; 326:2161-2171.
236. Xu Q, Wang T, Quin X, Zha L. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19; a case series. Crit Care 2020; 24:250.
237. Elharrar X, Trigui Y, Dois AM, Touchon F. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA 2020.
238. Reddy MP, Subramaniam A, Afroz A, Billah B, Lim ZJ, Wong SN. Prone positioning of nonintubated patients with Coronavirus Disease 2019- A systematic review and meta-analysis. Crit Care Med 2021.
239. Xin Y, Martin K, Morais CC, Gerard SE, Abate N, Sidhu U et al. Diminishing efficacy of prone positioning with late application in evolving lung injury. Crit Care Med 2021.
240. 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; 46:2248-2251.
241. Winslow RL, Zhou J, Windle EF, Nur I, Lall R, Ji C. SARS-CoV-2 environmental contamination from hospitalized patients with COVID-19 receiving erosol-generating procedures. Thorax 2021.
242. Francone M, Lafrate F, Masci GM, Coco S, Cilia F, Manganaro L et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. European Radiology 2020; 30:6808-6817.
243. Parry AH, Wani AH, Shah NN, Yaseen M, Jehangir M. Chest CT features of coronavirus disease-19 (COVID-19) pnemonia: which findings on initial CT can predict an adverse short-term outcome? BJR Open 2020; 2:20200016.

244. Zhang J, Meng G, Li W, Shi B, Dong H, Su Z. Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respiratory Research 2020; 21:180.
245. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q et al. Chest CT severity score: An imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging 2020; 2:e2000047.
246. Li K, Wu J, Wu F, Guo D, Cen L, Fang Z et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative Radiology 2020; 55:1-5.
247. Pan F, Ye T, Sun P, Gui S, Liang B, Li L. Time course of lung changes at Chest CT during recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2021; 295:715-721.
248. Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. European Journal of Radiology 2020; 127:109009.
249. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N et al. Chest CT findings in Coronavirus disease 2019 (COVID-19): relationship to duration of infection. Radiology 2020; 295:685-691.
250. Ichikado K, Suga M, Muranka H, Gushima Y, Miyakawa H. Prediction of prognosis for acute respiratory distress syndrome with thin-section CT: Validation in 44 cases. Radiology 2006; 238:321-329.
251. Ichikado K, Suga M, Muller NL, Tangiguchi H, Kondoh Y, akira M. Acute interstitial pneumonia. Comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002; 165:1551-1556.
252. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care 2020; 24:128.
253. Keith P, Wells AH, Hodges J, Fast SH. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: A single center experience. Crit Care 2020; 24:518.
254. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002; 28:1434-1439.
255. Morath C, Weigand MA, Zeier M, Speer C, Tiwari-Heckler S. Plasma exchange in critically ill COVID-19 patients. Crit Care 2020; 24:481.
256. Khamis F, Al-Zakwani I, Al Hashmi S, Al Dowaiki S, Al Bahrani M. Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect Dis 2020; 99:214-218.
257. Fernandez J, Gratacos-Gines J, Olivas P, Costa M, Nieto S, Mateo D. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. Crit Care Med 2020.
258. Gucyetmez B, Atalan HK, Sertdemir I, Cakir U, Telci L. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care 2020; 24:492.
259. Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfuncion responsive to thrombolysis. medRxiv 2020.
260. Wang J, Najizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA. Tissue plasminogen activator (tPA) treatment for COVID-19 associated respiratory distress syndrome (ARDS): A case series. J Thromb Haemost 2020.

261. Abou-Arab O, Huette P, Debouvries F, Dupont H, Jounieaux V. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. Crit Care 2020; 24:645.
262. Bagate F, Tuffet S, Masi P, Perier F, Razazi K. Rescue thearpy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. Ann Intensive Care 2020.
263. Caplan M, Goutay J, Bignon A, Jaillette E, Favory R. Almitrine infusion in severe acute respiratory syndrome coronavirus-2 indued acute respiratory distress syndrome: A single-center observational study. Crit Care Med 2020.
264. Payen D. Coronavirus disease 2019 acute respiratory failure: Almitrine drug resuscitaion or resuscitating patients by almitrine? Crit Care Med 2020.
265. 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.
266. Abrams D, Lorusso R, Vincent JL, Brodie D. ECMO during the COVID-19 pandemic: when is it unjustified. Crit Care 2020; 24:507.
267. Supady A, Taccone FS, Lepper PM, Ziegeler S, Staudacher DL. Survival after extracorporeal membrane oxygenation in severe COVID-19 ARDS: results from an international multicenter registry. Crit Care Med 2021; 25:90.
268. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020.
269. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. Lancet Resp Med 2021; 8:944-946.
270. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. N Engl J Med 2020.
271. Cerutti A, Chen K, Chorny A. Immunoglobulin responses at the mucosal interface. Annu Rev Immunol 2011; 29:273-293.
272. Jacobs JJ. Neutralizing antibodies mediate virus-immue pathology of COVID-19. Med Hypotheses 2020; 143:109884.
273. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. Medical Hypotheses 2020; 144:11005.
274. Saba A, Vaidya PJ, Chavhan VB, Achlerkar A, Leuppi J. Combined pirfenidone, azithromycin and prednisolone in post-H1N1 ARDS pulmonary firbosis. Sarcoidosis Vasc Diffuse Lung Dis 2018; 35:85-90.
275. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Resp Med 2020; 8:750-752.
276. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antibibrotic therapy. Lancet Resp Med 2020; 8:807-815.
277. Brouwer WP, Duran S, Kuijper M, Inc C. 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.
278. Villa G, Romagnoli S, De Rosa S, Greco M, Resta M. 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.

279. Ahmad Q, DePerrior SE, Dodani S, Edwards JF, Marik PE. Role of inflammatory biomarkers in the prediction of ICU admission and mortality in patients with COVID-19. Medical Research Archives 2020; 8:1-10.
280. 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; 60:135-139.
281. Ichikado K, Muranaka H, Gushima Y, Kotani T, Nader HM, Fujimoto K 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.
282. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020; 92:856-862.
283. 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.
284. Stephenson E, Hooper MH, Marik PE. Vitamin C and Point of Care glucose measurements: A retrospective, Observational study [Abstract]. Chest 2018; 154 (suppl.):255a.
285. Hekimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J. COVID-19 acute myocarditis and multisystem inflanmmatory syndrome in Adult Intensive and cardiac Care Units. Chest 2020.
286. Ma KL, Liu ZH, Cao CF, Liu MK, Liao J. COVID-19 myocarditis and severity factors: An adult cohort study. medRxiv 2020.
287. Brosnahan SB, Bhatt A, Berger JS, Yuriditsky E, Iturrate E. COVID-19 pneumonia hospitalizations followed by re-presentation for presumed thrombotic event. Chest 2020.
288. Giannis D, allen SL, Tsang J, Flint S, Pinhasov T, Williams S. Post-discharge thromboembolic outcomes and mortality of hospitalized COVID-19 patients: The CORE-19 registry. Blood 2021.
289. Spyropoulos AC, Lipardi C, Xu J, Peluso C, Spiro TE. 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.
290. Kunutsor SK, Seidu S, Blom AW, Khunti K. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. Eur J Epidemiol 2017; 32:657-667.

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PREVENTION & TREATMENT PROTOCOLS FOR COVID-19

# Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

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## Keywords

Ivermectin, COVID-19, infectious disease, pulmonary infection, respiratory failure

## Abstract

In March 2020, the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik to continuously review the rapidly emerging basic science, translational, and clinical data to develop a treatment protocol for COVID-19. The FLCCC then recently discovered that ivermectin, an anti-parasitic medicine, has highly potent anti-viral and anti-inflammatory properties against COVID-19. They then identified repeated, consistent, large magnitude improvements in clinical outcomes in multiple, large, randomized and observational controlled trials in both prophylaxis and treatment of COVID-19. Further, data showing impacts on population wide health outcomes have

resulted from multiple, large "natural experiments" that occurred when various city mayors and regional health ministries within South American countries initiated "ivermectin distribution" campaigns to their citizen populations in the hopes the drug would prove effective. The tight, reproducible, temporally associated decreases in case counts and case fatality rates in each of those regions compared to nearby regions without such campaigns, suggest that ivermectin may prove to be a global solution to the pandemic. This was further evidenced by the recent incorporation of ivermectin as a prophylaxis and treatment agent for COVID-19 in the national treatment guidelines of Belize, Macedonia, and the state of Uttar Pradesh in Northern India, populated by 210 million people. To our knowledge, the current review is the earliest to compile sufficient clinical data to demonstrate the strong signal of therapeutic efficacy as it is based on numerous clinical trials in multiple disease phases. One limitation is that half the controlled trials have been published in peer-reviewed publications, with the remainder taken from manuscripts uploaded to medicine pre-print servers. Although it is now standard practice for trials data from pre-print servers to immediately influence therapeutic practices during the pandemic, given the controversial therapeutics adopted as a result of this practice, the FLCCC argues that it is imperative that our major national and international health care agencies devote the necessary resources to more quickly validate these studies and confirm the major, positive epidemiological impacts that have been recorded when ivermectin is widely distributed among populations with a high incidence of COVID-19 infections.

## Introduction

In March 2020, an expert panel called the Front Line COVID-19 Critical Care Alliance (FLCCC) was created and led by Professor Paul E. Marik.[1] The group of expert critical care physicians and thought leaders immediately began continuously reviewing the rapidly emerging basic science, translational, and clinical data in COVID-19 which then led to the early creation of a treatment protocol for hospitalized patients based on the core therapeutic interventions of methylprednisolone, ascorbic acid, thiamine and heparin (MATH+), with the "+" referring to multiple, optional adjunctive treatments. The MATH+ protocol was based on the collective expertise of the group in both the research and treatment of multiple other severe infections causing lung injury.

Two manuscripts reviewing different aspects of both the scientific rationale and evolving published clinical evidence in support of the MATH+ protocol were published in major medical journals at two different time points in the pandemic (Kory et al., 2020;Marik et al., 2020). The most recent paper reported a 6.1% hospital mortality rate in COVID-19 patients measured in the two U.S hospitals that systematically adopted the MATH+ protocol (Kory et al., 2020). This was a markedly decreased mortality rate compared to the 23.0% hospital mortality rate calculated from a review of 45 studies including over 230,000 patients (unpublished data; available on request).

Although the adoption of MATH+ has been considerable, it largely occurred only after the treatment efficacy of the majority of the protocol components (corticosteroids, ascorbic acid, heparin, statins, Vitamin D, melatonin) were either validated in subsequent randomized controlled trials or more strongly supported with large observational data sets in COVID-19 (Entrenas Castillo et al., 2020;Horby et al., 2020;Jehi et al., 2020;Nadkarni et al., 2020;Rodriguez-Nava et al., 2020;Zhang et al., 2020a;Zhang et al., 2020b). Despite the plethora of supportive evidence, the MATH+ protocol for hospitalized patients has not yet become widespread. Further, the world is in a worsening crisis with

[1] https://www.flccc.net

the potential of again overwhelming hospitals and ICU's. As of December 31st, 2020, the number of deaths attributed to COVID-19 in the United States reached 351,695 with over 7.9 million active cases, the highest number to date.[2] Multiple European countries have now begun to impose new rounds of restrictions and lockdowns.[3]

Further compounding these alarming developments was a wave of recently published results from therapeutic trials done on medicines thought effective for COVID-19 which found a lack of impact on mortality with use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, tocilizumab, and mono-clonal antibody therapy (Agarwal et al., 2020;Consortium, 2020;Hermine et al., 2020;Salvarani et al., 2020).[4] One year into the pandemic, the only therapy considered "proven" as a life-saving treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness (Horby et al., 2020). Similarly, most concerning is the fact that little has proven effective to prevent disease progression to prevent hospitalization.

Fortunately, it now appears that ivermectin, a widely used anti-parasitic medicine with known anti-viral and anti-inflammatory properties is proving a highly potent and multi-phase effective treatment against COVID-19. Although growing numbers of the studies supporting this conclusion have passed through peer review, approximately half of the remaining trials data are from manuscripts uploaded to medical pre-print servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. The FLCCC expert panel, in their prolonged and continued commitment to reviewing the emerging medical evidence base, and considering the impact of the recent surge, has now reached a consensus in recommending that ivermectin for both prophylaxis and treatment of COVID-19 should be systematically and globally adopted.

The FLCCC recommendation is based on the following set of conclusions derived from the existing data, which will be comprehensively reviewed below:

1) Since 2012, multiple *in vitro* studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, Zika, Dengue and others (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020).
2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly et al., 2020a).
3) Ivermectin has potent anti-inflammatory properties with *in vitro* data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).
4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo et al., 2020;de Melo et al., 2020).
5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).

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2 https://www.worldometers.info/coronavirus/country/us/
3 https://www.npr.org/sections/coronavirus-live-updates/2020/12/15/946644132/some-european-countries-batten-down-for-the-holidays-with-new-coronavirus-lockdo
4 https://www.lilly.com/news/stories/statement-activ3-clinical-trial-nih-covid19

6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo et al., 2020a;Elgazzar et al., 2020;Gorial et al., 2020;Khan et al., 2020;Mahmud, 2020;Morgenstern et al., 2020;Robin et al., 2020).
7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Elgazzar et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Spoorthi V, 2020).
8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020;Hashim et al., 2020;Rajter et al., 2020).
9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).[5]
10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered (Kircik et al., 2016).
11) The World Health Organization has long included ivermectin on its "List of Essential Medicines".[6]

Following is a comprehensive review of the available efficacy data as of December 12, 2020, taken from *in vitro*, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

## History of ivermectin

In 1975, Professor Satoshi Omura at the Kitsato institute in Japan isolated an unusual *Streptomyces* bacteria from the soil near a golf course along the south east coast of Honshu, Japan. Omura, along with William Campbell, found that the bacterial culture could cure mice infected with the round-worm *Heligmosomoides polygyrus*. Campbell isolated the active compounds from the bacterial culture, naming them "avermectins" and the bacterium *Streptomyces avermitilis* for the compounds' ability to clear mice of worms (Crump and Omura, 2011). Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found. Ivermectin, a derivative of avermectin, then proved revolutionary. Originally introduced as a veterinary drug, it soon after made historic impacts in human health, improving the nutrition, general health and well-being of billions of people worldwide ever since it was first used to treat Onchocerciasis (river blindness) in humans in 1988. It proved ideal in many ways, given that it was highly effective, broad-spectrum, safe, well tolerated and could be easily administered (Crump and Omura, 2011). Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of two global disease elimination campaigns that has nearly eliminated the world of two of its most disfiguring and devastating diseases. The unprecedented partnership between Merck & Co. Inc., and the Kitasato Institute combined with the aid of international health care organizations has been recognized by many experts as one of the greatest medical accomplishments of the 20th century. One example was the decision by Merck & Co to donate ivermectin doses to support the Meztican Donation Program which then provided over 570 million treatments in its first 20 years alone (Tambo et al.). Ivermectins' impacts in controlling Onchocerciasis and Lymphatic filariasis, diseases which

[5] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/
[6] https://www.who.int/publications/i/item/WHOMVPEMPIAU201907

blighted the lives of billions of the poor and disadvantaged throughout the tropics, is why its discoverers were awarded the Nobel Prize in Medicine in 2015 and the reason for its inclusion on the WHO's "List of Essential Medicines." Further, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found (Crump and Omura, 2011).

## Pre-Clinical Studies of Ivermectin's activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has anti-viral properties against an increasing number of RNA viruses, including influenza, Zika, HIV, Dengue, and most importantly, SARS-CoV-2 (Mastrangelo et al., 2012;Wagstaff et al., 2012;Tay et al., 2013;Götz et al., 2016;Varghese et al., 2016;Atkinson et al., 2018;Lv et al., 2018;King et al., 2020;Yang et al., 2020). Insights into the mechanisms of action by which ivermectin both interferes with the entrance and replication of SARS-CoV-2 within human cells are mounting. Caly et al first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48h after exposure to ivermectin (Caly et al., 2020b). However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations employed in their experimental model using standard or even massive doses of ivermectin (Bray et al., 2020;Schmith et al., 2020). It should be noted that the concentrations required for effect in cell culture models bear little resemblance to human physiology given the absence of an active immune system working synergistically with a therapeutic agent such as ivermectin. Further, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short term cell model exposure. Further, multiple co-existing or alternate mechanisms of action likely explain the clinical effects observed, such as the competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, as proposed in six molecular modeling studies (Dayer, 2020; Hussien and Abdelaziz, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Nallusamy et al., 2020; Suravajhala et al., 2020). In four of the studies, ivermectin was identified as having the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules collectively examined, with ivermectin not being the particular focus of study in four of these studies (Scheim, 2020). This is the same mechanism by which viral antibodies, in particular, those generated by the Pfizer and Moderna vaccines, contain the SARS-CoV-2 virus. The high binding activity of ivermectin to the SARS-CoV-2 spike protein could limit binding to either the ACE-2 receptor or sialic acid receptors, respectively either preventing cellular entry of the virus or preventing hemagglutination, a recently proposed pathologic mechanism in COVID-19 (Dasgupta J, 2020;Dayer, 2020;Lehrer and Rheinstein, 2020;Maurya, 2020;Scheim, 2020). Ivermectin has also been shown to bind to or interfere with multiple essential structural and non-structural proteins required by the virus in order to replicate (Lehrer and Rheinstein, 2020;Sen Gupta et al., 2020). Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication (Swargiary, 2020).

Arevalo et al investigated in a murine model infected with a type 2 family RNA coronavirus similar to SARS-CoV-2, (mouse hepatitis virus), the response to 500 mcg/kg of ivermectin vs. placebo (Arevalo et al., 2020). The study included 40 infected mice, with 20 treated with ivermectin, 20 with phosphate buffered saline, and then 16 uninfected control mice that were also given phosphate buffered saline. At day 5, all the mice were euthanized to obtain tissues for examination and viral load assessment. The 20 non-ivermectin treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic

viral load (52,158 AU), while in the ivermectin treated mice a much lower viral load was measured (23,192 AU; $p<0.05$), with only few livers in the ivermectin treated mice showing histopathological damage such that the differences between the livers from the uninfected control mice were not statistically significant.

Dias De Melo and colleagues recently posted the results of a study they did with golden hamsters that were intranasally inoculated with SARS-CoV-2 virus, and at the time of the infection, the animals also received a single subcutaneous injection of ivermectin at a dose of 0.4mg/kg on day 1 (de Melo et al., 2020). Control animals received only the physiologic solution. They found the following among the ivermectin treated hamsters; a dramatic reduction in anosmia (33.3% vs 83.3%, p=.03) which was also sex-dependent in that the male hamsters exhibited a reduction in clinical score while the treated female hamsters failed to show any sign of anosmia. They also found significant reductions in cytokine concentrations in the nasal turbinate's and lungs of the treated animals despite the lack of apparent differences in viral titers.

Despite these mounting insights into the existing and potential mechanisms of action of ivermectin both as a prophylactic and treatment agent, it must be emphasized that significant research gaps remain and that many further *in vitro* and animal studies should be undertaken to better define not only these mechanisms but also to further support ivermectin's role as a prophylactic agent, especially in terms of the optimal dose and frequency required.

## Pre-Clinical studies of ivermectin's anti-inflammatory properties

Given that little viral replication occurs in the later phases of COVID-19, nor can virus be cultured, and only in a minority of autopsies can viral cytopathic changes be found (Perera et al., 2020;Polak et al., 2020;Young et al., 2020), the most likely pathophysiologic mechanism is that identified by Li et al. where they showed that the non-viable RNA fragments of SARS-CoV-2 leads to a high mortality and morbidity in COVID-19 via the provocation of an overwhelming and injurious inflammatory response (Li et al., 2013). Based on these insights and the clinical benefits of ivermectin in late phase disease to be reviewed below, it appears that the increasingly well described *in vitro* properties of ivermectin as an inhibitor of inflammation are far more clinically potent than previously recognized. The growing list of studies demonstrating the anti-inflammatory properties of ivermectin include its ability to; inhibit cytokine production after lipopolysaccharide exposure, downregulate transcription of NF-kB, and limit the production of both nitric oxide and prostaglandin $E_2$ (Zhang et al., 2008;Ci et al., 2009;Zhang et al., 2009).

## Exposure prophylaxis studies of ivermectin's ability to prevent transmission of COVID-19

Data is also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from three randomized controlled trials (RCT) and five observational controlled trials (OCT) with four of the eight (two of them RCT's) published in peer-reviewed journals (Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Chala, 2020;Elgazzar et al., 2020;Hellwig and Maia, 2020;Shouman, 2020).

Elgazzar and colleagues at Benha University in Egypt randomized 200 health care and households contacts of COVID-19 patients where the intervention group consisted of 100 patients given a high dose of 0.4mg/kg on day 1 and a second dose on day 7 in addition to wearing personal

protective equipment (PPE), while the control group of 100 contacts wore PPE only (Elgazzar et al., 2020). They reported a large and statistically significant reduction in contacts testing positive by RT-PCR when treated with ivermectin vs. controls, 2% vs 10%, p<.05.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated, 112 control) family members of patients positive for SARS-CoV-2 via PCR (Shouman, 2020). Ivermectin, (approximately 0.25mg/kg) was administered twice, on the day of the positive test and 72 hours later. After a two-week follow up, a large and statistically significant decrease in COVID-19 symptoms among household members treated with ivermectin was found, 7.4% vs. 58.4%, p<.001.

Recently Alam et al from Bangladesh performed a prospective observational study of 118 patients that were evenly split into those that volunteered for either the treatment or control arms, described as a persuasive approach. Although this method, along with the study being unblinded likely led to confounders, the differences between the two groups were so large (6.7% vs. 73.3%, p <.001) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain such a result (Alam et al., 2020). Carvallo et al also performed a prospective observational trial where they gave healthy volunteers ivermectin and carrageenan daily for 28 days and matched them to similarly healthy controls who did not take the medicines (Carvallo et al., 2020b). Of the 229 study subjects, 131 were treated with 0.2mg of ivermectin drops taken by mouth five times per day. After 28 days, none of those receiving ivermectin prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm (p<.001). In a much larger follow-up observational controlled trial by the same group that included 1,195 health care workers, they found that over a 3-month period, there were no infections recorded among the 788 workers that took weekly ivermectin prophylaxis while 58% of the 407 controls had become ill with COVID-19. This study demonstrates that protection against transmission can be achieved among high-risk health care workers by taking 12mg once weekly (Carvallo et al., 2020b). The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina where they found that among 234 health care workers, the intervention group that took 12 mg once weekly, only 3.4% contracted COVID-19 vs. 21.4% of controls, p<.0001(Chala, 2020).

The need for weekly dosing in the Carvallo study over a 4 month period may not have been necessary given that, in a recent RCT from Dhaka, Bangladesh, the intervention group (n=58) took 12mg only once monthly for a similar 4 month period and also reported a large and statistically significant decrease in infections compared to controls, 6.9% vs. 73.3%, p<.05 (Alam et al., 2020). Then, in a large retrospective observational case-control study from India, Behera et al. reported that among 186 case-control pairs (n=372) of health care workers, they identified 169 participants that had taken some form of prophylaxis, with 115 that had taken ivermectin prophylaxis (Behera et al., 2020). After matched pair analysis, they reported that in the workers who had taken two dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% CI, 0.15–0.51). Notably, one dose prophylaxis was not found to be protective in this study. Based on both their study finding and the Egyptian prophylaxis study, the All-India Institute of Medical Sciences instituted a prophylaxis protocol for their health care workers where they now take two 0.3mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

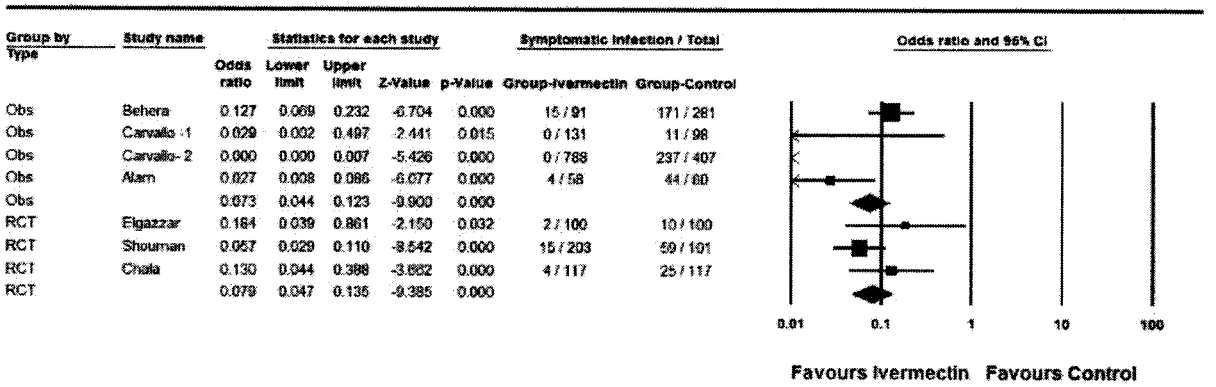
Data which further illuminates the protective role of ivermectin against COVID-19 comes from a study of nursing home residents in France which reported that in a facility that suffered a scabies outbreak where all 69 residents and 52 staff were treated with ivermectin (Behera et al., 2020), they found that during the time period surrounding this event, 7/69 residents fell ill with COVID-19 (10.1%). In this group with an average age of 90 years, only one resident required oxygen support and

no resident died. In a matched control group of residents from surrounding facilities, they found 22.6% of residents fell ill and 4.9% died.

Likely the most definitive evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the International Journal of Anti-Microbial agents where a group of researchers analyzed data using the prophylactic chemotherapy databank administered by the WHO along with case counts obtained by Worldometers, a public data aggregation site used by among others, the Johns Hopkins University (Hellwig and Maia, 2020). When they compared the data from countries with active ivermectin mass drug administration programs for the prevention of parasite infections, they discovered that the COVID-19 case counts were significantly lower in the countries with recently active programs, to a high degree of statistical significance, p<.001.

Figure 1 below presents a meta-analysis performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

**Figure 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19**



| Group by Type | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Symptomatic infection / Total: Group-Ivermectin | Group-Control |
|---|---|---|---|---|---|---|---|---|
| Obs | Behera | 0.127 | 0.069 | 0.232 | -6.704 | 0.000 | 15 / 91 | 171 / 281 |
| Obs | Carvallo -1 | 0.029 | 0.002 | 0.497 | -2.441 | 0.015 | 0 / 131 | 11 / 98 |
| Obs | Carvallo- 2 | 0.000 | 0.000 | 0.007 | -5.426 | 0.000 | 0 / 788 | 237 / 407 |
| Obs | Alam | 0.027 | 0.008 | 0.086 | -6.077 | 0.000 | 4 / 58 | 44 / 60 |
| Obs | | 0.073 | 0.044 | 0.123 | -9.900 | 0.000 | | |
| RCT | Elgazzar | 0.184 | 0.039 | 0.861 | -2.150 | 0.032 | 2 / 100 | 10 / 100 |
| RCT | Shouman | 0.057 | 0.029 | 0.110 | -8.542 | 0.000 | 15 / 203 | 59 / 101 |
| RCT | Chala | 0.130 | 0.044 | 0.388 | -3.682 | 0.000 | 4 / 117 | 25 / 117 |
| RCT | | 0.079 | 0.047 | 0.135 | -9.385 | 0.000 | | |



Figure 1 legend – OBS: Observational study, RCT: Randomized Controlled Trial

Symbols – Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Further data supporting a role for ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" appear to have occurred. For instance, beginning as early as May, various regional health ministries and governmental authorities within Peru, Brazil, and Paraguay initiated "ivermectin distribution" campaigns to their citizen populations (Chamie, 2020). In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to their city's population, where, in the case of Natal, 1 million doses were distributed.[7] The distribution campaign of Itajai began in mid-July, and in Natal they began on June 30th , and in Macapa, the capital city of Amapa and others nearby incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 below was obtained from the official Brazilian government site and the national press

[7] https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/

consortium and show large decreases in case counts in the three cities soon after distribution began compared to their neighboring cities without such campaigns.

The decreases in case counts among the three Brazilian cities shown in Table 1 was also associated with reduced mortality rates as seen in Table 2 below.

**Table 1. Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns** (bolded cities distributed ivermectin, neighboring regional city below did not)

| REGION | NEW CASES | JUNE | JULY | AUGUST | POPULATION 2020 (1000) | % DECLINE IN NEW CASES BETWEEN JUNE AND AUGUST 2020 |
|---|---|---|---|---|---|---|
| **South** | **Itajaí** | **2123** | **2854** | **998** | **223** | **−53%** |
| | Chapecó | 1760 | 1754 | 1405 | 224 | −20% |
| **North** | **Macapá** | **7966** | **2481** | **2370** | **503** | **−70%** |
| | Ananindeua | 1520 | 1521 | 1014 | 535 | −30% |
| **North East** | **Natal** | **9009** | **7554** | **1590** | **890** | **−82%** |
| | João Pessoa | 9437 | 7963 | 5384 | 817 | −43% |

**Table 2. Change in death rates among neighboring regions in Brazil** (bolded regions contained a major city that distributed Ivermectin to its citizens, the other regions did not)

| REGION | STATE | % CHANGE IN AVERAGE DEATHS/ WEEK COMPARED TO 2 WEEKS PRIOR |
|---|---|---|
| **South** | **Santa Catarina** | **−36%** |
| | PARANÁ | −3% |
| | Rio Grande do Sul | −5% |
| **North** | **Amapá** | **−75%** |
| | AMAZONAS | −42% |
| | Pará | +13% |
| **North East** | **Rio Grande do Norte** | **−65%** |
| | CEARÁ | +62% |
| | Paraíba | −30% |

## Clinical studies on the efficacy of ivermectin in treating mildly ill outpatients

Currently, seven trials which include a total of over 3,000 patients with mild outpatient illness have been completed, a set comprised of 7 RCT's and four case series (Babalola et al.;Cadegiani et al., 2020;Carvallo et al., 2020a;Chaccour et al., 2020;Chowdhury et al., 2020;Espitia-Hernandez et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Mahmud, 2020;Podder et al., 2020;Ravikirti et al., 2021).

The largest, a double blinded RCT by Mahmud et al. was conducted in Dhaka, Bangladesh and targeted 400 patients with 363 patients completing the study (Mahmud, 2020). In this study, as in many other of the clinical studies to be reviewed, either a tetracycline (doxycycline) or macrolide antibiotic (azithromycin) was included as part of the treatment. The importance of including antibiotics such as doxycycline or azithromycin is unclear, however, both tetracycline and macrolide antibiotics have recognized anti-inflammatory, immunomodulatory, and even antiviral effects (*58-61*). Although the posted data from this study does not specify the amount of mildly ill outpatients vs. hospitalized patients treated, important clinical outcomes were profoundly impacted, with increased rates of early improvement (60.7% vs. 44.4% p<.03) and decreased rates of clinical deterioration (8.7% vs 17.8%, p<.02). Given that mildly ill outpatients mainly comprised the study cohort, only two deaths were observed (both in the control group).

Ravikirti performed a double-blind RCT of 115 patients, ang although the primary outcome of PCR positivity on Day 6 was no different, the secondary outcome of mortality was 0%vs. 6.9%, p=.019 (Ravikirti et al., 2021). Babalola in Nigeria also performed a double blind-RCT of 62 patients, and, in contrast to Ravikirti, they found a significant difference in viral clearance between both the low and high dose treatment groups and controls in a dose dependent fashion, p=.006 (Babalola et al.).

Another RCT by Hashim et al. in Baghdad, Iraq included 140 patients equally divided; the control group received standard care, the treated group included a combination of both outpatient and hospitalized patients (Hashim et al., 2020). In the 96 patients with mild-to-moderate outpatient illness, they treated 48 patients with a combination of ivermectin/doxycycline and standard of care and compared outcomes to the 48 patients treated with standard of care alone. The standard of care in this trial included many elements of the MATH+ protocol, such as dexamethasone 6mg/day or methyl-prednisolone 40mg twice per day if needed, Vitamin C 1000mg twice/day, Zinc 75–125mg/day, Vitamin D3 5000 IU/day, azithromycin 250mg/day for 5 days, and acetaminophen 500mg as needed. Although no patients in either group progressed or died, the time to recovery was significantly shorter in the ivermectin treated group (6.3 days vs 13.7 days, p<.0001).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin vs placebo and although they found no difference in PCR positivity at day 7, they did find statistically significant decreases in viral loads, patient days of anosmia (76 vs 158, p<.05), and patient days with cough (68 vs 98, p<.05) (Chaccour et al., 2020).

Another RCT of ivermectin treatment in 116 outpatients was performed by Chowdhury et al. in Bangladesh where they compared a group of 60 patients treated with the combination of ivermectin/ doxycycline to a group of 60 patients treated with hydroxychloroquine/doxycycline with a primary outcome of time to negative PCR (Chowdhury et al., 2020). Although they found no difference in this outcome, in the treatment group, the time to symptomatic recovery approached statistical significance (5.9 days vs. 7.0 days, p=.07). In another smaller RCT of 62 patients by Podder et al., they also found a shorter time to symptomatic recovery that approached statistical significance (10.1 days vs 11.5 days, p>.05, 95% CI, 0.86–3.67) (Podder et al., 2020).

A medical group in the Dominican Republic reported a case series of 2,688 consecutive symptomatic outpatients seeking treatment in the emergency room, the majority of whom were diagnosed using a clinical algorithm. The patients were treated with high dose ivermectin of 0.4mg/kg for one dose along with five days of azithromycin. Only 16 of the 2,688 patients (0.59%) required subsequent hospitalization with one death recorded (Morgenstern et al., 2020).

In another case series of 100 patients in Bangladesh, all treated with a combination of 0.2mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients' symptoms improved within 72 hours (Robin et al., 2020).

A case series from Argentina reported on a combination protocol which used ivermectin, aspirin, dexamethasone and enoxaparin. In the 135 mild illness patients, all survived (Carvallo et al., 2020a). Similarly, a case series from Mexico of 28 consecutively treated patients with ivermectin, all were reported to have recovered with an average time to full recovery of only 3.6 days (Espitia-Hernandez et al., 2020).

## Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin amongst more severely ill hospitalized patients include 6 RCT's, 5 OCTs, and a database analysis study (Ahmed et al., 2020;Budhiraja et al., 2020;Camprubi et al., 2020;Chachar et al., 2020;Elgazzar et al., 2020;Gorial et al., 2020;Hashim et al., 2020;Khan et al., 2020;Niaee et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020;Soto-Becerra et al., 2020;Spoorthi V, 2020).

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al (Elgazzar et al., 2020). 400 patients were randomized amongst 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients only, with Group 1 treated with one dose 0.4mg/kg ivermectin plus standard of care (SOC) and Group 2 received hydroxychloroquine (HCQ) 400mg twice on day 1 then 200mg twice daily for 5 days plus standard of care. There was a statistically significant lower rate of progression in the ivermectin treated group (1% vs. 22%, p<.001) with no deaths and 4 deaths respectively. Groups 3 and 4 all included only severely ill patients, with group 3 again treated with single dose of 0.4mg/kg plus SOC while Group 4 received HCQ plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% vs. 30%, and mortality 2% vs 20% (p<.001).

The one largely outpatient RCT done by Hashim reviewed above also included 22 hospitalized patients in each group. In the ivermectin/doxycycline treated group, there were 11 severely ill patients and 11 critically ill patients while in the standard care group, only severely ill patients (n=22) were included due to their ethical concerns of including critically ill patients in the control group (*45*). This decision led to a marked imbalance in the severity of illness between these hospitalized patient groups. However, despite the mismatched severity of illness between groups and the small number of patients included, beneficial differences in outcomes were seen, but not all reached statistical significance. For instance, there was a large reduction in the rate of progression of illness (9% vs. 31.8%, p=0.15) and, most importantly, there was a large difference in mortality amongst the severely ill groups which reached a borderline statistical significance, (0% vs 27.3%, p=.052). Another important finding was the surprisingly low mortality rate of 18% found among the subset of critically ill patients, all of whom were treated with ivermectin.

A recent RCT from Iran found a dramatic reduction in mortality with ivermectin use (Niaee et al., 2020). Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3% while the average mortality within the standard care and placebo arms was 18.8%, with an OR of 0.18 (95% CI 0.06-0.55, p<.05).

Spoorthi and Sasanak performed a prospective RCT of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline while the 50 controls were given a placebo consisting of Vitamin B6 (Spoorthi V, 2020). Although no deaths were reported in either group, the ivermectin treatment group had a shorter hospital LOS 3.7 days vs 4.7 days, p=.03, and a shorter time to complete resolution of symptoms, 6.7 days vs 7.9 days, p=.01.

The largest OCT (n=280) in hospitalized patients was done by Rajter et al. at Broward Health Hospitals in Florida and was recently published in the major medical journal *Chest* (*43*). They

performed a retrospective OCT with a propensity matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. 173 patients were treated with ivermectin (160 received a single dose, 13 received a 2nd dose at day 7) while 107 were not (Rajter et al., 2020). In both unmatched and propensity matched cohort comparisons, similar, large, and statistically significant lower mortality was found amongst ivermectin treated patients (15.0% vs. 25.2%, p=.03). Further, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, p=.001).

Another large OCT in Bangladesh compared 115 pts treated with ivermectin to a standard care cohort consisting of 133 patients (Khan et al., 2020). Despite a significantly higher proportion of patients in the ivermectin group being male (i.e., with well-described, lower survival rates in COVID), the groups were otherwise well matched, yet the mortality decrease was statistically significant (0.9% vs. 6.8%, p<.05). The largest OCT is a study from Brazil which included almost 1,500 patients (Portmann-Baracco et al., 2020). Although the primary data was not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15mg/kg ivermectin compared to 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001). Similarly, in the patients on mechanical ventilation, mortality was also reduced (1.3% vs. 7.3%). A small study from Baghdad, Iraq compared 16 ivermectin treated patients to 71 controls (Gorial et al., 2020). This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, p<.001) in the ivermectin group. In a study reporting on the first 1000 patients treated in a hospital in India, they found that in the 34 patients treated with ivermectin alone, all recovered and were discharged, while in the over 900 patients treated with other agents, there was an overall mortality of 11.1% (Budhiraja et al., 2020).

One retrospective analysis of a database of hospitalized patients compared responses in patients receiving ivermectin, azithromycin, hydroxychloroquine or combinations of these medicines. In this study, no benefit for ivermectin was found, however the treatment groups in this analysis all included a number of patients who died on day 2, while in the control groups no early deaths occurred, thus the comparison appears limited (Soto-Becerra et al., 2020).

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the two important clinical outcomes: time to clinical recovery and mortality (Figures 2 and 3). The consistent and reproducible signals leading to large overall statistically significant benefits from within both study designs is remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

**Figure 2. Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19**

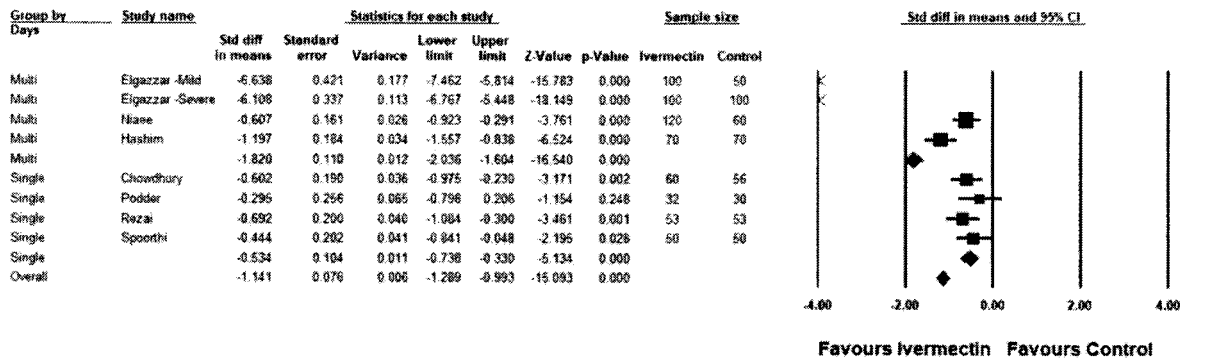



Figure 2 legend — Multi: multiple day dosing regimen. Single: single dose regimen.

Symbols — Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

**Figure 3. Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19**

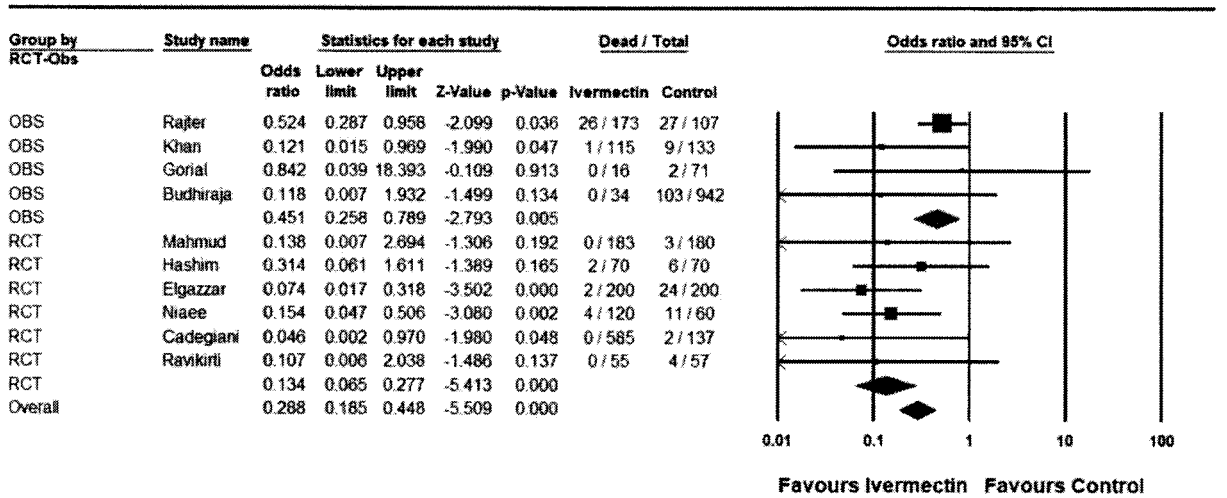



Figure 3 legend — OBS: Observational study, RCT: Randomized Controlled Trial.

Symbols — Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Details of the prophylaxis, early, and late treatment trials of ivermectin in COVID-19 can be found in Table 3 below.

**Table 3. Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19**

| **Prophylaxis Trials** | | | | | |
|---|---|---|---|---|---|
| **AUTHOR, COUNTRY, SOURCE** | **STUDY DESIGN, SIZE** | **STUDY SUBJECTS** | **IVERMECTIN DOSE** | **DOSE FREQUENCY** | **CLINICAL OUTCOMES REPORTED** |
| Shouman W, Egypt<br>*www.clinicaltrials.gov*<br>NCT04422561 | RCT<br>N=340 | Household members of pts with +COVID-19 PCR test | 40–60kg: 15mg<br>60–80kg: 18mg<br>> 80kg: 24mg | Two doses, 72 hours apart | 7.4% vs. 58.4% developed COVID-19 symptoms, p<.001 |
| Elgazzar A, Egypt<br>ResearchSquare<br>doi.org/10.21203/rs.3.rs-100956/v1 | RCT<br>N=200 | Health care and Household contacts of pts with +COVID-19 PCR test | 0.4mg/kg | Two doses, Day 1 and Day 7 | 2% vs. 10% tested positive for COVID-19 p<.05 |
| Chala R. Argentina<br>NCT04701710<br>*Clinicaltrials.gov* | RCT<br>N=234 | Health Care Workers | 12mg | Every 7 days | 3.4% vs. 21.4%, p=.0001. |
| Carvallo H, Argentina<br>*Journal of Biochemical Research and Investigation*<br>doi.org/10.31546/2633-8653.1007 | OCT<br>N=229 | Healthy patients negative for COVID-19 PCR | 0.2mg drops | 1 drop five times a day x 28 days | 0.0% vs. 11.2% contracted COVID-19 p<.001 |
| Alam MT. Bangladesh<br>*European J Med Hlth Sciences*<br>10.24018/ejmed.2020.2.6.599 | OCT<br>N=118 | Health Care Workers | 12mg | Monthly | 6.9% vs. 73.3%, p<.05 |
| Carvallo H. Argentina<br>*Journal of Biochemical Research and Investigation*<br>doi.org/10.31546/2633-8653.1007 | OCT<br>N=1,195 | Health Care Workers | 12 mg | Once weekly for up to ten weeks | 0.0% of the 788 workers taking ivermectin vs. 58% of the 407 controls contracted COVID-19. |
| Behera P, India<br>*medRxiv*<br>doi.org/10.1101/2020.10.29.20222661 | OCT<br>N=186 case control pairs | Health Care Workers | 0.3 mg/kg | Day 1 and Day 4 | 2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53) |
| Bernigaud C. France<br>*Annales de Dermatologie et de Venereologie*<br>doi.org/10.1016/j.annder.2020.09.231 | OCT<br>N=69 case control pairs | Nursing Home Residents | 0.2 mg/kg | Once | 10.1% vs. 22.6% residents contracted COVID-19<br>0.0% vs 4.9% mortality |
| Hellwig M. USA<br>*J Antimicrobial Agents*<br>doi.org/10.1016/j.ijantimicag.2020.106248 | OCT<br>N=52 countries | Countries with and without IVM prophylaxis programs | Unknown | Variable | Significantly lower-case incidence of COVID-19 in African countries with IVM prophylaxis programs p<.001 |
| **Clinical Trials – Outpatients** | | | | | % Ivermectin vs. % Controls |
| **AUTHOR, COUNTRY, SOURCE** | **STUDY DESIGN, SIZE** | **STUDY SUBJECTS** | **IVERMECTIN DOSE** | **DOSE FREQUENCY** | **CLINICAL OUTCOMES REPORTED** |
| Mahmud R, Bangladesh<br>*www.clinicaltrials.gov*<br>NCT0452383 | DB-RCT<br>N=363 | Outpatients and hospitalized | 12mg + doxycycline | Once, within 3 days of PCR+ test | Early improvement 60.7% vs. 44.4%, p<.03, deterioration 8.7% vs 17.8%, p<.02 |
| Chowdhury A, Bangladesh<br>*Research Square*<br>doi.org/10.21203/rs.3.rs-38896/v1 | DB-RCT<br>N=116 | Outpatients | 0.2 mg//kg + doxycycline | Once | Recovery time 5.9 vs 9.3 days (p=.07) |

| | | | | | |
|---|---|---|---|---|---|
| Ravikirti, India<br>*medRxiv*<br>doi.org/10.1101/2021.01.05.21249310 | DB-RCT<br>N=115 | Mild-moderate illness | 12mg | Daily for 2 days | No diff in day 6 PCR+ 0% vs 6.9% mortality, p=.019 |
| Babalola OE, Nigeria<br>medRxiv<br>doi.org/10.1101/2021.01.05.21249131 | DB-RCT<br>N=62 | Mild-moderate illness | 6mg and 12 mg | Every 48h x 2 weeks | Time to viral clearance: 4.6 days high dose vs 6.0 days low dose vs 9.1 days control (p=.006) |
| Podder CS, Bangladesh<br>*IMC J Med Sci 2020;14(2)* | RCT<br>N=62 | Outpatients | 0.2 mg/kg | Once | Recovery time 10.1 vs 11.5 days (NS), average time 5.3 vs 6.3 (NS) |
| Chaccour C. Spain<br>*Research Square*<br>doi.org/10.21203/rs.3.rs-116547/v1 | RCT<br>N=24 | Outpatients | 0.4mg/kg | Once | No diff in PCR+ Day 7, lower viral load days 4 and 7, (p<.05), 76 vs 158 pt. days of anosmia (p<.05), 68 vs 98 pt. days of cough (p<.05) |
| Morgenstern J, Dominican Republic<br>*medRxiv*<br>doi.org/10.1101/2020.10.29.20222505 | Case Series<br>N=3,099 | Outpatients and hospitalized | Outpatients: 0.4mg/kg<br>Hospital Patients: 0.3mg/kg | Outpatients:0.3 mg/kg x 1 dose<br>Inpatients: 0.3mg/kg, Days 1,2,6,7 | Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, 30.6% in 111 ICU patients |
| Carvallo H, Argentina<br>*medRxiv*<br>doi.org/10.1101/2020.09.10.20191619 | Case Series<br>N=167 | Outpatients and hospitalized | 24mg=mild, 36mg=moderate, 48mg=severe | Days 0 and 7 | All 135 with mild illness survived, 1/32 (3.1% of hospitalized patients died |
| Alam A, Bangladesh, *J of Bangladesh College Phys and Surg*, 2020;38:10-15<br>doi.org/10.3329/jbcps.v38i0.47512 | Case series<br>N=100 | Outpatients | 0.2 mg/kg/kg + doxycycline | Once | All improved within 72 hours |
| Espatia-Hernandez G, Mexico<br>*Biomedical Research*<br>www.biomedres.info/biomedi..-proof-of-concept-study-14435.html | Case Series<br>N=28 | Outpatients | 6mg | Days 1,2, 7, 8 | All pts recovered Average recovery time 3.6 days |

| **Clinical Trials – Hospitalized Patients** | | | | | % Ivermectin vs. % Controls |
|---|---|---|---|---|---|
| **AUTHOR, COUNTRY, SOURCE** | **STUDY DESIGN, SIZE** | **STUDY SUBJECTS** | **IVERMECTIN DOSE** | **DOSE FREQUENCY** | **CLINICAL OUTCOMES REPORTED** |
| Elgazzar A, Egypt<br>*ResearchSquare*<br>doi.org/10.21203/rs.3.rs-100956/v1 | OL-RCT<br>N=400 | Hospitalized Patients | 0.4 mg/kg | Once | Moderately Ill: worsened 1% vs 22%, p<.001. Severely ill: worsened 4% vs 30% mortality 2% vs 20% both with p<.001 |
| Niaee S. M.<br>*Research Square*<br>doi.org/10.21203/rs.3.rs-109670/v1 | DB-RCT<br>N=180 | Hospitalized Patients | 0.2, 0.3, 0.4 mg/kg (3 dosing strategies) | Once vs. Days 1,3,5 | Mortality 3.3% vs. 18.3%. OR 0.18, (.06-0.55, p<.05) |
| Hashim H, Iraq<br>*medRxiv*<br>doi.org/10.1101/2020.10.26.20219345 | SB-RCT<br>N=140 | 2/3 outpatients, 1/3 hospital pts | 0.2 mg/kg + doxycycline | Daily for 2–3 days | Recovery time 6.3 vs 13.6 days (p<.001), 0% vs 27.3% mortality in severely ill (p=.052) |

| | | | | | |
|---|---|---|---|---|---|
| Spoorthi S, India<br>*AIAM, 2020; 7(10):177-182* | RCT<br>N=100 | Hospitalized Patients | 0.2mg/kg+ Doxycycline | Once | Shorter Hospital LOS, 3.7 vs. 4.7 days, p=.03, faster resolution of symptoms, 6.7 vs 7.9 days, p=.01 |
| Ahmed S. Dhaka, Bangladesh<br>*International Journal of Infectious Disease*<br>doi.org/10.1016/j.ijid.2020.11.191 | DB-RCT<br>N=72 | Hospitalized Patients | 12mg | Daily for 5 days | Faster viral clearance 9.7 vs 12.7 days, p=.02 |
| Chachar AZK, Pakistan<br>*Int J Sciences*<br>doi.org/10.18483/ijSci.2378 | DB-RCT<br>N=50 | Hospitalized Patients-Mild | 12mg | Two doses Day 1, one dose Day 2 | 64% vs 60% asymptomatic by Day 7 |
| Portman-Baracco A, Brazil<br>*Arch Bronconeumol. 2020*<br>doi.org/10.1016/j.arbres.2020.06.011 | OCT<br>N=1408 | Hospitalized patients | 0.15 mg/kg | Once | Overall mortality 1.4% vs. 8.5%, HR 0.2, 95% CI 0.12-0.37, p<.0001 |
| Soto-Beccerra P, Peru<br>*medRxiv*<br>doi.org/10.1101/2020.10.06.20208066 | OCT<br>N=5683,<br>IVM, N=563 | Hospitalized patients, database analysis | Unknown dose <48hrs after admission | Unknown | No benefits found |
| Rajter JC, Florida<br>*Chest 2020*<br>doi.org/10.1016/j.chest.2020.10.009 | OCT<br>N=280 | Hospitalized patients | 0.2 mg/kg + azithromycin | Day 1 and Day 7 if needed | Overall mortality 15.0% vs. 25.2%, p=.03, Severe illness mortality 38.8% vs. 80.7%, p=.001 |
| Khan X, Bangladesh<br>*Arch Bronconeumol. 2020*<br>doi.org/10.1016/j.arbres.2020.08.007 | OCT<br>N=248 | Hospitalized patients | 12 mg | Once on admission | Mortality 0.9% vs. 6.8%, p<.05, LOS 9 vs. 15 days, p<.001 |
| Gorial FI, Iraq<br>*medRxiv*<br>doi.org/10.1101/2020.07.07.20145979 | OCT<br>N=87 | Hospitalized patients | 0.2 mg/kg + HCQ and azithromycin | Once on admission | LOS 7.6 vs. 13.2 days, p<.001, 0/15 vs. 2/71 died |
| Budiraja S. India<br>*medRxiv*<br>doi.org/10.1101/2020.11.16.20232223 | OCT<br>N=1000<br>IVM=34 | Hospitalized Patients | n/a | n/a | 100% IVM pts recovered<br>11.1% mortality in non-IVM treated pts |

Legend: DB-RCT = double-blind randomized controlled trial, HCQ = hydroxychloroquine, IVM = ivermectin, LOS = Length of stay, NS = non-statistically significant, p>.05, OCT = observational controlled trial, OL = open label, PCR – polymerase chain reaction, RCT = randomized controlled trial, SB-RCT =single blind, randomized controlled trial

## Ivermectin in post-COVID-19 syndrome

Increasing reports of persistent, vexing, and even disabling symptoms after recovery from acute COVID-19 have been reported and which many have termed the condition as "long Covid" and patients as "long haulers", estimated to occur in approximately 10% of cases (Callard and Perego, 2020;Rubin, 2020;Siegelman, 2020). Generally considered as a post-viral syndrome consisting of a chronic and sometimes disabling constellation of symptoms which include, in order, fatigue, shortness of breath, joint pains and chest pain. Many patients describe their most disabling symptom as impaired memory and concentration, often with extreme fatigue, described as "brain fog", and are highly suggestive of the condition myalgic encephalomyelitis/chronic fatigue syndrome, a condition well-reported to begin after viral infections, in particular with Epstein-Barr virus. Although no specific

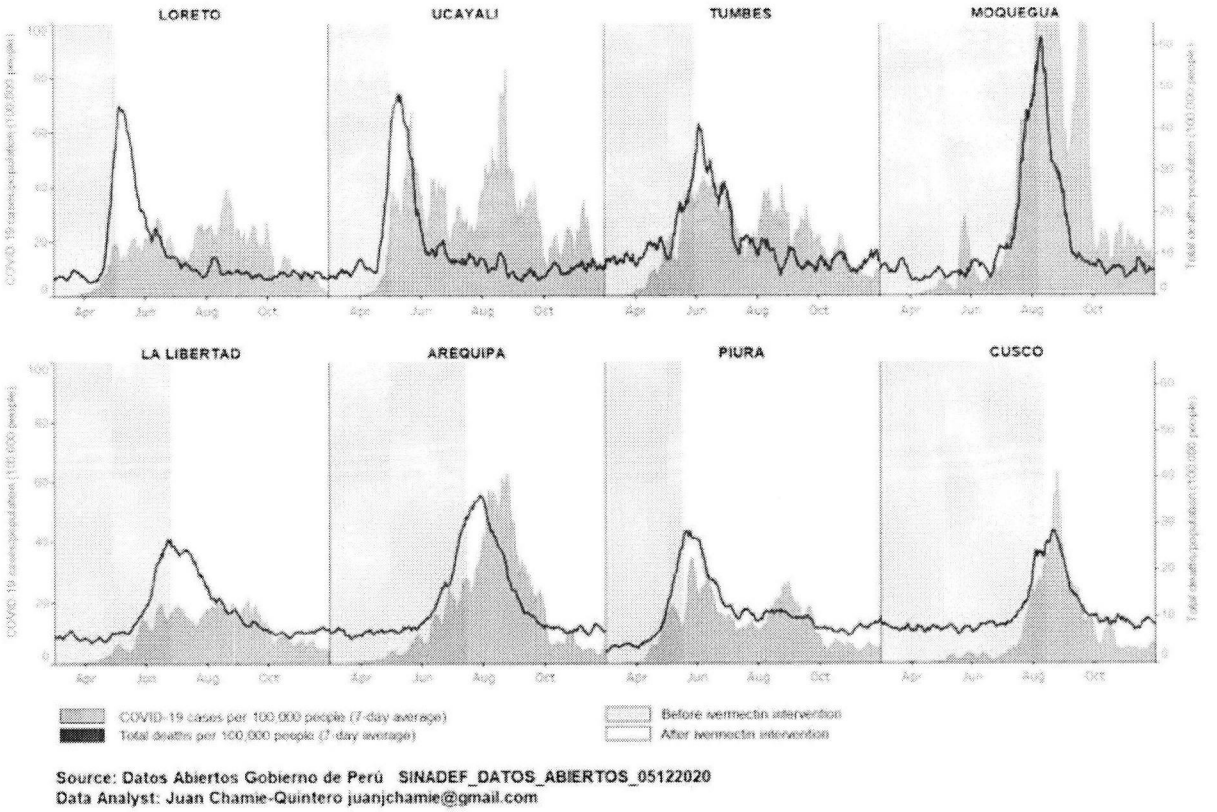
treatments have been identified for long COVID, a recent manuscript by Aguirre-Chang et al from the National University of San Marcos in Peru reported on the experience with ivermectin in such patients (Aguirre-Chang, 2020). They treated 33 patients who were between 4 and 12 weeks from the onset of symptoms with escalating doses of ivermectin; 0.2mg/kg for 2 days if mild, 0.4mg/kg for 2 days if moderate, with doses extended if symptoms persisted. They found that in 87.9% of the patients, resolution of all symptoms was observed after two doses with an additional 7% reporting complete resolution after additional doses. Their experience suggests the need for controlled studies to better test efficacy in this vexing syndrome.

## Epidemiological data showing impacts of widespread ivermectin use on population case counts and case fatality rates

Similar to the individual cities in Brazil that measured large decreases in case counts soon after distributing ivermectin in comparison to neighboring cities without such campaigns, in Peru, the government approved the use of ivermectin by decree on May 8, 2020, solely based on the *in vitro* study by Caly et al. from Australia (Chamie, 2020).[8] Soon after, multiple state health ministries initiated ivermectin distribution campaigns in an effort to decrease what was at that time some of the highest COVID-19 morbidity and mortality rates in the world. Juan Chamie, a data analyst and member of the FLCCC Alliance recently posted a paper based on two critical sets of data that he compiled and compared; first he identified the timing and magnitude of each region's ivermectin interventions via a review of official communications, press releases, and the Peruvian Situation Room database in order to confirm the dates of effective delivery, and second, he extracted data on the total all-cause deaths from the region along with COVID-19 case counts in selected age groups over time from the registry of the National Computer System of Deaths (SINADEF), and from the National Institute of Statistics and Informatics (Chamie, 2020). It should be noted that he restricted his analyses to only those citizens over 60 years old in order to avoid the confounding of rises in the numbers of infected younger patients. With these data, he was then able to compare the timing of major decreases in this age group of both total COVID-19 cases and total deaths per 1000,000 people among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 4 below.

[8] https://trialsitenews.com/trialsite-news-original-documentary-in-peru-about-ivermectin-and-covid-19/

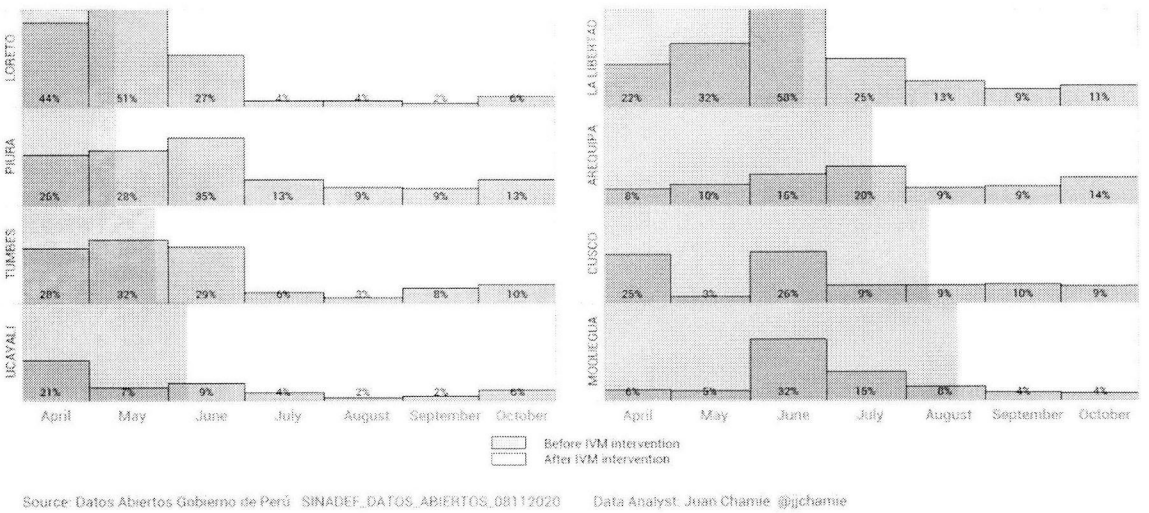
**Figure 4. Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns**




Source: Datos Abiertos Gobierno de Perú SINADEF_DATOS_ABIERTOS_05122020
Data Analyst: Juan Chamie-Quintero juanjchamie@gmail.com

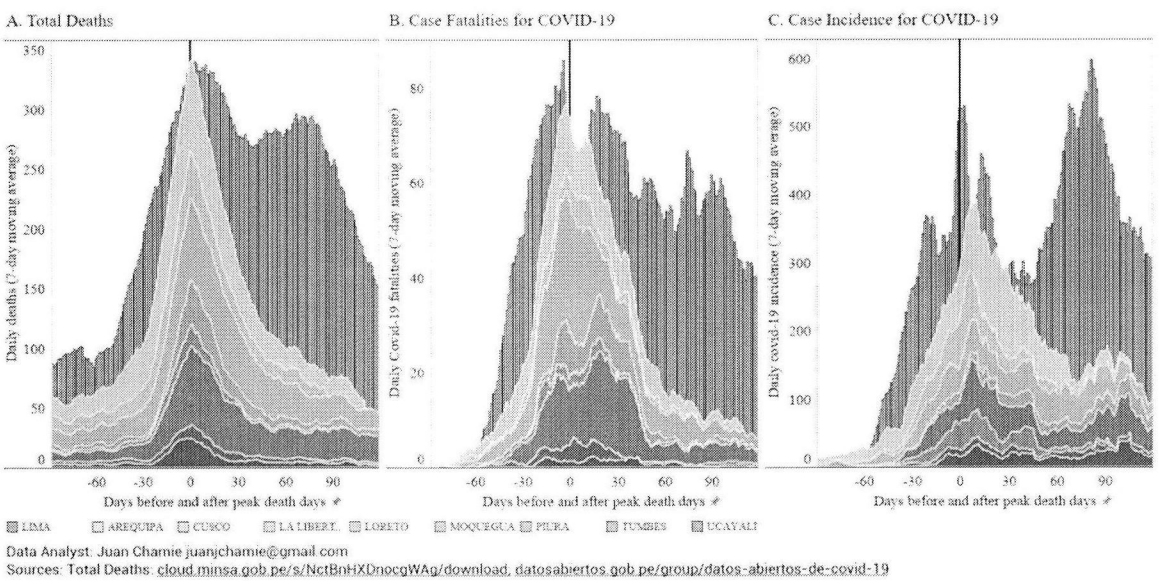
Figure 5 below from the same study presents data on the case fatality rates in patients over 60, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients with COVID-19 after ivermectin became widely distributed in those areas.

**Figure 5. Monthly reported case fatality rates among patients over 60 in eight Peruvian states after deploying mass ivermectin treatment.**




In an even more telling example, Chamie compared the case counts and fatality rates of the 8 states above with the city of Lima, where ivermectin was not distributed nor widely used in treatment during the same time period. Figure 6 below compares the lack of significant or sustained reductions in case counts or fatalities in Lima with the dramatic reductions in both outcomes among the 8 states with widespread ivermectin distribution.

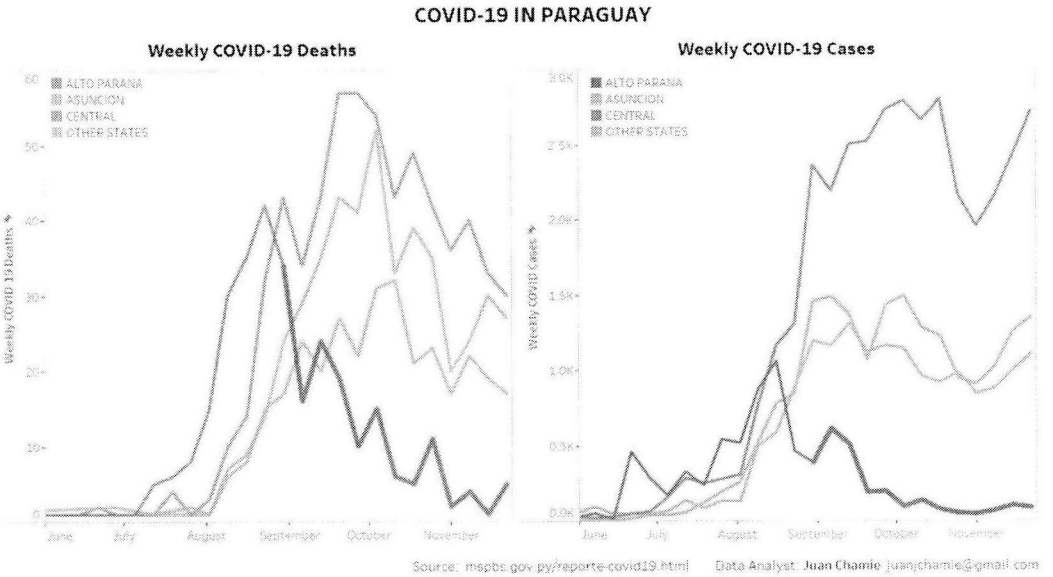
**Figure 6. Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru**




Legend: Daily total deaths, case fatalities and case incidence for COVID-19 in populations of patients age 60 and above for eight states in Peru deploying early mass ivermectin treatments vs. the state of Lima, including the capital city, where ivermectin treatment was applied months later.

Another compelling example can be seen from the data compiled from Paraguay, again by Chamie, who noted that the government of the state of Alto Parana had launched an ivermectin distribution campaign in early September. Although the campaign was officially described as a "de-worming" program, this was interpreted as a guise by the region's governor to avoid reprimand or conflict with the National Ministry of Health that recommended against use of ivermectin to treat COVID-19 in Paraguay.[9] The program began with a distribution of 30,000 boxes of ivermectin and by October 15, the governor declared that there were very few cases left in the state as can be seen in Figure 5 below.[10]

**Figure 7. Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.**




## The clinical evidence base for ivermectin against COVID-19

A summary of the statistically significant results from the above controlled trials are as follows:

**Controlled trials in the prophylaxis of COVID-19 (8 studies)**

- All 8 available controlled trial results show statistically significant reductions in transmission
- 3 RCT's with large statistically significant reductions in transmission rates, N=774 patients (Chala, 2020;Elgazzar et al., 2020;Shouman, 2020)
- 5 OCT's with large statistically significant reductions in transmission rates, N=2052 patients (Alam et al., 2020;Behera et al., 2020;Bernigaud et al., 2020;Carvallo et al., 2020b;Hellwig and Maia, 2020)

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9 https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay
10 https://public.tableau.com/profile/jchamie#!/vizhome/COVID-19PARAGUAY/Paraguay

**Controlled trials in the treatment of COVID-19 (19 studies)**

- 5 RCT's with statistically significant impacts in time to recovery or hospital length of stay (Elgazzar et al., 2020;Hashim et al., 2020;Mahmud, 2020;Niaee et al., 2020;Spoorthi V, 2020)
- 1 RCT with a near statistically significant decrease in time to recovery, p=.07, N=130 (Chowdhury et al., 2020)
- 1 RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N=363 (Mahmud, 2020)
- 2 RCT's with a statistically significant decrease in viral load, days of anosmia and cough, N=85 (Chaccour et al., 2020;Ravikirti et al., 2021)
- 3 RCT's with large, statistically significant reductions in mortality (N=695) (Elgazzar et al., 2020;Niaee et al., 2020;Ravikirti et al., 2021)
- 1 RCT with a near statistically significant reduction in mortality, p=0.052 (N=140) (Hashim et al., 2020)
- 3 OCT's with large, statistically significant reductions in mortality (N=1,688) (Khan et al., 2020;Portmann-Baracco et al., 2020;Rajter et al., 2020)

## Safety of Ivermectin

Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of the parasites and include itching, rash, swollen lymph nodes, joint paints, fever and headache (Kircik et al., 2016). In a study which combined results from trials including over 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa loa (Gardon et al., 1997). Further, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of anti-tuberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors such as tacrolimus or cyclosporine or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist which can affect these levels. A longer list of drug interactions can be found on the *drugs.com* database, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given escalating high doses of ivermectin, toxicity is unlikely although a reduced efficacy due to decreased levels may be a concern (Guzzo et al., 2002).

Concerns of safety in the setting of liver disease are unfounded given that, to our knowledge, only two cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment. (Sparsa et al., 2006;Veit et al., 2006). Further, no dose adjustments are required in patients with liver disease. Some have described ivermectin as potentially neurotoxic, yet one study performed a search of a global pharmaceutical database and found only 28 cases of serious neurological adverse events such as ataxia, altered consciousness, seizure, or tremor (Chandler, 2018). Potential explanations included the effects of concomitantly administered drugs which increase absorption past the blood brain barrier or polymorphisms in the mdr-1 gene. However, the total number of reported cases suggests that such events are rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

## Discussion

Currently, as of December 14, 2020, the accumulating evidence demonstrating the safety and efficacy of ivermectin in COVID-19 strongly supports its immediate use on a risk/benefit calculation in the context of a pandemic. Large-scale epidemiologic analyses validate the findings of *in vitro*, animal, prophylaxis, and clinical studies. Regions of the world with widespread ivermectin use have demonstrated a sizable reduction in case counts, hospitalizations, and fatality rates. This approach should be urgently considered in the presence of an escalating COVID-19 pandemic and as a bridge to vaccination. A recent systematic review of eight RCTs by Australian researchers, published as a pre-print, similarly concluded that ivermectin treatment led to a reduction in mortality, time to clinical recovery, the incidence of disease progression, and duration of hospital admission in patients across all stages of clinical severity (Kalfas et al., 2020). Our current review includes a total of 6,612 patients from 27 controlled studies [16 of them were RCTs, 5 double blinded, one single blinded, (n= 2,503)]; 11 published in peer-reviewed journals including 3,900 patients.

Pre-print publications have exploded during the COVID-19 pandemic. Except for hydroxychloroquine and convalescent plasma that were widely adopted before availability of any clinical data to support, almost all subsequent therapeutics were adopted after pre-print publication and *prior to peer review*. Examples include remdesivir, corticosteroids, and monoclonal antibodies. An even more aggressive example of rapid adoption was the initiation of inoculation programs using novel mRNA vaccines prior to review of either pre-print or peer-reviewed trials data by physicians ordering the inoculations for patients.[11] In all such situations, both academia and governmental health care agencies relaxed their standard to rise to the needs dictated by the pandemic.

In the context of ivermectin's long standing safety record, low cost, and wide availability along with the consistent, reproducible, large magnitude findings on transmission rates, need for hospitalization, mortality, and population-wide control of COVID-19 case and fatality rates in areas with widespread ivermectin distribution, insisting on the remaining studies to pass peer review prior to widespread adoption appears to be imprudent and to deviate from the now established standard approach towards adoption of new therapeutics during the pandemic. In fact, insisting on such a barrier to adoption would actually violate this new standard given that 12 of the 24 controlled trials have already been published in peer reviewed journals.

In regard to concerns over the validity of observational trial findings, it must be recognized that in the case of ivermectin; 1) half of the trials employed a randomized, controlled trial design (12 of the 24 reviewed above), and 2) that observational and randomized trial designs reach equivalent conclusions on average in nearly all diseases studied, as reported in a large Cochrane review of the topic from 2014 (Anglemyer et al., 2014). In particular, OCTs that employ propensity-matching techniques (as in the Rajter study from Florida), find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery (Dahabreh et al., 2012;Lonjon et al., 2014;Kitsios et al., 2015). Similarly, as evidenced in the prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs align in both direction and magnitude of benefit. Such a consistency of benefit amongst numerous trials of varying designs from multiple different countries and centers around the world is both unique in the history of evidence-based medicine and provides strong, additional support to the conclusions reached in this review. All must consider Declaration 37 of the World Medical Association's "Helsinki Declaration on the Ethical Principles for Medical Research Involving Human Subjects," first established in 1964, which states:

[11] https://www.wsj.com/articles/u-k-begins-rollout-of-pfizers-covid-19-vaccine-in-a-first-for-the-west-11607419672

> *In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention* ***if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.*** *This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.*

The continued challenges faced by health care providers in deciding on appropriate therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and definitive evidence-based guidance came from the leading governmental health care agencies. Currently, in the United States, the treatment guidelines for COVID-19 are issued by the National Institutes of Health (NIH). Unfortunately, the NIH's recommendation on the use of ivermectin in COVID-19 patients was last updated on August 27, 2020. At that time, ivermectin received a recommendation of A-III *against* use outside of a clinical trial. An A-III recommendation, per the NIH recommendation scheme, means that it was a strong opinion (A), and based on expert opinion only (III) given that presumably little clinical evidence existed at the time to otherwise inform that recommendation.

Based on the totality of the clinical and epidemiologic evidence presented in this review, and in the context of a worsening pandemic in parts of the globe where ivermectin is not widely used, the authors believe the recommendation must be immediately updated to support and guide the nation's health care providers. One aspect that the NIH expert panel may debate is on the grade of recommendation that should be assigned to ivermectin. Based on the NIH rating scheme, the strongest recommendation possible would be an A-I in support of ivermectin which requires "one or more randomized trials with clinical outcomes and/or laboratory endpoints." Given that data from 16 randomized controlled trials (RCT's) demonstrate consistent and large improvements in "clinical outcomes" such as transmission rates, hospitalization rates, and death rates, it appears that the criteria for an A-I level recommendation has been exceeded. However, although troubling to consider, if experts somehow conclude that the entirety of the available RCT data should be invalidated and dismissed given that either; they were conducted outside of US shores and not by US pharmaceutical companies or academic research centers, that some studies were small or of "low quality", or that such data from foreign countries are not generalizable to American patients, an A-II level recommendation would then have to be considered. In the context of worsening pandemic conditions, when considering a safe, low-cost, widely available early treatment option, even an A-II would result in immediate, widespread adoption by providers in the treatment of COVID-19. The criteria for an A-II requires supportive findings from "one of more well-designed non-randomized, or observational cohort studies". Fortunately, there are many such studies on ivermectin in COVID-19, with one of the largest and best designed being Dr. Rajter's study from Florida, published in the major peer-reviewed medical journal *Chest*, where they used propensity matching, a technique accorded by many to be as valid a design as RCT's. Thus, at a minimum, an A-II recommendation is met, which again would and should lead to immediate and widespread adoption in early outpatient treatment, an area that has been little investigated and is devoid of any highly effective therapies at the time of this writing. Further, it is clear that these data presented far exceed any other NIH strength or quality level such as moderate strength (B), weak strength (C) or grade III quality. To merit the issuance of these lower grades of recommendation would require both a dismissal of the near entirety of the evidence presented in this review in addition to a risk benefit calculation resulting in the belief that the risks of widespread ivermectin use would far exceed any possible benefits in the context of rising case counts, deaths, lockdowns, unemployment, evictions, and bankruptcies.

It is the authors opinion, that based on the totality of these data, the use of ivermectin as a prophylactic and early treatment option should receive an A-I level recommendation by the NIH in support of use by the nation's health care providers. When, or if, such a recommendation is issued, the Front Line COVID-19 Critical Care Alliance has developed a prophylaxis and early treatment protocol for COVID-19 (I-MASK+), centered around ivermectin combined with masking, social distancing, hand hygiene, Vitamin D, Vitamin C, quercetin, melatonin, and zinc, with all components known for either their anti-viral, anti-inflammatory, or preventive actions (Table 4). The I-MASK+ protocol suggests treatment approaches for prophylaxis of high-risk patients, post-exposure prophylaxis of household members with COVID-19, and an early treatment approach for patients ill with COVID-19.

**Table 4. I-MASK+ Prophylaxis & Early Outpatient Treatment Protocol for COVID-19**

| **Prophylaxis Protocol** | |
|---|---|
| MEDICATION | RECOMMENDED DOSING |
| **Ivermectin** | *Prophylaxis for high-risk individuals*:<br>0.2 mg/kg per dose* — one dose today, 2nd dose in 48 hours, then one dose every 2 weeks |
| | *Post COVID-19 exposure prophylaxis****: 0.2 mg/kg per dose, one dose today, 2nd dose in 48 hours |
| **Vitamin D3** | 1,000–3,000 IU/day |
| **Vitamin C** | 1,000 mg twice daily |
| **Quercetin** | 250 mg/day |
| **Melatonin** | 6 mg before bedtime (causes drowsiness) |
| **Zinc** | 50 mg/day of elemental zinc |
| **Early Outpatient Treatment Protocol**** | |
| MEDICATION | RECOMMENDED DOSING |
| **Ivermectin** | 0.2 mg/kg per dose – one dose daily for minimum of 2 days, continue daily until recovered (max 5 days) |
| **Vitamin D3** | 4,000 IU/day |
| **Vitamin C** | 2,000 mg 2–3 times daily and **Quercetin** 250 mg twice a day |
| **Melatonin** | 10 mg before bedtime (causes drowsiness) |
| **Zinc** | 100 mg/day elemental zinc |
| **Aspirin** | 325 mg/day (unless contraindicated) |

* Example for a person of 60 kg body weight: 60 kg × 0.2 mg = 12 mg (1 kg = 2.2 lbs) = 4 tablets (3mg/tablet). To convert pounds, divide weight in pounds by 11: example for a person of 165 pounds: 165 ÷ 11 = 15 mg
** The dosing may be updated as further scientific studies emerge.
*** To use if a household member is COVID-19 positive, or if you have had prolonged exposure to a COVID-19+ patient without wearing a mask
**** For late phase – hospitalized patients – see the FLCCC's "MATH+" protocol on www.flccc.net

In summary, based on the existing and cumulative body of evidence, we recommend the use of ivermectin in both prophylaxis and treatment for COVID-19. In the presence of a global COVID-19 surge, the widespread use of this safe, inexpensive, and effective intervention would lead to a drastic reduction in transmission rates and the morbidity and mortality in mild, moderate, and even severe disease phases. The authors are encouraged and hopeful at the prospect of the many favorable public health and societal impacts that would result once adopted for use.

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## Contribution to the field statement

COVID-19 has caused a worldwide pandemic that has caused over 1.5 million global deaths along with continued rising case counts, lockdowns, unemployment and recessions in multiple countries. In response, the Front Line COVID-19 Critical Care Alliance (FLCCC), formed early in the pandemic, began to review the rapidly emerging basic science, translational, and clinical data to develop effective treatment protocols. The supportive evidence and rationale for their highly effective hospital treatment protocol called "MATH+" was recently published in a major medical journal. More recently, during their ongoing review of the studies on a wide range of both novel and repurposed drugs, they identified that ivermectin, a widely used anti-parasitic medicine with known anti-viral and anti-inflammatory properties is proving a highly potent and multi-phase effective treatment against COVID-19. This manuscript comprehensively reviews the diverse and increasing amount of available evidence from studies on ivermectin which then concludes with the FLCCC consensus recommendation that ivermectin for both the prophylaxis and treatment of COVID-19 should be systematically and globally adopted with the achievable goal of saving countless lives and reversing the rising and persistent transmission rates in many areas of the world.

## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Author Contributions

Study conception and design: Pierre Kory, G. Umberto Meduri, Howard Kornfeld, Keith Berkowitz. Acquisition of data: Scott Mitchell, Eivind Norjevoll, Paul Marik, Fred Wagshul Analysis and interpretation of data: Paul Marik, Pierre Kory Drafting of manuscript: Pierre Kory Critical revision: Umberto Meduri, Joseph Varon.

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## References

Agarwal, A., Mukherjee, A., Kumar, G., Chatterjee, P., Bhatnagar, T., Malhotra, P., and Collaborators, P.T. (2020). Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 371, m3939.

Aguirre-Chang, G. (2020). Post-Acute or prolonged COVID-19: treatment with ivermectin for patietns with persistent, or post-acute symptoms *ResearchGate*.

Ahmed, S., Karim, M.M., Ross, A.G., Hossain, M.S., Clemens, J.D., Sumiya, M.K., Phru, C.S., Rahman, M., Zaman, K., and Somani, J. (2020). A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *International Journal of Infectious Diseases*.

Alam, M., R, M., Pf, G., Md, M.Z., S, S., and Ma, C. (2020). Ivermectin as Pre-exposure Prophylaxis for COVID 19 among Healthcare Providers in a Selected Tertiary Hospital in Dhaka An Observational Study. *European Journal of Medical and Health Sciences*.

Anglemyer, A., Horvath, H.T., and Bero, L. (2014). Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*, MR000034.

Arevalo, A.P., Pagotto, R., Porfido, J., Daghero, H., Segovia, M., Yamasaki, K., Varela, B., Hill, M., Verdes, J.M., and Vega, M.D. (2020). Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. *bioRxiv*.

Atkinson, S.C., Audsley, M.D., Lieu, K.G., Marsh, G.A., Thomas, D.R., Heaton, S.M., Paxman, J.J., Wagstaff, K.M., Buckle, A.M., Moseley, G.W., Jans, D.A., and Borg, N.A. (2018). Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. *Scientific Reports* 8, 358.

Babalola, O.E., Bode, C.O., Ajayi, A.A., Alakaloko, F.M., Akase, I.E., Otrofanowei, E., Salu, O.B., Adeyemo, W.L., Ademuyiwa, A.O., and Omilabu, S.A. Ivermectin shows clinical benefits in mild to moderate Covid19 disease: A randomised controlled double blind dose response study in Lagos. *medRxiv*, 2021.2001. 2005.21249131.

Behera, P., Patro, B.K., Singh, A.K., Chandanshive, P.D., Ravikumar, S., Pradhan, S.K., Pentapati, S.S.K., Batmanabane, G., Padhy, B.M., and Bal, S. (2020). Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study. *medRxiv*.

Bernigaud, C., Guillemot, D., Ahmed-Belkacem, A., Grimaldi-Bensouda, L., Lespine, A., Berry, F., Softic, L., Chenost, C., Do-Pham, G., and Giraudeau, B. (Year). "Bénéfice de l'ivermectine: de la gale à la COVID-19, un exemple de sérendipité", in: *Annales de Dermatologie et de Vénéréologie*: Elsevier), A194.

Bray, M., Rayner, C., Noël, F., Jans, D., and Wagstaff, K. (2020). Ivermectin and COVID-19: a report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Research*.

Budhiraja, S., Soni, A., Jha, V., Indrayan, A., Dewan, A., Singh, O., Singh, Y., Chugh, I., Arora, V., and Pandey, R. (2020). Clinical Profile of First 1000 COVID-19 Cases Admitted at Tertiary Care Hospitals and the Correlates of their Mortality: An Indian Experience. *medRxiv*.

Cadegiani, F.A., Goren, A., Wambier, C.G., and Mccoy, J. (2020). Early COVID-19 Therapy with Azithromycin Plus Nitazoxanide, Ivermectin or Hydroxychloroquine in Outpatient Settings Significantly Reduced Symptoms Compared to Known Outcomes in Untreated Patients. *medRxiv*.

Callard, F., and Perego, E. (2020). How and why patients made Long Covid. *Social Science & Medicine*, 113426.

Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., and Wagstaff, K.M. (2020a). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 178, 104787.

Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., and Wagstaff, K.M. (2020b). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research* 178, 104787.

Carvallo, H.E., Hirsch, R.R., and Farinella, M.E. (2020a). Safety and Efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. *medRxiv*.

Carvallo, H.E., Roberto, H., Psaltis, A., and Veronica, C. (2020b). Study of the Efficacy and Safety of Topical Ivermectin+ Iota-Carrageenan in the Prophylaxis against COVID-19 in Health Personnel.

Chaccour, C., Casellas, A., Blanco-Di Matteo, A., Pineda, I., Fernandez-Montero, A., Castillo, P.R., Richardson, M.-A., Mateos, M.R., Jordan-Iborra, C., and Brew, J. (2020). The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.

Chachar, A.Z.K., Khan, K.A., Asif, M., Tanveer, K., Khaqan, A., and Basri, R. (2020). Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. *International Journal of Sciences* 9, 31-35.

Chala (2020). Prophylaxis Covid-19 in Healthcare Agents by Intensive Treatment With Ivermectin and Iota-carrageenan (Ivercar-Tuc). *ClinicalTrials.gov* NCT04701710.

Chamie, J. (2020). *Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate.*

Chandler, R.E. (2018). Serious neurological adverse events after ivermectin—do they occur beyond the indication of onchocerciasis? *The American journal of tropical medicine and hygiene* 98, 382-388.

Chowdhury, A.T.M.M., Shahbaz, M., Karim, M.R., Islam, J., Guo, D., and He, S. (2020). A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.

Ci, X., Li, H., Yu, Q., Zhang, X., Yu, L., Chen, N., Song, Y., and Deng, X. (2009). Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol* 23, 449-455.

Consortium, W.S.T. (2020). Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. medRxiv. *Preprint posted online* 15.

Crump, A., and Omura, S. (2011). Ivermectin,'wonder drug'from Japan: the human use perspective. *Proceedings of the Japan Academy, Series B* 87, 13-28.

Dahabreh, I.J., Sheldrick, R.C., Paulus, J.K., Chung, M., Varvarigou, V., Jafri, H., Rassen, J.A., Trikalinos, T.A., and Kitsios, G.D. (2012). Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. *European Heart Journal* 33, 1893-1901.

Dasgupta J, S.U., Bakshi a, Dasgupta a, Manna K, Saha, C De, Rk, Mukhopadhyay S, Bhattacharyya Np (2020). Nsp7 and Spike Glycoprotein of SARS-CoV-2 Are Envisaged as Potential Targets of Vitamin D and Ivermectin. *Preprints*.

Dayer, M.R. (2020). Coronavirus (2019-nCoV) Deactivation via Spike Glycoprotein Shielding by Old Drugs, Bioinformatic Study.

De Melo, G.D., Lazarini, F., Larrous, F., Feige, L., Kergoat, L., Marchio, A., Pineau, P., Lecuit, M., Lledo, P.-M., Changeux, J.-P., and Bourhy, H. (2020). Anti-COVID-19 efficacy of ivermectin in the golden hamster. *bioRxiv*, 2020.2011.2021.392639.

Elgazzar, A., Hany, B., Youssef, S.A., Hafez, M., and Moussa, H. (2020). Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic.

Entrenas Castillo, M., Entrenas Costa, L.M., Vaquero Barrios, J.M., Alcala Diaz, J.F., Lopez Miranda, J., Bouillon, R., and Quesada Gomez, J.M. (2020). "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* 203, 105751.

Espitia-Hernandez, G., Munguia, L., Diaz-Chiguer, D., Lopez-Elizalde, R., and Jimenez-Ponce, F. (2020). Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: a proof of concept study.

Gardon, J., Gardon-Wendel, N., Demanga, N., Kamgno, J., Chippaux, J.-P., and Boussinesq, M. (1997). Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *The Lancet* 350, 18-22.

Gorial, F.I., Mashhadani, S., Sayaly, H.M., Dakhil, B.D., Almashhadani, M.M., Aljabory, A.M., Abbas, Hassan M, Ghanim, M., and Rasheed, J.I. (2020). Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial). *medRxiv*.

Götz, V., Magar, L., Dornfeld, D., Giese, S., Pohlmann, A., Höper, D., Kong, B.-W., Jans, D.A., Beer, M., Haller, O., and Schwemmle, M. (2016). Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific Reports* 6, 23138.

Guzzo, C., Furtek, C., Porras, A., Chen, C., Tipping, R., Clineschmidt, C., Sciberras, D., Hsieh, J., and Lasseter, K. (2002). Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects. *Journal of clinical pharmacology* 42, 1122-1133.

Hashim, H.A., Maulood, M.F., Rasheed, A.M., Fatak, D.F., Kabah, K.K., and Abdulamir, A.S. (2020). Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*.

Hellwig, M.D., and Maia, A. (2020). A COVID-19 Prophylaxis? Lower incidence associated with prophylactic administration of Ivermectin. *Int J Antimicrob Agents*, 106248.

Hermine, O., Mariette, X., Tharaux, P.L., Resche-Rigon, M., Porcher, R., Ravaud, P., and Group, C.-C. (2020). Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*.

Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., and Elmahi, E. (2020). Dexamethasone in hospitalized patients with Covid-19-preliminary report. *The New England journal of medicine*.

Hussien, M.A., and Abdelaziz, A.E. (2020). Molecular docking suggests repurposing of brincidofovir as a potential drug targeting SARS-CoV-2 ACE2 receptor and main protease. *Network Modeling Analysis in Health Informatics and Bioinformatics* 9, 1-18.

Jehi, L., Ji, X., Milinovich, A., Erzurum, S., Rubin, B.P., Gordon, S., Young, J.B., and Kattan, M.W. (2020). Individualizing Risk Prediction for Positive Coronavirus Disease 2019 Testing: Results From 11,672 Patients. *Chest* 158, 1364-1375.

Kalfas, S., Visvanathan, K., Chan, K., and Drago, J. (2020). THE THERAPEUTIC POTENTIAL OF IVERMECTIN FOR COVID-19: A REVIEW OF MECHANISMS AND EVIDENCE. *medRxiv*.

Khan, M.S.I., Khan, M.S.I., Debnath, C.R., Nath, P.N., Mahtab, M.A., Nabeka, H., Matsuda, S., and Akbar, S.M.F. (2020). Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19. *Archivos de Bronconeumología*.

King, C.R., Tessier, T.M., Dodge, M.J., Weinberg, J.B., and Mymryk, J.S. (2020). Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. *Journal of Virology* 94.

Kircik, L.H., Del Rosso, J.Q., Layton, A.M., and Schauber, J. (2016). Over 25 Years of Clinical Experience With Ivermectin: An Overview of Safety for an Increasing Number of Indications. Journal of drugs in dermatology : JDD 15, 325-332.

Kitsios, G.D., Dahabreh, I.J., Callahan, S., Paulus, J.K., Campagna, A.C., and Dargin, J.M. (2015). Can We Trust Observational Studies Using Propensity Scores in the Critical Care Literature? A Systematic Comparison With Randomized Clinical Trials. *Crit Care Med* 43, 1870-1879.

Kory, P., Meduri, G.U., Iglesias, J., Varon, J., and Marik, P.E. (2020). Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. *Journal of Intensive Care Medicine*.

Lehrer, S., and Rheinstein, P.H. (2020). Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. *In Vivo* 34, 3023-3026.

Li, Y., Chen, M., Cao, H., Zhu, Y., Zheng, J., and Zhou, H. (2013). Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. *Microbes Infect* 15, 88-95.

Lonjon, G., Boutron, I., Trinquart, L., Ahmad, N., Aim, F., Nizard, R., and Ravaud, P. (2014). Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. *Ann Surg* 259, 18-25.

Lv, C., Liu, W., Wang, B., Dang, R., Qiu, L., Ren, J., Yan, C., Yang, Z., and Wang, X. (2018). Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antiviral Research* 159, 55-62.

Mahmud, R. (2020). A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid-19 Infection.

Marik, P.E., Kory, P., Varon, J., Iglesias, J., and Meduri, G.U. (2020). MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. *Expert Review of Anti-infective Therapy*, 1-7.

Mastrangelo, E., Pezzullo, M., De Burghgraeve, T., Kaptein, S., Pastorino, B., Dallmeier, K., De Lamballerie, X., Neyts, J., Hanson, A.M., Frick, D.N., Bolognesi, M., and Milani, M. (2012). Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *Journal of Antimicrobial Chemotherapy* 67, 1884-1894.

Maurya, D.K. (2020). A combination of ivermectin and doxycycline possibly blocks the viral entry and modulate the innate immune response in COVID-19 patients.

Morgenstern, J., Redondo, J.N., De Leon, A., Canela, J.M., Torres, N., Tavares, J., Minaya, M., Lopez, O., Placido, A.M., and Castillo, A. (2020). The use of compassionate Ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from may 1 to august 10, 2020. *medRxiv*.

Nadkarni, G.N., Lala, A., Bagiella, E., Chang, H.L., Moreno, P.R., Pujadas, E., Arvind, V., Bose, S., Charney, A.W., Chen, M.D., Cordon-Cardo, C., Dunn, A.S., Farkouh, M.E., Glicksberg, B.S., Kia, A., Kohli-Seth, R., Levin, M.A., Timsina, P., Zhao, S., Fayad, Z.A., and Fuster, V. (2020). Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. *J Am Coll Cardiol* 76, 1815-1826.

Nallusamy, S., Mannu, J., Ravikumar, C., Angamuthu, K., Nathan, B., Nachimuthu, K., Ramasamy, G., Muthurajan, R., Subbarayalu, M., and Neelakandan, K. (2020). Shortlisting Phytochemicals Exhibiting Inhibitory Activity against Major Proteins of SARS-CoV-2 through Virtual Screening.

Niaee, M.S., Gheibi, N., Namdar, P., Allami, A., Zolghadr, L., Javadi, A., Karampour, A., Varnaseri, M., Bizhani, B., and Cheraghi, F. (2020). Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial.

Perera, R.A., Tso, E., Tsang, O.T., Tsang, D.N., Fung, K., Leung, Y.W., Chin, A.W., Chu, D.K., Cheung, S.M., and Poon, L.L. (2020). SARS-CoV-2 virus culture from the upper respiratory tract: Correlation with viral load, subgenomic viral RNA and duration of illness. *MedRXiv*.

Podder, C.S., Chowdhury, N., Sina, M.I., and Haque, W. (2020). Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. *IMC J. Med. Sci* 14.

Polak, S.B., Van Gool, I.C., Cohen, D., Von Der Thusen, J.H., and Van Paassen, J. (2020). A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol* 33, 2128-2138.

Portmann-Baracco, A., Bryce-Alberti, M., and Accinelli, R.A. (2020). Antiviral and Anti-Inflammatory Properties of Ivermectin and Its Potential Use in Covid-19. *Arch Bronconeumol*.

Rajter, J.C., Sherman, M.S., Fatteh, N., Vogel, F., Sacks, J., and Rajter, J.J. (2020). Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study). *Chest*.

Ravikirti, Roy, R., Pattadar, C., Raj, R., Agarwal, N., Biswas, B., Majhi, P.K., Rai, D.K., Shyama, Kumar, A., and Sarfaraz, A. (2021). Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial. *medRxiv*, 2021.2001.2005.21249310.

Robin, R.C., Alam, R.F., Saber, S., Bhiuyan, E., Murshed, R., and Alam, M.T. (2020). A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *Journal of Bangladesh College of Physicians and Surgeons*, 10-15.

Rodriguez-Nava, G., Trelles-Garcia, D.P., Yanez-Bello, M.A., Chung, C.W., Trelles-Garcia, V.P., and Friedman, H.J. (2020). Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 24, 429.

Rubin, R. (2020). As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts. *JAMA* 324, 1381-1383.

Salvarani, C., Dolci, G., Massari, M., Merlo, D.F., Cavuto, S., Savoldi, L., Bruzzi, P., Boni, F., Braglia, L., Turra, C., Ballerini, P.F., Sciascia, R., Zammarchi, L., Para, O., Scotton, P.G., Inojosa, W.O., Ravagnani, V., Salerno, N.D., Sainaghi, P.P., Brignone, A., Codeluppi, M., Teopompi, E., Milesi, M., Bertomoro, P., Claudio, N., Salio, M., Falcone, M., Cenderello, G., Donghi, L., Del Bono, V., Colombelli, P.L., Angheben, A., Passaro, A., Secondo, G., Pascale, R., Piazza, I., Facciolongo, N., Costantini, M., and Group, R.-T.-C.-S. (2020). Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*.

Scheim, D. (2020). "From Cold to Killer: How SARS-CoV-2 Evolved without Hemagglutinin Esterase to Agglutinate, Then Clot Blood Cells in Pulmonary and Systemic Microvasculature". SSRN).

Schmith, V.D., Zhou, J., and Lohmer, L.R. (2020). The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clinical Pharmacology & Therapeutics*.

Sen Gupta, P.S., Biswal, S., Panda, S.K., Ray, A.K., and Rana, M.K. (2020). Binding mechanism and structural insights into the identified protein target of COVID-19 and importin-alpha with in-vitro effective drug ivermectin. *J Biomol Struct Dyn*, 1-10.

Shouman, W. (2020). Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contact for Patient with COVID-19. *Clincal Trials.gov*.

Siegelman, J.N. (2020). Reflections of a COVID-19 Long Hauler. *JAMA*.

Soto-Becerra, P., Culquichicón, C., Hurtado-Roca, Y., and Araujo-Castillo, R.V. (2020). Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *Azithromycin, and Ivermectin Among Hospitalized COVID-19 Patients: Results of a Target Trial Emulation Using Observational Data from a Nationwide Healthcare System in Peru*.

Sparsa, A., Bonnetblanc, J., Peyrot, I., Loustaud-Ratti, V., Vidal, E., and Bedane, C. (Year). "Systemic adverse reactions with ivermectin treatment of scabies", in: *Annales de Dermatologie et de Venereologie*), 784-787.

Spoorthi V, S.S. (2020). Utility of Ivermectin and Doxycycline combination for the treatment of SARS-CoV2. *International Archives of Integrated Medicine* 7, 177-182.

Suravajhala, R., Parashar, A., Malik, B., Nagaraj, A.V., Padmanaban, G., Kishor, P.K., Polavarapu, R., and Suravajhala, P. (2020). Comparative Docking Studies on Curcumin with COVID-19 Proteins.

Swargiary, A. (2020). Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from in silico studies.

Tambo, E., Khater, E.I., Chen, J.H., Bergquist, R., and Zhou, X.N. Nobel prize for the artemisinin and ivermectin discoveries: a great boost towards elimination of the global infectious diseases of poverty.

Tay, M.Y.F., Fraser, J.E., Chan, W.K.K., Moreland, N.J., Rathore, A.P., Wang, C., Vasudevan, S.G., and Jans, D.A. (2013). Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Research* 99, 301-306.

Varghese, F.S., Kaukinen, P., Gläsker, S., Bespalov, M., Hanski, L., Wennerberg, K., Kümmerer, B.M., and Ahola, T. (2016). Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Research* 126, 117-124.

Veit, O., Beck, B., Steuerwald, M., and Hatz, C. (2006). First case of ivermectin-induced severe hepatitis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100, 795-797.

Wagstaff, Kylie m., Sivakumaran, H., Heaton, Steven m., Harrich, D., and Jans, David a. (2012). Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochemical Journal* 443, 851-856.

Yang, S.N.Y., Atkinson, S.C., Wang, C., Lee, A., Bogoyevitch, M.A., Borg, N.A., and Jans, D.A. (2020). The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Research* 177, 104760.

Young, B.E., Ong, S.W., Ng, L.F., Anderson, D.E., Chia, W.N., Chia, P.Y., Ang, L.W., Mak, T.-M., Kalimuddin, S., and Chai, L.Y.A. (2020). Viral dynamics and immune correlates of COVID-19 disease severity. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*.

Zhang, J., Rao, X., Li, Y., Zhu, Y., Liu, F., Guo, G., Luo, G., Meng, Z., De Backer, D., and Xiang, H. (2020a). High-dose vitamin C infusion for the treatment of critically ill COVID-19.

Zhang, X., Song, Y., Ci, X., An, N., Ju, Y., Li, H., Wang, X., Han, C., Cui, J., and Deng, X. (2008). Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res* 57, 524-529.

Zhang, X., Song, Y., Xiong, H., Ci, X., Li, H., Yu, L., Zhang, L., and Deng, X. (2009). Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. *Int Immunopharmacol* 9, 354-359.

Zhang, X.-J., Qin, J.-J., Cheng, X., Shen, L., Zhao, Y.-C., Yuan, Y., Lei, F., Chen, M.-M., Yang, H., and Bai, L. (2020b). In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell metabolism* 32, 176-187. e174.

**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF TEXAS**
**GALVESTON DIVISION**

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|---|---|---|
| **ROBERT L. APTER, ET AL** | § | **3:22-CV-00184** |
| | § | |
| **V.** | § | **10:32 A.M. TO 11:39 A.M.** |
| | § | |
| **DEPARTMENT OF HEALTH AND** | § | |
| **HUMAN SERVICES, ET AL** | § | **NOVEMBER 1, 2022** |

**HEARING ON MOTION TO DISMISS**
**BEFORE THE HONORABLE JEFFREY V. BROWN**
**Volume 1 of 1 Volume**

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**VOLUME 1 OF 1 VOLUME**
**(Hearing on Motion to Dismiss)**

**November 1, 2022**

**PROCEEDINGS**

**(Call to order of the Court.)**

THE COURT: All right. One case on the Court's docket this morning. It's in Cause Number 3:22-CV-184, Robert L. Apter v. United States Department of Health and Human Services and others -- Robert Apter and others v. Department of Health and Human Services and others.

Will the attorneys make their appearances, please. Plaintiff first.

10:32:42 MR. KELSON: Jared Kelson for plaintiffs, Your Honor.

THE COURT: Good morning.

MR. McCOTTER: Trent McCotter for plaintiffs, Your Honor.

10:32:49 THE COURT: Good morning. Welcome.

MR. BELFER: Good morning, Your Honor. Isaac Belfer for the government.

THE COURT: Great. Good to have you.

MR. McDONALD: Good morning. Oliver McDonald for

10:32:57 the government.

THE COURT: Great. And I understand we have some folks on the phone who are listening in, and I think George has already asked for you to mute your phones a couple of times and there are people who have not muted

10:33:09 their phones and we're going to cut the thing off if --

we're getting a lot of feedback here in the courtroom. Please mute your phones if you want to listen in.

All right. I have read the briefing in the case. I appreciate y'all coming down this morning. Sorry the 10:33:30 weather is not ideal. This is our first time back in our courtroom since -- in a few months. So it's nice to be back in our regular courtroom.

I have a series of questions I want to ask you all; but I would like to get kind of a general argument from 10:33:50 both sides first, recognizing that I am familiar with the case and the briefing. If there is anything that y'all want to add to the briefing you have already provided to the Court, this is your opportunity to do it; and then, we'll discuss some of the questions that I have for both 10:34:07 sides.

So it's the government's motion, if you would like to get us started.

MR. BELFER: Can I come up here?

THE COURT: You can argue from there or from 10:34:17 right here in front of the bench, whichever you prefer, as long as you are speaking into a microphone.

MR. BELFER: I'll try up there.

THE COURT: All right. Come on up. I'm sorry. Hold on a second.

10:34:37 George, can you just mute them so we don't get --

CASE MANAGER: Yes. I can do that.

THE COURT: Just so we don't -- or just turn the volume down so we don't hear them.

CASE MANAGER: Yeah. I lowered the volume.

10:34:47 THE COURT: I'm sorry. Go ahead.

MR. BELFER: After receiving multiple reports of patients requiring medical attention, including hospitalization, after self-medicating with ivermectin products intended for livestock, FDA made several public
10:35:02 statements on social media and on its website written in informal conversational language warning the public about certain risks of using ivermectin products to treat COVID-19.

These statements included non-binding recommendations
10:35:15 to consumers who could purchase animal-use ivermectin over the counter not to take ivermectin to treat COVID-19, but the statements did not say that doctors could not prescribe ivermectin to treat COVID-19 or that consumers could not take ivermectin for that purpose.

10:35:31 Instead, they said that, "If your healthcare provider writes you an ivermectin prescription, fill it through a legitimate source such as a pharmacy and take it exactly as prescribed."

Because the statements simply provided nonbinding
10:35:44 recommendations to consumers, they are not rules and,

thus, are not agency action as required for waiver of sovereign immunity. They did not bind the public or FDA, did not interpret any substantive rules, and did not set agency policy.

10:35:57 The statements are also not final agency action. They do not mark the consummation of FDA's decision-making process because they do not state FDA's final position on the use of ivermectin to treat COVID-19 but instead present FDA's tentative recommendations based on currently

10:36:14 available data.

They also do not have legal consequences for anyone but simply provide nonbinding recommendations to consumers.

Plaintiffs have also failed to meet their burden to

10:36:24 show standing. The amended complaint alleges five injuries to plaintiffs and three injuries to their patients.

Regarding injuries to the plaintiffs, the amended complaint alleges: First, that there was interference

10:36:36 with their ability to practice medicine; second, that they were referred to state medical boards; third, that they were forced to resign from their jobs; fourth, they were subjected to public ridicule; and fifth, that patients delayed seeking treatment from plaintiffs.

10:36:51 And then with regard to injuries to their patients,

the amended complaint alleges three injuries: First, that pharmacists refused to fill patients' ivermectin prescriptions; second, that insurance companies refused to pay for those prescriptions; and third, that patients
10:37:06 delayed seeking treatment from plaintiffs or delayed taking ivermectin.

As discussed in our briefs, many of those injuries are not an adequate injury in fact. Plaintiffs have also not shown that any of their claimed injuries are fairly
10:37:22 traceable to defendants' statements because their injuries were caused by independent third-party conduct that was not a predictable response to those statements.

For example, it was not predictable that plaintiffs' employers would punish them for prescribing ivermectin to
10:37:33 treat COVID-19 when the statements themselves acknowledged doctors' discretion to do just that.

Furthermore, plaintiffs have not shown that the requested relief would likely redress their claimed injuries. Many organizations, in addition to FDA, have
10:37:46 recommended against taking ivermectin to treat COVID-19; and plaintiffs have not shown that removing just the cited FDA statements would likely cause the third parties that allegedly injured them to reverse their past decisions.

Finally, plaintiffs have failed to state a claim
10:38:01 because they did not present their issues in the amended

complaint to FDA. They thereby deprived the agency of the opportunity to consider their issues in the first instance and prevented the agency from creating an administrative record that addressed those issues.

10:38:15 So I would be happy to talk about any further issues but I think that's a good summary and I'll answer any questions the Court has.

THE COURT: Okay. All right. First of all, just a couple of things on -- well, the -- you mentioned the

10:38:32 informational conversational tone of the social media statements. To me, that seems like part of the problem in that those statements don't include the qualifier statements that the article has that was referred to; and I think those -- I think as far as reputational harm goes,

10:39:04 it's the social media statements are what bother me the most. And I don't even know where I'm going with the question here.

But can you understand my concern with that? I mean, it's like was the purpose of those statements really to

10:39:20 advise patients not to self-medicate with ivermectin? The social media -- the social media comments in particular.

MR. BELFER: Right. So I don't think the record shows the FDA's motivation for those statements in particular. We do know that the article was motivated by

10:39:43 people self-medicating with animal-use ivermectin and

requiring hospitalization. So we do know that that was part of FDA's motivation.

And so I think with regards to the social media posts, which are two tweets and an Instagram post, those statements were clearly aimed at consumers. As we discussed, they used this conversational language, you know, "Hold your horses. You are not a horse. You are not a cow." Information like that.

So clearly this was aimed at consumers. It was not aimed at medical professionals or hospitals; and it was not predictable that hospitals or insurance companies or pharmacies would act based on these statements, let alone it was not predictable that they would respond to these statements by firing plaintiffs.

And indeed, the tweets linked to the article. And so if you look at the tweets, they include the link to the article. And so it was predictable that if you include the link to the article, people, you know, will click on the link and will see the full article, which includes that disclaimer that if your doctor writes you a prescription, you should fill it exactly as prescribed.

So in terms of the standing analysis when you are asking was it predictable that third parties would take the actions that they took based on the cited statements, you know -- and it's plaintiffs' burden to show that; and

plaintiffs have not met that burden because, first of all, the tweets included links to the article and those statements were clearly -- they were aimed at consumers, and they were not the sort of statements FDA would make to
10:41:20 influence, for instance, hospitals or, you know, pharmacies or insurance companies. Right.

So I think for those reasons plaintiffs have not shown -- certainly have not shown traceability regarding those statements.

10:41:33 And also, they have not shown redressability regarding those statements because, as we discussed in our brief, many organizations, in addition to FDA, have made public statements advising against the use of ivermectin to treat COVID-19.

10:41:45 So, you know, even if FDA's tweets and other statements were taken down, there would still be many statements by other organizations, like the World Health Organization and Merck, which makes one of these drugs, and CDC and NIH, all advising against the use of
10:41:58 ivermectin to treat COVID-19.

And so it would not -- plaintiffs have not shown that they would -- that the third parties would likely undo their actions, reverse their past decisions, given that all those statements by other parties are still out there.

10:42:14 THE COURT: Okay. It's not just common sense

that it would be predictable that state boards would react to statements by the FDA in ways that they did?

MR. BELFER: So state board -- no state board has made any discipline against plaintiffs. There is an allegation that Apter was referred to a state medical board, but that's all we have. There is no indication there has been any action whatsoever by that state medical board and it's speculative, you know, if or when that medical board will take any action. And as we discussed in our brief, merely being referred to a state medical board is not adequate injury in fact. So, you know, again, it's purely speculative, you know, if or when that state medical board will act and then what weight it might give to that -- to that statement.

Importantly, it wasn't the state medical board that cited the FDA statements. It was some unidentified third party that included the statement in the referral to the state medical board.

So, you know, I think to close the loop on that, essentially, you have this simple allegation after it was referred for discipline but, you know, we don't know if or when the state medical board will act on the referral.

And, you know, if and when it does ultimately act, we don't know to what extent it will give the FDA statements any -- any weight and the fact that there are all these

statements by other organizations, like the World Health Organization and CDC and NIH, indicating that there is not a showing that simply taking away the FDA statements would make any difference or would cause them to act any
10:43:42 differently.

THE COURT: Okay. And you are getting into redressability here. The plaintiffs say that I should presume redressability at this stage. Are you aware of any cases in which a motion to dismiss was granted on a
10:43:54 failure to show redressability?

MR. BELFER: Again, off the top of my head, I can't. I can't think of one right now. But we do cite a case in our brief. I believe it's the *Renal Physicians* case from the, I think, DC Circuit, which says that you
10:44:10 can't presume redressability simply based on traceability.

So even if it's true that the government's statements caused a third party to make a certain action, you don't -- you can't presume redressability because it's possible that some independent factor is holding those
10:44:26 third parties' actions in place.

So here, even if, you know, presuming that the FDA cited statements influenced some third parties to take adverse actions against the plaintiffs, you can't presume redressability because there are these independent third
10:44:40 -- other organization statements, again, like the WHO and

NIH and CDC, that are out there; and those statements are still in place recommending against the use of COVID-19 -- against the use of ivermectin to treat COVID-19.

Additionally, you know, if the Court were to rule, for 10:44:55 instance, that the FDA does not have authority to make the cited statements, that wouldn't affect the scientific -- the third-party's scientific understanding of the risks and benefits of treating COVID-19. It would be a legal ruling on, essentially, procedural authority grounds. It 10:45:09 wouldn't go to the scientific merits. And so it wouldn't give the third parties any reason to change their understanding of whether you should use ivermectin to treat COVID-19.

And so for all those reasons, even if the Court were 10:45:21 to order that the cited statements be taken down, plaintiffs haven't shown that that would make any difference because there are all these other statements out there; and their requested relief itself wouldn't give the third parties any reason to change their understanding 10:45:34 of the risks and benefits of taking ivermectin to treat COVID-19. So, you know, the plaintiffs have failed to show redressability as well as traceability.

And, of course, that's only part of the jurisdictional analysis. There is also sovereign immunity. And we think 10:45:48 that's actually an even clearer case why there is no

jurisdiction here.

You know, again, these were -- these were tweets, social media posts in conversational language. They were nonbinding recommendations. They did not make -- they
10:46:02 were not binding on anyone. They were not binding on private parties or the FDA. They did not set agency policy. They were simply nonbinding recommendations to the public. And so they were not agency action or final agency action.

10:46:15 And as discussed in our briefs, an important requirement for final agency action is that you need to have a direct effect on the regulated party. So, for instance, in the *Franklin v. Massachusetts* case, the Supreme Court held that the secretary of commerce's report
10:46:30 to the president was not final agency action because it was simply a nonbinding recommendation. The president's report to Congress about congressional apportionment did have a direct effect and was final; but the secretary of commerce's report to the president was not final agency
10:46:46 action because it had, at most, an indirect effect on apportionment. It was simply a nonbinding recommendation to the president.

And similarly, in the *Bennett v. Spear* case the Supreme Court upheld this notion that you need a direct
10:46:58 effect to be final agency action. And here, the

plaintiffs have not shown any direct effect of any of the cited statements on any other party. At most, they show an indirect theory of causation, whereby the cited statements influenced third parties, who in turn allegedly injured plaintiffs. But that indirect line of causation is not sufficient for final agency action.

THE COURT: And on exhaustion, is a citizen petition the only way that the plaintiffs could have challenged the FDA's actions with the agency itself in this case? What else could they have done?

MR. BELFER: So I am -- I think in this particular case I'm not -- I'm not aware of another mechanism that they could have used.

I think, generally, in terms of the issue of exhaustion, there is not only one mechanism. The focus is not on which mechanism you use. Instead, the focus is on just raising your issues somehow to the agency.

So, for instance, if there were, like, a drug approval, then you could raise the issue in the course of the back and forth with FDA about the drug approval or you could raise it, you know, as appropriate, as a citizen petition.

Here, I think a citizen petition would have been appropriate. They could have filed a citizen petition after FDA made its cited statements challenging those

statements and they could have presented all of the issues in their amended complaints to FDA in that citizen petition and that would have been beneficial to the agency by giving the FDA an opportunity to consider the issues, 10:48:19 in the first instance, to apply its expertise and discretion, and it would have allowed the agency to compile an administrative record that addressed their issues.

And so, it would have benefited both the agency and 10:48:31 the Court; but they failed to do that. The plaintiffs ran straight to court without giving FDA an opportunity to address their issues in the first instance. And under kind of core principles of administrative law, that's unacceptable.

10:48:43 THE COURT: Okay. Let me hear from the plaintiffs. I may have some more questions for you once I have heard from them.

MR. BELFER: Thank you, Your Honor.

THE COURT: Thank you.

10:48:51 MR. KELSON: Good morning, Your Honor.

THE COURT: Good morning.

MR. KELSON: As a general matter, the FDA has no authority to regulate the off-label use of drugs. It never has. That dates back to the -- to when the FDCA was 10:49:08 first passed in 1938. It's been a repeated consideration

by Congress. They have never given the FDA that authority. Going so far as to add a provision in 21 USC 396 to expressly prohibit interference, courts across the entire country have repeatedly relied upon that
10:49:25 provision to show that -- to show that it applies to the practice of medicine, including the prescription of drugs.

The government is trying to frame this case and its actions and its response to reports about the use of animal ivermectin. That doesn't explain why they then
10:49:42 pivoted to talk about human-use ivermectin. There is a disconnect in what they are claiming the justification for these actions were and what they actually did.

This is reaffirmed by the internal FDA documents that talk about this new engagement strategy they had to
10:49:53 promote their recommendations to the public and the United States. And it belies the fact that what they were trying to do was stop the use of ivermectin. Their tweets are explicit on that point.

So when the government says this was purely
10:50:05 informational, conversational, essentially a PR scheme or a -- excuse me -- a PR endeavor, that doesn't explain why -- that doesn't explain the language they actually used, "Stop it. Stop it with the ivermectin."

In the government's brief when it refers to a number
10:50:20 of these statements, including the statements why you

should not use ivermectin to treat or prevent COVID-19, the government has to qualify the statements in its own brief and say "if a doctor prescribes you ivermectin for the use of COVID-19." The government's briefs, therefore, implicitly recognize the title of that document; and the FDA's other actions clearly convey that this is not an acceptable way to treat these patients. The only reason the FDA would engage in these actions is because of their predictable effect, the only explanation.

10:50:49 The Court is right to understand -- recognize that this is a very much common-sense case. The Supreme Court recently, within the last year and a half, has made very, very clear that courts are -- that courts and judges are not required to exhibit a naivete from which ordinary

10:51:03 citizens are free. That was -- you know, that was -- excuse me. That was in 2019 in *Department of Commerce v. New York*. That was Chief Justice Roberts. That applies directly to this case.

To address some of -- to address upfront some of the

10:51:21 government's arguments and some of the government's briefing, I want to be very clear to the Court that the government did not move under 12(b)(6) to challenge any of these claims on their merits. The government is, thus, conceding that the plaintiffs have alleged plausible

10:51:32 interference in their practice of medicine, that they have

alleged plausible claims under the APA. The government has, instead, challenged them all on standing grounds or challenged them on administrative exhaustion grounds or sovereign immunity.

10:51:37 That should inform the Court's position and that should also -- the Court should also take that into consideration when the government tries to backdoor merits considerations into other aspects of this case.

Second, in the government's reply brief the government

10:51:54 replies or the government cites *TransUnion* and says that the plaintiffs are only alleging statutory violations. That is incorrect. We are alleging real harms to real people that are reinforced by the statute that Congress passed in 21, Section 396 and, to be honest, the entirety

10:52:10 of the FDCA, which does not give the FDA the authority that it is trying to assume.

More importantly, if the Court would like to look at -- if the Court would look at *TransUnion*, the government omits the rest of the case, which weighs heavily in favor

10:52:22 of the plaintiffs here. *TransUnion* is very clear that there is an injury in fact when there is a harm that is traditionally recognized as providing the basis for a lawsuit in America or if there is some sort of common-law analog. The Court is also very clear that it doesn't have

10:52:35 to be an exact duplicate. That Congress through statute

or Congress through its own expressions can recognize harms that might have been too trivial at common law but were, nonetheless, harms.

In fact, in *TransUnion* the exact example that the
10:52:48 Court used is various intangible harms, including reputational harm. That is one of the -- that is one of the allegations the plaintiffs have made here and, in fact, provided evidence that they have been maligned on line and that they constantly suffer reputational harm.

10:52:59 If the government is going to label ivermectin a horse medicine or a horse dewormer and promulgate the idea that it is only for animals, then the natural correlation is that doctors who prescribe it are horse doctors or quack doctors, which has been -- which has played out. That is
10:53:12 enough of a harm to get into court.

In addition, *TransUnion* also emphasizes the due respect that courts should pay to the decisions of Congress; and Congress has been very clear that the FDA should not interfere in the practice of medicine. Now the
10:53:27 Court has -- while the Court has recognized that that cannot completely -- that cannot completely remove the necessity of showing injury, it should inform the Court's decision that it is consistent with the Fifth Circuit's decision that the plaintiffs need only show an
10:53:39 identifiable trifle of an injury. The bar is low. Any

sort of injury will do, and the plaintiffs have alleged many here. That injury is sufficient, even if the harm is difficult to prove or difficult to quantify.

Moving forward, the government places a lot of
10:53:56 emphasis on traceability. The government's arguments in this regard are flawed.

I'm sorry. I have one more thought I just had about the injury. When the Court talked about injury in *Lujan*, it discussed both a forward and a backward looking
10:54:16 analysis. The exact language in *Lujan* allows plaintiffs to present evidence of harms that have accrued.

So even if -- I guess this transitions into the -- sorry. This transitions into traceability. So even if this wasn't predictable, which is a standard for
10:54:34 traceability, if in retrospect the plaintiffs can show how these harms were determinative or were caused by the plaintiffs, de facto causality, that is traceability. The plaintiffs are not cabined into the predictability test, even though that is one way of establishing traceability
10:54:50 under the constitution, recognized by both the Fifth Circuit and by the Supreme Court.

It's unclear what the -- what the government would have thought their tweets were going to do if -- by saying "stop it with the ivermectin" or "stop it" except to,
10:55:03 well, stop the use of ivermectin. The government engaged

in a singularly effective campaign here to malign a common drug that has been used for a very long time and has been dispensed in billions of doses. It's one of the most famously safe drugs in the history of human medicine.

10:55:18 And when people did exactly what the FDA said to "Stop it. Stop it with the ivermectin," I don't understand how that would not be traceable back to the FDA.

So if it wasn't -- so it was predictable. It also, in retrospect, clearly points back to the FDA. When everyone

10:55:36 points to the FDA, there is a pretty good chance that that's where it is coming from.

The plaintiff -- or the government has repeatedly stated that people have their own scientific intuitions about the ivermectin. That's not what is happening here.

10:55:47 People are pointing back and saying, "The FDA said no. The FDA said no."

That is not a scientific analysis. That is a deference to the FDA, to an agency that the federal government set up to be an authoritative voice on the use

10:55:59 of drugs but limited that authority not to practice medicine and not to make recommendations about medicine.

So in that regard the FDA's actions cannot be excused simply because they presume that everyone else has these scientific understanding -- this scientific understanding.

10:56:14 That transitions into redressability. Again, this

is -- there is a common-sense intuition that when everyone points to these FDA statements if a court were to come out and say they were made without lawful authority and vacate them that they would somehow retain their same equal
10:56:30 persuasive force. That seems to brink reality, as well.

In addition, the government points to a number of other entities that have taken positions on ivermectin. Each of them are severely flawed. I am not aware of the FDA ever pointing to a pharmaceutical company and saying
10:56:44 that its statements have the same force and effect or are of the same persuasive nature as the FDA. That, to me, is a strange argument I have never heard from the FDA before.

And I don't suspect the FDA plans on deferring to pharmaceutical companies in the future. In addition, the
10:57:00 FDA regularly disagrees with the World Health Organization. Remdesivir is a great example of that. And the FDA seems to think that its -- that its voice on these drugs is more important than the World Health Organization's. That's enough to undermine reliance on
10:57:14 the World Health Organization, which also is not an American body and doesn't have the same effect in the United States.

The CDC regularly cites to the FDA, and the CDC does not specialize in the use of drugs in America. And the
10:57:23 NIH for a long period of time took no position on

ivermectin, a long period of time during which harm was caused to these plaintiffs. So the FDA can't point to the NIH and say that it has some sort of -- that it has the same effect.

10:57:38 In addition, the Fifth Circuit has made very clear with redressability, especially at this stage of litigation, that plaintiffs have established their standing if a favorable ruling could potentially lessen the plaintiffs' injury. It's a very low bar, and there is

10:57:54 absolutely a potential chance that the injury could be lessened here. That case is *Sanchez v. R.G.L.* It's 761 F.3d 495. I believe it's cited in our brief, as well.

But it seems very clear that when everyone is pointing to the FDA that if this court were to vacate those FDA

10:58:12 statements that there is a potential chance or that it could potentially lessen the injury that these doctors are suffering.

In addition, in *McClure v. Ashcroft*, the Fifth Circuit as well, says you only need to show an arguable chance

10:58:25 that a third party might consider changing its policy. The government points out that Dr. Apter is subject to current investigation or current proceedings against his medical license. That referral came from the Iowa State Board of Medicine. It came from another state board.

10:58:39 This was not some random person throwing a document into a

referral and sending it to a state board.

The FDA's actions here, their statements, their tweets, they are showing up in court filings. They are being relied upon by courts as the standard of care in 10:58:53 malpractice proceedings. They are showing up in state board proceedings, as we have shown here. They are showing up in public discourse as a way to malign and ruin the reputations of doctors who have been working their level best to fight a pandemic.

10:59:04 What the FDA has done is pervasive throughout the entirety of healthcare and has caused significant injury to these plaintiffs. And for this court to declare them unlawful and to vacate them and to enjoin the agency from engaging in an unlawful practice of medicine in the 10:59:19 future, it undoubtedly would not only address those injuries it would -- it would undoubtedly redress those injuries.

More importantly, the practice of medicine is so well established in this country in the use of off-label drugs. 10:59:32 Up to about 40 percent of off label -- of drugs are used off label in critical care. The presumption there should be that if the FDA -- if that has changed somehow for ivermectin and it started with the FDA, if that -- if that action by the FDA is vacated that will -- that somehow 10:59:46 that normal will resurface. It's been that way since the

beginning of the practice of medicine in this country and it's unclear why the FDA has decided in this particular case to try and interfere with it but that's exactly what's happened.

10:59:59 On the sovereign immunity points that the government points out, I would like to respond in a few ways. The first is that this court should be careful to make sure that -- to view the ultra vires claim and the APA claim separately. They are separate claims, and the standards

11:00:14 for them are separate.

First off, under *Larson* the Supreme Court has been clear that when you are seeking injunctive relief against federal officers for exceeding their authority that that's not barred by sovereign immunity. *Larson* resolves the

11:00:28 case for the ultra vires -- *Larson* resolves the sovereign immunity issue for the ultra vires case.

THE COURT: Wait. Say -- say that again, please, on *Larson*.

MR. KELSON: *Larson* resolves the sovereign

11:00:41 immunity issue for the ultra vires claim. The government has exceeded its authority; and under *Larson*, sovereign immunity does not bar -- sovereign immunity does not bar injunctive relief against, quote, a federal officer that acted in excess of his authority or under authority not

11:00:56 validly conferred. That's *Larson* at 333 -- sorry -- 337

in the U.S. Reports, Pages 690 to 691. It's also cited in our brief extensively.

In addition, the government decides -- the government waited until the reply brief to challenge the plaintiffs' 11:01:13 interpretation of Section 396. Not only have multiple circuit courts applied that -- the plaintiffs' interpretation of Section 396 about prohibiting the interference of the practice of medicine, but this case is not dependent upon that provision.

11:01:28 Whether or not Section 396 is in effect, the FDCA does not give the FDA authority to do what it's doing here. That provision is an emphasis that was added by Congress to make sure the FDA did not overstep. But if you go back to the debates leading up to the 1938 Act and all through 11:01:44 the present, Congress has repeatedly expressed that the FDCA does not have the authority to interfere with the practice of medicine. This is nothing new.

And so whether or not this court finds that Section 396 applies here, it doesn't change the outcome of 11:01:56 this case. Section 396 is merely an exclamation point showing that Congress really did not want the agency doing what it's doing now.

Moving on to the APA waiver of sovereign immunity, in 5 USC, Section 702, again, the difference between the 11:02:13 ultra vires and the APA claims is important. The ultra

vires claim does not require final agency action. It only requires agency action. That is very, very clear from the Fifth Circuit's precedent, for example, the *Alabama-Coushatta* case.

11:02:27 The Fifth Circuit has also been clear that pretty much everything an agency does qualifies as an agency action under the -- under the APA. There is Fifth Circuit precedent that is directly on point.

I don't how to pronounce the case, *Avoyelles Sportsmen's League;* but that one is very explicit that 11:02:42 anything the agency does is at least an agency action. The question then becomes if it's final.

In addition, you have the *Data Processing* [sic] case, which very clearly says for even informational statements 11:02:51 or agency action the debate will be over whether they are final.

So to be very clear, as soon as the agency acted they waived -- Section 702 waived sovereign immunity for an ultra vires claim. Finality is not a requirement.

11:03:03 For the other APA claims where finality would be a requirement, it is also clear the agency has acted with finality here. The agency has maintained this position for a year and a half. While they say -- while the agency has said that they might change their position based upon 11:03:17 further factual analysis, the Fifth Circuit expressly

rejected that argument recently in the *Data Processing* case -- or the *Data Marketing* case. If you would like a citation, that's 45 F.4th at 854.

The Fifth Circuit was very clear and actually 11:03:33 chastising the government that it recycles an argument the Supreme Court has repeatedly rejected. The action isn't final because the agency can change its position after more fact finding. This argument is squarely foreclosed by numerous Supreme Court decisions.

11:03:44 It would also mean that no agency action is ever final because the agency can always change its mind after further fact finding.

Looking at this case then, the agency has maintained its position for a year and a half. Their statements are 11:03:55 not qualified: "Stop it" and "Stop it with the ivermectin," "Should I take ivermectin to treat COVID-19" or "Should I take ivermectin to treat or prevent COVID-19? No." Those are not qualified statements.

And the fact that they are followed up with "if my 11:04:08 doctor gives me ivermectin, take it exactly as prescribed" -- whatever that language exactly is -- does not change the fact that they have just stated unequivocally, "Should I take ivermectin? No." Period.

And so even if -- in reading those statements 11:04:21 together, it's very clear that the government is either --

it's very clear that the best way to interpret that statement is that -- the best way to interpret that statement is that if my doctor prescribes me ivermectin for something else.

11:04:37 If the government was -- wanted to be clear that if the government -- that doctors could prescribe ivermectin for COVID-19 and then should be taken exactly as prescribed, it could have said that; but it chose not to, instead, putting all its emphasis and references to

11:04:50 COVID-19 to tell doctors and to tell patients they should not -- to tell patients they should not take it and to tell the public that they should not take it either.

I'm sure that this court is aware that doctors and patients are part of the public and that patients are

11:05:01 consumers. So saying that this document -- saying that the government's main document why you should not take ivermectin to treat or prevent COVID-19, by saying that that was directed to consumers is not a fail proof -- is not some sort of argument to get out of the real effect

11:05:17 that that document had or the fact that it is directly talking to people that are in the doctor-patient relationship.

In addition, on the finality point, the Fifth Circuit and the Supreme Court have been very clear that finality

11:05:28 is flexible and pragmatic. As part of that flexibility

and that pragmatic consideration, this court should be mindful of the fact that Congress in Section 396 said that the FDA can't interfere in the practice of medicine.

It would be very passing strange if the agency could 11:05:44 do exactly what Congress told them not to and they could turn around and say, "Our action wasn't final though. So it's okay." Congress recognized that there was some sort of real-world effect of the agency interfering in the practice of medicine; and in so doing, that agency action 11:05:57 would have to -- would be final.

In addition, the Fifth Circuit has said it's a -- the action only has to be binding as a practical matter, where private parties might rely on it as the norm. That's the *Texas v. EEOC* case. And it's very clear that it's become 11:06:13 a norm. Courts are relying on it as the standard of care.

Like, directly under the Fifth Circuit's precedent in *Texas v. EEOC* you would -- as a practical matter the FDA statements have now become a norm in society. They have been the norm that is being relied upon by professional 11:06:28 bodies, by advisory bodies and by courts.

In that same case, the Fifth Circuit continued that private party -- an agency action is final if private parties are reasonably led to believe that failure to conform will bring adverse consequences. I think it's 11:06:42 safe to say that failure to conform with the FDA's

position here has brought adverse consequences to these doctors both reputationally, the fact that Dr. Apter is now facing board charges.

So viewed in that flexible and pragmatic sense, there are numerous factors which weigh in favor of finality here, not to mention the common sense -- not to mention the common sense view of what the agency has done in reading its own language.

As an additional point, just in response to the government, in *Bennett* the government was acting on a third party. So there is -- there is some -- there is other cases where the fact -- the fact of the matter is there are legal consequences. The government can't launder its actions by making -- setting up some sort of standard that can then be relied upon as a third party to impose those -- by a third party to impose those consequences.

In addition or finally, in response to the government's reply brief, I would like to point out to the Court specifically that on page, I believe it was, 21 the government makes very clear in its reply brief that it is not arguing a citizen petition is required. That concession is incredibly important because the Fifth Circuit has been very, very clear that unless exhaustion is required by statute or by regulation, the only time

administrative exhaustion is necessary is when there is some sort of adversarial proceeding below.

In fact, the government cites repeatedly *Palm Valley*. In Footnote 6 of that opinion Judge Costa is explicit that 11:08:06 the administrative exhaustion requirements only apply in that case because there is a regulation that requires it.

If there is no regulation, you have to have adversarial proceedings below. You have to have something tantamount to a judicial proceeding. That is not present 11:08:19 here. That is not in any way present here because the government gave no process. Instead, it acted unilaterally to push its -- to push its public campaign.

In fact, the examples that the government gives talk about when there is, for example, some sort of agency 11:08:34 proceeding over a drug approval, when there is some sort of existing agency proceeding. There was none here. And if a citizen petition is not required, which we contend it is not, based upon the plain language but also based upon the government's own admission that a citizen petition is 11:08:46 not required, then we are in a separate world of administrative exhaustion.

And what the government would purport to this court would be a fundamental change in how administrative exhaustion has been run in this country and they would 11:08:56 impose a brand new requirement that has never been

recognized that a party must go to an agency and litigate its case with an agency before it goes to the government when the agency gave no process ahead of time.

The whole purpose of administrative exhaustion is to
11:09:09 avoid parties sandbagging an agency and waiting until court to raise their claims or to give the agency the opportunity to engage -- to apply its expertise during its proceedings.

None of that applies here. None of these
11:09:20 considerations are relevant. There were no proceedings. The government has acted. It's been final. In addition, this is a legal question. This is not some sort of factual dispute for the agency. And so the fact that there is no agency expertise here that the Court would
11:09:36 need to defer to, none of the factors that weigh in favor of agency exhaustion would otherwise apply.

So agency -- by the government's own admission, agency exhaustion is not required by the law. It is not required by a statute. By very clear Fifth Circuit case law and by
11:09:51 -- it is not required as a prudential matter; and even if it were required as a prudential matter, there are ample reasons for this court to weigh that exhaustion requirement because none of the factors that weigh in favor of exhaustion are present here.

11:10:06 I think that that is -- those are my main responses to

what the government has said. If you have -- you know, if the Court has any questions, I would happy to answer them.

THE COURT: Sure. No. I appreciate that. Are you aware of any cases anywhere else where patients are the plaintiffs suing over the FDA's comments on ivermectin?

11:10:21

MR. KELSON: I don't know of any -- I am not aware of any cases where patients are suing the FDA.

THE COURT: All right. Any idea why there aren't any -- I guess this is a doctors' case, not a patients' case is why there aren't any --

11:10:35

MR. KELSON: It's a doctors' case.

THE COURT: -- patients among the plaintiffs in this case here today.

And another kind of general question.

11:10:44

MR. KELSON: Just as one consideration for the Court, when it comes to the need for ivermectin, the plaintiffs see these things every day. They are well immersed in the science; and they are well immersed, actually, in the practice of medicine prescribing ivermectin or trying to prescribe ivermectin and dealing with the public backlash they get for doing so.

11:11:03

With patients, most patients are only seeking treatment for COVID; and then once it's over, it's done. But the benefits of a lawsuit and the motivation for a

11:11:14

lawsuit are significantly diminished in that regard.

Whereas with these doctors, they have been living in this world for a year or a year and a half now and they have suffered significant reputational harm as a result of it. They see this interference with their practice of medicine every year -- every day. It takes an extreme toll on them but also then makes it difficult when they are constantly battling trying to write prescriptions and get prescriptions for their patients and then they are fighting with pharmacists who are saying, "Well, the FDA says no."

11:11:26 11:11:39

And so, just as a practical matter in that regard, the explicit answer or the exact answer to your question is I am not aware of any plaintiffs that are suing the FDA. I do know some plaintiffs -- I do know of some plaintiffs who have sued hospitals to try and get ivermectin in the past. There were a few of them in the news.

11:11:51

But it also is very easy for the Court to see why this is a particularly problematic issue for doctors, and that is why the three plaintiffs in this case that I represent have been willing to undertake the expensive burden of litigation to try and rectify the injuries that they have suffered.

11:12:05

THE COURT: I believe the government noted that it was, like, 26 months or something from the time the FDA

11:12:18

first started making these statements that the lawsuit was filed. Is there a reason for that delay?

MR. KELSON: So I think there are -- there are a number of reasons that could be relevant. I'm not sure
11:12:33 that they are in any way required to bring a lawsuit within a certain -- they have a four-year statute of limitations under the APA or six-year statute of limitations.

When the government first started in 2020 or early
11:12:44 2021, the statements were significantly more benign. They were problematic, but they were more benign. It really took off in August when they started with the "You are not a horse. You are not a cow" campaign and when they started labeling doctors as essentially horse doctors or
11:12:59 quack doctors. And so that -- that exacerbated the injury. The government then doubled down recently, I believe it was in April, with another tweet.

So to say this is anything about animal ivermectin is even more problematic under the light of the fact that
11:13:14 they are continuing the horse trope many, many months afterwards.

As a result, because the government has maintained these documents and has been doubling down on them, like, the injury has been increasingly severe. And, quite
11:13:26 frankly, sometimes it takes a while to find a lawyer who

will take your case.

There are a number of considerations and then, you know, we put an extensive amount of work into trying to find all the publicly-available examples we could have to track down what was going on and to make sure that we could substantiate the plaintiffs' claims.

So for those reasons and the fact that the plaintiffs have a significantly long runway, six years to bring APA claims, 26 months isn't actually unreasonable at all.

11:13:56 THE COURT: You argue for a very broad interpretation of agency -- of what constitutes agency action. If everything an agency does is agency action under the APA, then does that mean the APA is kind of a general waiver of sovereign immunity? That's kind of what 11:14:15 it sounds like.

MR. KELSON: No. No. Because, yes, everything -- the Fifth Circuit has been explicit that everything an agency does is going to fall under the definition of agency action; but to bring a claim under the APA, for 11:14:27 example, and to claim a waiver of sovereign immunity under the APA, you have to show final agency action. So that is one distinction.

The ultra vires claim, which is not -- which does not have a finality requirement to it under the Fifth 11:14:38 Circuit's precedent, yes, if an agency acts then there is

a waiver of sovereign immunity but it's very limited and it only applies to injunctive relief, not damages. That also should not concern the Court because it only becomes relevant when the agency has acted unlawfully.

11:14:51 All the government's arguments here have nothing to do about whether or not their actions were lawful. They have everything to do about setting up barriers for the plaintiffs to begin a course to seek remedy.

And so to the extent that the agencies act unlawfully,

11:15:01 then, yes, they would be subject to suit. If the agencies haven't acted unlawfully, it actually becomes immaterial whether or not agency action is brought because any agency action that would be -- any challenge to any agency action -- I'm sorry. I might have been speaking to quickly.

11:15:15 Any challenge to any agency action that is lawful will be promptly dismissed, and so it's not going to be a burden on the agency either.

THE COURT: Is any informational statement that the FDA makes an ultra vires act by the agency?

11:15:31 MR. KELSON: That would be an agency specific inquiry, Your Honor. The FDA in this particular case is -- the FDA sits in a very unique spot in the United States because of the authority that the government has given it to regulate the approval of drugs to let the

11:15:49 drugs enter into the market and withholding the ability to

interfere with the practice of medicine.

Most informational statements are not going to be problematic. The FDA talks about how, well, we've issued warning letters in the past. That's not -- that might be
11:16:03 an agency action, but it's not unlawful for them to issue a warning letter to a doctor or to someone who has -- to someone who is marketing a drug -- who is marketing a drug contrary to the FDCA.

The statements here go far beyond purely
11:16:22 informational. These are not informational statements. These are directives to the public. These are directives to patients or these are strong medical -- these are medical recommendations. That is the heart of the practice of medicine.

11:16:32 And so this case needs to be viewed in the context-specific capacity of the fact that we are dealing with the FDA which has significant authority in this area, which has outsized -- which throws around outsized weight in this area and the fact that Congress has explicitly
11:16:49 recognized the problems that the FDA could cause if it started meddling in the practice of medicine. It's relevant throughout the debates. It's relevant in Section 396 of Title 21.

And so in this particular case we are not talking
11:17:01 about informational statements only. We are talking about

statements that are making recommendations about medicine. We're talking about statements that are directing the public to "stop it" or to "stop it with the ivermectin."

So in that regard, this case is not about whether or not informational statements are illegal. It's about the statements here that the FDA has made.

Also, if the government -- the government has mentioned or has tried to make the argument that it's just -- that it can speak freely. That's a merits argument, and that should not be resolved at the motion to dismiss stage because the government has not raised a 12(b)(6) motion challenging the merits of the claims.

THE COURT: You mentioned warning letters. Warning letters seem like they are more than informational. They can approach being a directive, too, can't they?

MR. KELSON: The FDCA has the authority to police how drugs are marketed. That's like -- that is within their express statutory authority. So it's -- it's somewhat of a red herring or a straw man where the government says, "Look, we send out these warning letters telling a pharmacist we heard that you are promoting this drug and saying that it is -- it should be used for these purposes."

That is separate from what is going on here because we

are not talking about advertising drugs for this -- for sale and distribution. We're talking about how doctors deal with their patients and what drugs should be used for particular treatments off label.

11:18:11 The FDA has authority over what -- over when drugs can be admitted to the market, what labeling they can use, and how they can be marketed. If they issue a warning label on those conditions that is within their authority, then they are within their authority; but that's not what they

11:18:25 are doing here. They are telling people to stop -- they are telling consumers, not distributors. They are telling consumers to stop it. They are telling doctors, the public, to stop it. That is a totally different thing that is outside of their authority.

11:18:38 THE COURT: I know that courts have held that warnings letters are not final agency action. If warning letters aren't, then how can the statements in this case be?

MR. KELSON: So, in the first instance, a warning

11:18:56 letter is more tentative than a statement like "Stop it" or "Stop it with the ivermectin." So there is a difference in the tone of the letter -- of the statements.

In addition, Section 396 should inform this court's flexible and pragmatic approach to finality.

11:19:13 In addition, the warning letters -- the warning

letters are explicitly, by their terms, in preparation for a potential enforcement action. And so they are very clearly non-final by their nature. They are issuing a warning that in the future they may choose to take action; whereas, these statements about ivermectin have no such future action attached. They are not -- they are not in anticipation of something else. They are not a warning. They are not an initial volley in an ongoing conversation with a regulated party. These are direct and final statements to the public, to doctors, to consumers, to patients. And so, in that regard, they are different.

And in the event the Court feels otherwise, none of that affects the ultra vires claim which, in any event, should proceed.

THE COURT: Okay. Well, thank you. I'm going to see if the government has anything else, but I appreciate it.

Counsel, you are welcome to -- go ahead. You are welcome to cover whatever you would like in response to the plaintiffs' arguments; but I would like you to specifically address, for one thing, the allegation that the statements the FDA made that the plaintiffs are complaining about in this case were not merely informational but were more like directives.

MR. BELFER: Yes, Your Honor. The cited

statements were not directives. They were not mandatory. They were recommendations. They said what parties should do. They said, for example, why you should not take ivermectin to treat COVID-19. They did not say you may
11:20:50 not do it, you must not do it. They did not say it's prohibited or it's unlawful. They also did not say that doctors may not prescribe ivermectin.

THE COURT: Well, they very flippantly say "stop it" in the tweet.

11:21:04 MR. BELFER: Yeah. They use informal language, that is true; but they did not -- they did not say you may not do this or it is unlawful. If you look at the language they used, it is -- yes, it's informal. It's conversational, but it's not mandatory. It never said
11:21:17 this is unlawful, it's prohibited. And so that contrasts with, you know, other things that FDA might say where it is more -- more mandatory.

And if you look at the kind of statements at issue here, we are not talking about a publication of the CFR or
11:21:31 an official memorandum. We're talking about tweets and Instagram posts and website posts. These are much more informal fora.

And so if you look at the informal fora, the fact that this is informal conversational language, plaintiffs
11:21:45 cannot show that it was predictable that anyone would look

at these statements and think that they were prohibited from taking ivermectin to treat COVID-19, especially given that, you know, the tweets both linked to the article and the article said that doctors have discretion and that if
11:21:56 your doctor prescribes ivermectin, take it exactly as prescribed.

So a few general points before we get into the specific issues that plaintiffs raised. So plaintiffs argue that -- they tried to frame this case as about the
11:22:15 off-label use of drugs, off-label prescription; but this is not a case about off-label prescription. This is a case in particular about the use of ivermectin to treat COVID-19.

No one is questioning that doctors generally have
11:22:26 authority to prescribe off-label in appropriate circumstances. Instead, what FDA is saying here is it's warning consumers about the risks of using ivermectin to treat COVID-19.

And the fact that FDA generally does not prohibit
11:22:40 doctors from prescribing off-label has never been taken to be a limitation of FDA's authority to communicate publicly. FDA communicates publicly about the risks of drugs all the time. And, in fact, in the amended complaint the plaintiffs concede that FDA generally has
11:22:53 authority to communicate to the public about the risks of

drugs. So there is no dispute that FDA generally has authority to communicate with the public about the risk of drugs.

Plaintiffs argue that Section 396 is a limitation on
11:23:05 that authority. But tellingly, in their argument, the plaintiffs don't really defend 396 and for good reason. Section 396 is directed to medical devices, not drugs. And even beyond that, 396 is -- does not establish any general interest in -- against interference with the
11:23:22 practice of medicine, let alone any interest to get into FDA communications. It's not about that.

Instead, 396 is very specific. It's about doctors' authority to prescribe or administer medical devices; and even if you could strike out the word "devices" and
11:23:38 replace it with "drugs," it would still only be about doctors' authority to prescribe or administer drugs. And here there is no allegation that doctors' authority to prescribe or administer drugs was ever impaired.

The plaintiffs, by their own admission, have continued
11:23:51 to prescribe ivermectin. So they always had the authority. It may be that patients were not able to fill prescriptions, but the doctors themselves always had the authority. So Section 396 is not applicable, and there is -- there is really no general interest against
11:24:05 interference with the practice of medicine at issue here.

So I would like to respond in particular to a few of the arguments that have been made on the various issues in this case. Starting with sovereign immunity, plaintiffs argue that their ultra vires claim is essentially an exception to sovereign immunity.

11:24:23

But in the *Danos* case from the Fifth Circuit, the court said that it's not enough simply to allege that an agency action is unlawful or unauthorized. You have to do more. You have to show that the agency had no colorable basis for its exercise of authority; and plaintiffs have not done that here because, again, they concede that FDA generally has authority to communicate with the public about the risk of drugs. They argue that 396 is a limitation on that authority; but as we discussed, 396 is inapposite here.

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11:24:51

And so plaintiffs have not met the standard under *Danos* of showing the FDA had no colorable basis for the exercise of its authority. Right.

And so with regard to agency action, plaintiffs take the position that essentially any -- any statements by the agency is agency action. And they say that the Fifth Circuit has held that essentially everything an agency does is agency action, but that's simply not true.

11:25:06

If you look at cases like *Alabama-Coushatta* or *Walmart,* both Fifth Circuit cases, those make clear that

11:25:22

not everything is agency action. In their briefing, plaintiffs rely specifically on their contention that the agency -- the cited statements are a rule. That is their basis for saying there is agency action.

11:25:37 So let's look at the definition of a rule. The definition of a rule -- I can pull it up right here. So, essentially, to be a rule you need to be binding on either the agency or a private party or you need to interpret a substantive rule or you need to set agency policy. Those

11:25:53 are all the rules. But here the cited statements are none of those things. They are not binding on anyone. They don't interpret any rule, and they do not -- they don't set agency policy.

And so you need to meet -- plaintiffs rely on a rule,

11:26:09 but here the cited statements simply don't meet the statutory definition of a rule.

And then, with regard to final agency action, I guess starting with consummation of the agency decision-making process, we do not argue that the consummation prong is

11:26:25 met simply because the cited statements might be revised in the future.

Sure. An agency can always take future action, but that's not what we're arguing. Instead, our argument is that if you look at the face of the cited statements

11:26:38 themselves, they are expressly tentative. They state that

they are based on currently available data, that more data is needed, and that clinical trials are ongoing.

So if you just look at the face of the statements, they are expressly tentative and based on currently
11:26:50 available data. They do not state FDA's final definitive position on the use of ivermectin to treat COVID-19.

You know, plaintiffs say that these statements -- going to the legal consequence prong, plaintiffs say that these statements are unequivocal. They are not
11:27:06 unequivocal. They generally recommend against using ivermectin but they also say if your doctor prescribes it, take it exactly as prescribed. And there is no allegation that anyone read part of the statement but not the entire statement. And so plaintiffs have not shown that
11:27:18 plaintiffs would not read the entire statement and see that nuance in the statements.

Plaintiffs cite *Texas v. EEOC* regarding this notion that if the agency establishes a norm that that's final agency action; but the *Texas v. EEOC* case is plainly
11:27:33 inapposite. In that case, the agency established a norm; and if private parties did not comply with the norm, they were subject to legal liability. They could be sued for failing to comply with the norm. That's a direct effect on those third parties by changing their legal liability.

11:27:47 Here, there is no effect. The cited statements have

no effect on anyone's legal liability. There is no direct legal consequence on anyone.

And, similarly, the plaintiffs cite the *Bennett* case but *Bennett* -- and that's *Bennett v. Spear* with the
11:28:00 Supreme Court -- is, again, different. In *Bennett* the Fish and Wildlife Service issued a biological opinion; and if other agencies did not comply with that biological opinion, they could be subject to criminal and civil liability. So in *Bennett* there was a direct legal effect
11:28:15 on other agencies. If they did not comply with the Fish and Wildlife Services statement, they could be subject to criminal or civil liability.

Again, here there is no similar direct effect. No one would be subject to criminal or civil liability if they
11:28:28 prescribed ivermectin to treat COVID-19. Instead, the statement expressly acknowledged that doctors can prescribe ivermectin for that purpose.

So I would like to say a few words about standing. So the plaintiffs argue that FDA is trying to stop the use of
11:28:48 ivermectin and that its purpose -- its purpose was to stop the use of ivermectin; but again, if you look at the language of the statements, FDA never said that doctors cannot prescribe ivermectin to treat COVID-19. They said doctor -- if your doctor writes you a prescription, fill
11:29:03 it and take it exactly as prescribed. So the FDA

expressly acknowledged that you can use ivermectin for this purpose if your doctor prescribes it.

And, you know, looking at FDA's intent, FDA was really focused on consumers. It was advising consumers who could
11:29:20 buy this product over the counter that they shouldn't take it. They did not say that if your doctor prescribes it, don't take it. They said follow your doctor's advice. If your doctor prescribes it, take it exactly as prescribed.

You -- right. So regarding the *TransUnion* case, you
11:29:35 know, plaintiffs say that essentially that there is injury in fact here, and they cite that case. So what the Supreme Court held is that you cannot presume an injury in fact just because there is an alleged statutory violation. You still need to look under Article III at whether
11:29:55 plaintiffs have met the requirement for standing.

So, as we discussed, there is no violation of 396. FDA did not exceed its authority. But even if plaintiffs had shown a violation of Section 396, that is not itself alone -- that itself is not alone -- that alone is not
11:30:10 sufficient to show standing. You would still need to show an injury in fact under Article III.

And because the alleged violation, interference with the practice of medicine, is a vague conclusory allegation and plaintiffs were always able to prescribe ivermectin,
11:30:26 they have not shown any injury in fact under Article III.

Regarding traceability, you know, plaintiffs try to minimize their burden to show traceability; but importantly, the standard is that -- or, sorry. Under the *Daves* case from the Fifth Circuit the Court held that it's substantially more difficult to show traceability when the causal chain relies on independent third-party conduct. And so to meet that much higher burden when, as here, plaintiffs rely on this indirect causal chain, you need to show that the third-party conduct would be a predictable response to the cited statements.

And because FDA statements were directed at consumers, they were, you know, informal, conversational, and because they expressly acknowledged doctors' discretion to prescribe ivermectin, it would not be predictable that, for example, a hospital would punish a doctor for prescribing ivermectin when the statements themselves acknowledged that doctors could prescribe ivermectin to treat COVID-19.

You know, plaintiffs state that everyone is pointing to FDA. So, surely, FDA must have caused the third-party conduct. But if you look at what is alleged in the complaints in the exhibits, it's clear that third parties are not just relying on FDA.

For example, Exhibit 12, which is the statement of Sentara, which is a former employer of Dr. Marik, they did

not simply rely on FDA. Instead, they cited statements from many organizations -- FDA, CDC and several other organizations -- and they provided independent medical analysis. They said there is no randomized control trial
11:31:59 that supports use of ivermectin to treat COVID-19.

So, you know, plaintiffs' employers, pharmacies, insurance companies, these are sophisticated entities that make independent -- that exercise independent professional judgment as shown by Exhibit 12. They did not simply take
11:32:13 what FDA said and accept it at face value. They looked at FDA statements in combination with the statements made by many other organizations. They also performed independent scientific analysis. They looked at the data. And based on all of that, they concluded that they would not
11:32:27 recommend prescribing ivermectin.

And so, you know, that undermines redressability because it shows that even if you took away FDA cited statements, just those statements, you would still have all those other third-party statements that Sentara and
11:32:42 other organizations relied on.

And I would just give you a few more citations. Exhibit 25, which is the joint statement by the American Medical Association and other organizations, also. So it's not just FDA but many other -- many other statements.
11:32:55 And the *DeMarco* case the plaintiffs cite, that cites

not just FDA but many other organizations.

And so simply taking away these particular FDA statements, plaintiffs have not shown that that would likely cause third parties to reverse their past conduct; and again, that's the standard. You have to show -- you have to -- you have to have allegations that plausibly allege that it would be likely that third parties would reverse their past conduct and redress plaintiffs' injuries, and plaintiffs have not shown that it would be likely. Right.

So I think, for all those reasons, plaintiffs have not shown that there is any waiver of sovereign immunity because they have not shown agency action or final agency action. And they also have not shown that they have standing because they have not shown injury in fact for many of their injuries, and none of their injuries satisfied the traceability or addressability prongs.

So unless Your Honor has any further questions.

THE COURT: No. I don't think I do right now. I appreciate it. I'm going to give the plaintiffs the last word. Thank you, Counsel. Appreciate it.

MR. BELFER: Thank you, Your Honor.

MR. KELSON: I believe the government began by saying that these were only informal tweets, these were only informal Instagram posts or LinkedIn posts.

The government can't launder unlawful action as a good PR scheme or as a good PR endeavor. The agency acted. Whether it acted through an informal way with definitive language or whether it went through the Federal Register
11:34:33 doesn't change the fact that the agency acted here.

The government is trying to -- tries to downplay *TransUnion;* but *TransUnion* explicitly recognizes that while you can't merely allege statutory harm, other injuries can be drawn from past precedent, from common-law
11:34:52 analogs. It specifically points out reputational harm, which we have alleged here.

There is a common-law analog to tortious interference with a doctor-patient relationship that's recognized in Texas. If you -- you know, if you want a case for that,
11:35:02 you can look at the *Garcia* case from the Northern District of Texas. It's 1999 -- it's an unpublished case; but it cites a number of other Texas cases -- 1999 Westlaw 362787.

So *TransUnion* squarely supports the plaintiffs here.
11:35:19 It shows that their injuries are real, that while there is a statutory violation, which should inform the Court's interpretation of the injury, and since they only need an identifiable trifle, there is also plenty of common-law analogs to show exactly what it is the doctors have
11:35:35 alleged here.

One of the amicus briefs, the American Association of Physicians and Surgeons also points out the *Tozzi* case where an agency labeling something as dioxin was enough to cause harm. It was enough to establish standing.

11:35:43 The FDA has labeled this a horse drug. The FDA has maligned the use of ivermectin and that the agency has told people to stop it. If there was standing in the *Tozzi* case from the DC Circuit, then there is definitely standing here.

11:35:59 I am not in any way backing away from the plaintiffs' interpretation of Section 396. That statute has been repeatedly interpreted by circuits across the entire United States as applying to the practice of medicine, including the prescription of drugs.

11:36:12 The government in its briefing says that by using a "see" statement, a "see" signal to introduce the citation that the government is -- that the Fifth Circuit was saying that it was an unrelated -- it was a related but not directly on point case. That is not what a "see" 11:36:26 signal means. A "see" signal means that the cited -- or the citation directly supports the proposition stated in the preceding sentence. That is Bluebook Rule 1.2.

As a result, all these courts have recognized that it applies. If you look at the -- to the extent there is a 11:36:41 scriveners error in that provision, so be it; but that

provision was clearly intended to stop the FDA. And even if it wasn't, the FDA doesn't have this authority. That has been very clear for 100 years.

I don't -- I don't -- unless the Court would prefer otherwise, I don't need to walk through all the -- I don't need to re-walk through all the arguments that we have already made in response to the government, except I would -- the only additions I would make is to point the Court to *Avoyelles Sportsmen's League* where the Fifth Circuit was explicit that the APA defines the term "rule" broadly enough to include virtually every statement an agency may make. That's a direct quote from a Fifth Circuit case.

In addition, the definition of "rule" in the rule -- in the APA is not exhaustive. It is prefaced by the word "includes." That means that there -- it is giving examples of a fall within a rule; and as the Fifth Circuit has recognized, that includes every statement an agency may make.

And if the Fifth Circuit's precedent isn't sufficient to satisfy this case, which we believe it is, there is also a DC Circuit case on the finality issue called *Ciba-Geigy Corp.* It's cited in our briefs. But it talks about how a hyper-technical approach is not appropriate and that a series of pronouncements may constitute final agency action if their cumulative effect causes injury.

That case is directly on point.

So to the extent this court wants to look outside the Fifth Circuit, the DC Circuit has a case that is directly on point with both *Tozzi* and *Ciba-Geigy*, both of which are
11:38:13 cited either in our brief or in the amicus brief.

In sum, the doctors here have been suffering -- have suffered injuries at the hands of the FDA's public pressure campaign for a long time now, well over a year. And this court has the power to stop that or to give them
11:38:39 the possibility of seeking relief. The redressability standard is low. They just have to show the potential for some sort of relief.

Especially at this stage of the proceedings, the standard is plausibility; and the plaintiffs have
11:38:51 unquestionably made plausible arguments, cited numerous -- numerous public statements, numerous public actions by the agency that establish more than a plausible injury, more than a plausible traceability back to the FDA, and more than plausible redressability. That's all that is
11:39:10 required at this stage in the proceeding.

And that just -- that is only the publicly-available information that we have been able -- that we have seen, that we have been able to find. Recently, in *Biden v. Missouri* it's become very apparent that government
11:39:24 officials have been acting in nonpublic ways to pressure

-- to pressure private parties.

All we can say is that in this case, from the publicly-available information, it is more than necessary to satisfy the plausibility standard that is necessary at this stage of the proceedings.

Unless the Court has any further questions.

THE COURT: No, I don't. I appreciate the -- the issues are very interesting; and the briefing and the argument has been very helpful to the Court. And we'll get a ruling out as quickly as we can for y'all.

MR. KELSON: Thank you, Your Honor.

THE COURT: All right. The Court stands in recess.

COURT SECURITY OFFICER: All rise.

*(Proceedings concluded at 11:39 a.m.)*

*Date: November 2, 2022*

***COURT REPORTER'S CERTIFICATE***

*I, Laura Wells, certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.*

*/s/ Laura Wells*

*Laura Wells, CRR, RMR*