MATH+®

COVID HOSPITAL TREATMENT

A GUIDE TO MANAGING THE HOSPITALIZED COVID-19 PATIENT

July 20, 2022

FLCCC ALLIANCE

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

Table of Contents

Disclaimer **3**

The Use of "Off-Label" Drugs **3**

Overview of MATH+ and Key Concepts **3**

First Line Therapies (in order of priority) 11

Second Line and Optional Treatments 12

Treatment for Patients Admitted to ICU **16**

First line treatments 16

Additional Treatment Components 17

Second Line Treatments 18

Optional Treatments (and those of uncertain benefit) 18

The "FULL MONTY" for Severe COVID Pulmonary Disease 23

Salvage Treatments **24**

Salvage Treatments of unproven/no benefit 24

Monitoring **25**

Post ICU Management 25

Post Hospital Discharge Management 25

References **27**

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.

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 1-3 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 7).

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 3). [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 3). [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).

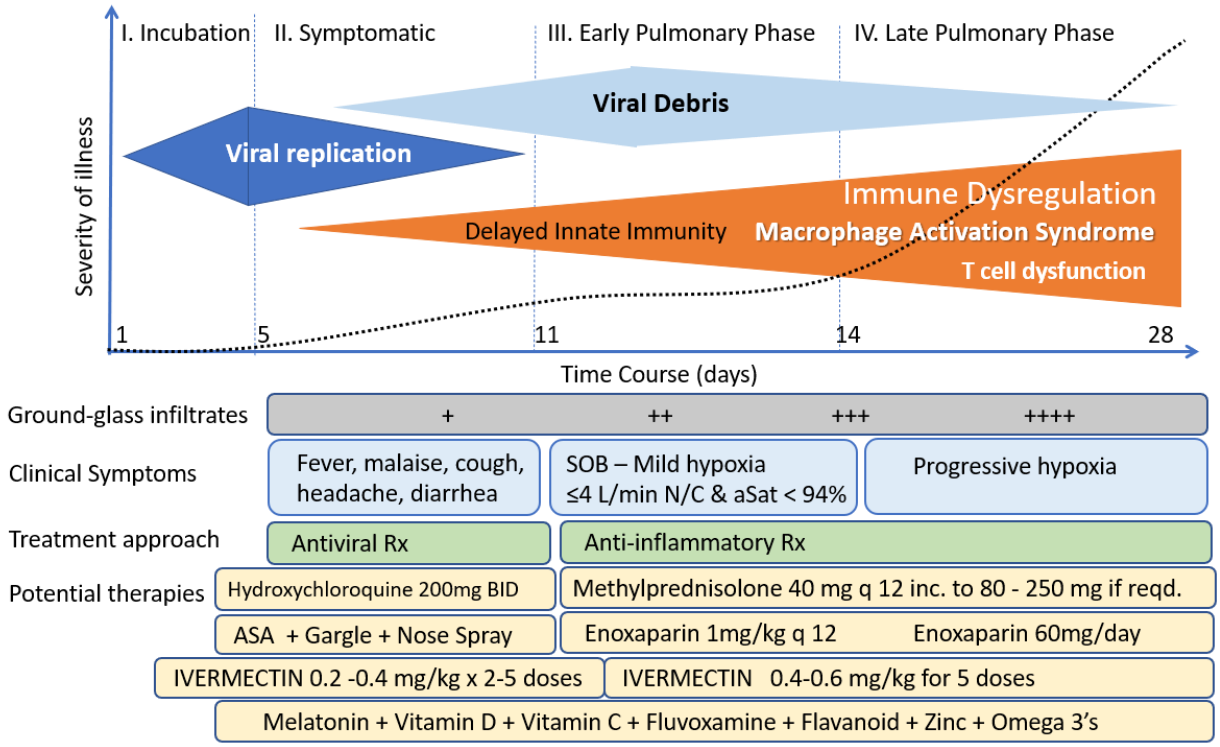
The combination of steroids and ascorbic acid (Vitamin C) is essential. Both have powerful synergistic anti-inflammatory actions. [80;81] Vitamin C protects the endothelium from oxidative injury. [82-85] Furthermore, Vitamin C Increases the expression of interferon-alpha [86] while corticosteroids (alone) 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

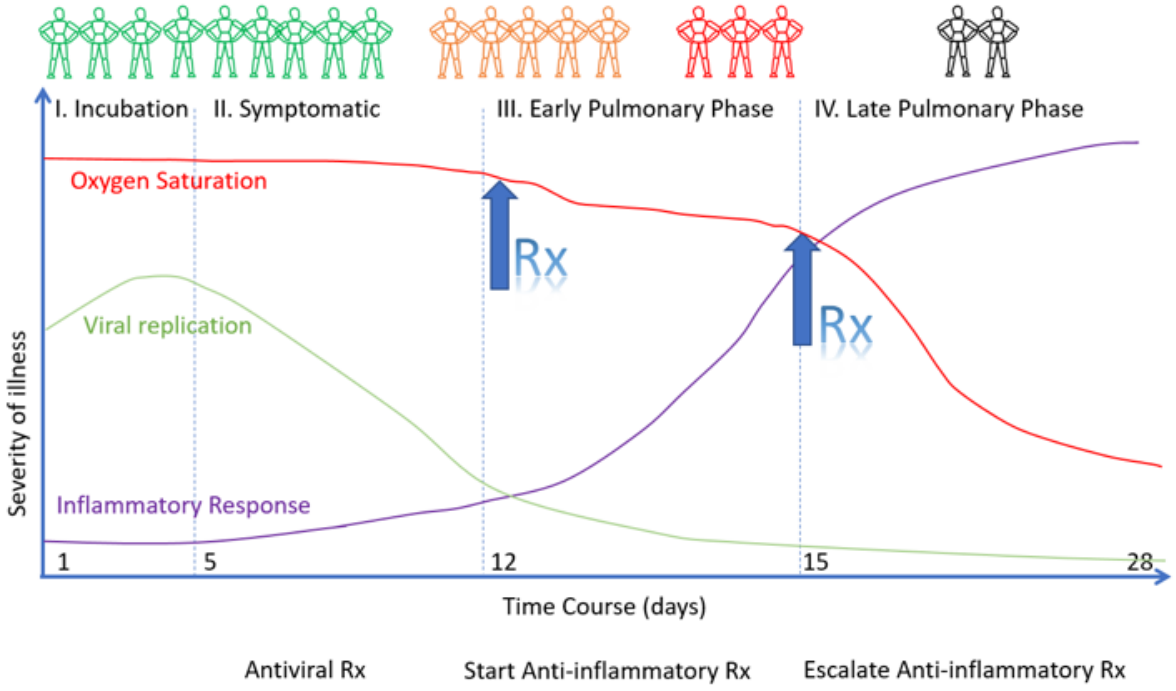
Source: FLCCC

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

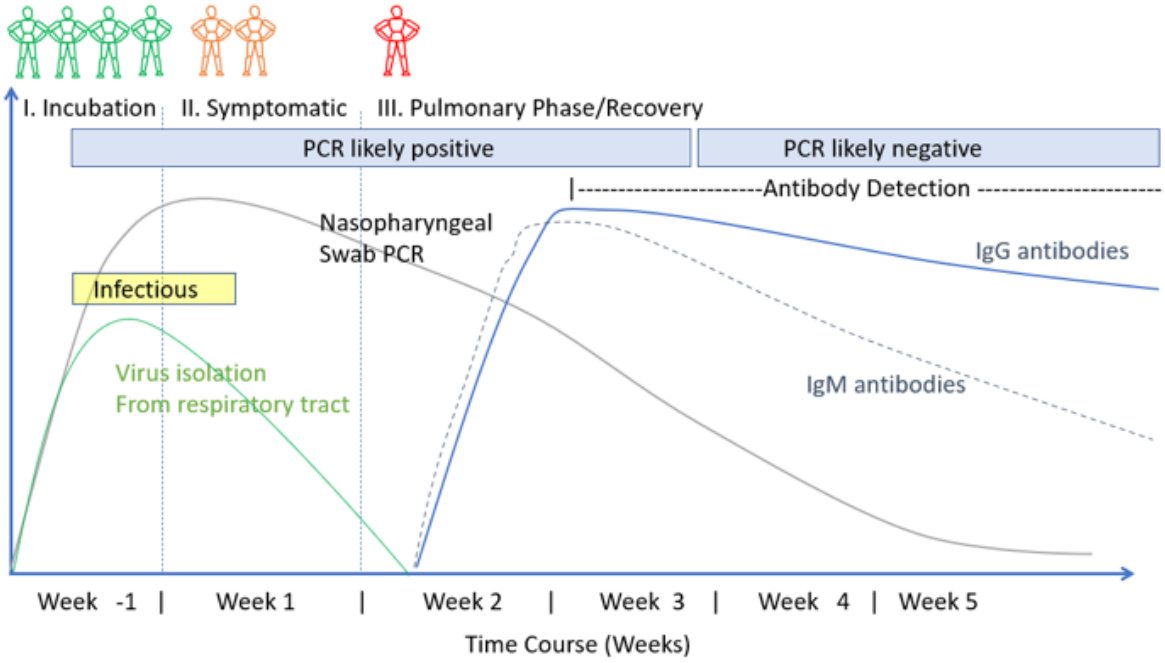
Note: Viral replication in Figures 2 and 3 are typical for the original Wuhan SARS-CoV-2 virus (Alpha strain). The time course of Omicron BA.4 and BA.5 appears to be contracted/shortened compared to the Wuhan (Alpha) strain.

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) 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]

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]

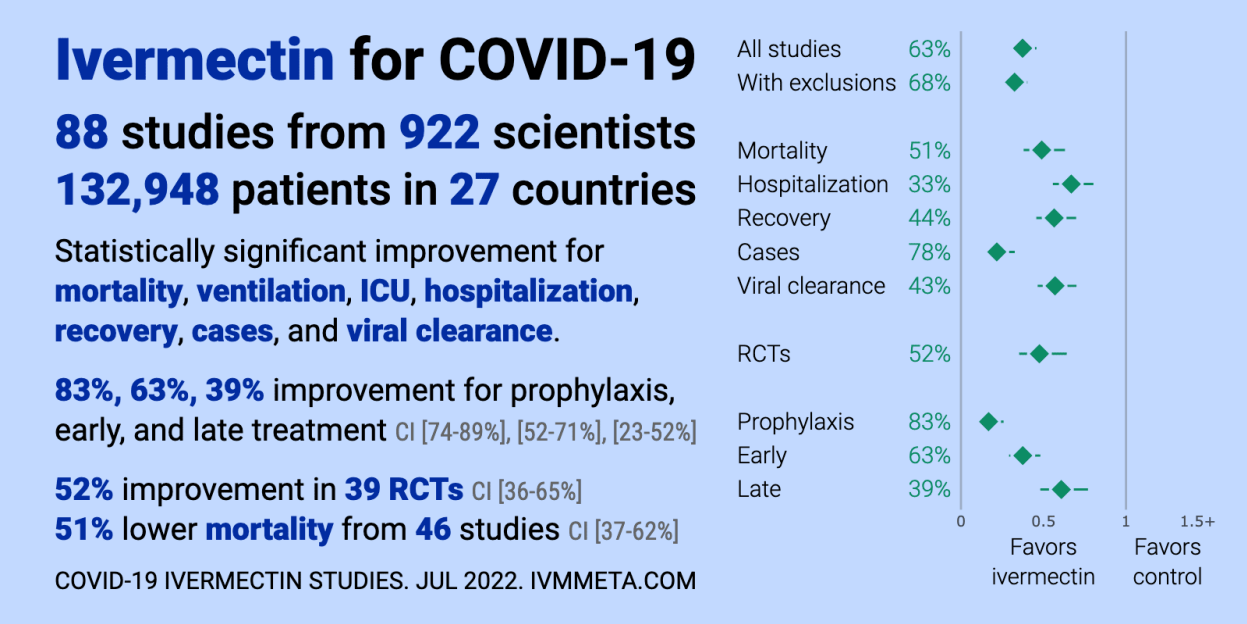
NOTE: Transfer patients to ICU as early as possible if respiratory symptoms worsen, oxygen requirements increase, or arterial desaturation emerges.

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

Body Weight (lbs.)	Body Weight (kgs)	Calcifediol (mg)	Equivalent in IU	If calcifediol is not available, a bolus of Vitamin D_3
15 – 21	7 – 10	0.1	16,000	20,000
22 – 30	10 – 14	0.15	24,000	35,000
31 – 40	15 – 18	0.2	32,000	50,000
41 – 50	19 – 23	0.3	48,000	60,000
51 – 60	24 – 27	0.4	64,000	75,000
61 – 70	28 – 32	0.5	80,000	100,000
71 – 85	33 – 39	0.6	96,000	150,000
86 – 100	40 – 45	0.7	112,000	200,000
101 – 150	46 – 68	0.8	128,000	250,000
151 – 200	69 – 90	1.0	160,000	300,000
201 – 300	91 – 136	1.5	240,000	400,000
>300	> 137	2.0	320,000	500,000

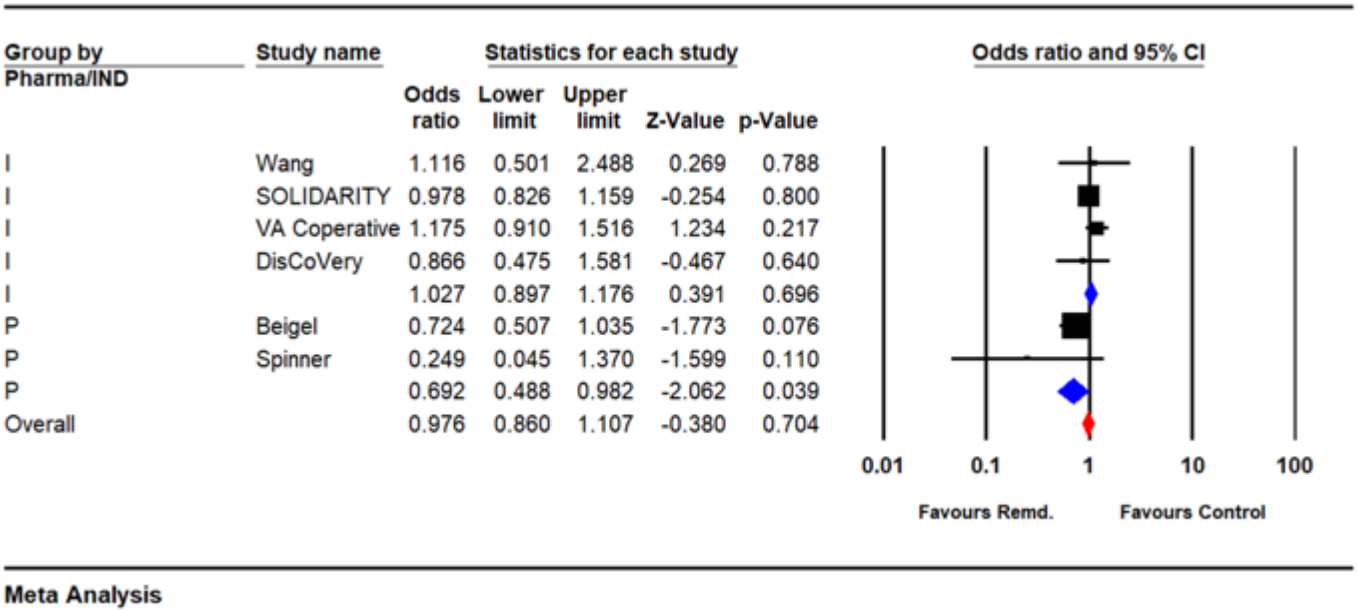
Source: From SJ Wimalawansa with permission

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)



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. [174;175] 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;176-186]. *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. [187] 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. [188] 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. [187] 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. [189] 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;178] 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). [190-192] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [193]

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;194]. 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 [195-200] Thiamine may play a role in dampening the cytokine storm. [196;201]
- **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). [202;203] **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.

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. [204] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [205-207]

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). [208-210]
- *Unclear benefit.* **Maraviroc** 300 mg twice daily for 10 days. Maraviroc is a CCR5 antagonist. [211] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19. [212;213] 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** [214-219] nor **monoclonal antibodies**. [220] However, convalescent serum/monoclonal antibodies may have a role in patients with hematologic malignancies. [221] The role of bebtetovimab requires further evaluation. [222]
- *Not recommended.* **Colchicine** (see above).
- *Not recommended.* **Tocilizumab**. Five RCTs have now failed to demonstrate a clinical benefit from tocilizumab. [223-227] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [228] Tocilizumab may have benefit in patients receiving an inadequate dose of corticosteroids. [229] 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

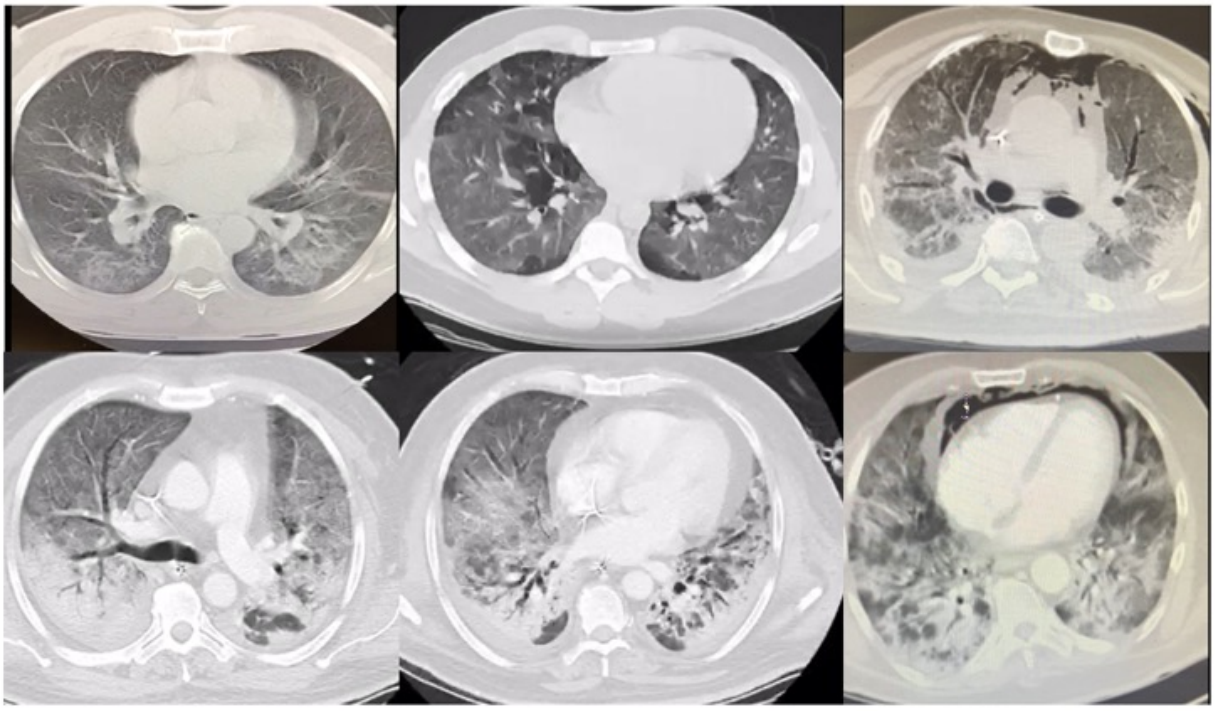
on CD14 monocytes, T cell dysfunction and decreased CD4 and CD8 counts) secondary bacterial and fungal infections (Candida and Aspergillus species) and viral reactivation is not uncommon. [230-232] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [233] 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 [234]
    d. Trial of inhaled Flolan (epoprostenol)
    e. Attempt proning (cooperative repositioning-proning) [235-238]
    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. [239;240] HFNC is a better option for the patient and the healthcare system than intubation and mechanical ventilation. HFNC is preferred over

conventional oxygen therapy. [234] 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 – RECOVERY (Hornsby et al) 6mg/day x 10 days	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4

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. [241] 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). [241-248] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19. [249;250] 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. [241] 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 [251-257]. 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. [187;188]
- 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. [258;259]
- 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". [260-263]
- ECMO [264-266]. 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. [267]
- Lung transplantation. [268]

Salvage Treatments of Unproven/No Benefit

- Convalescent serum/monoclonal antibodies: Four RCTs failed to demonstrate a clinical benefit with the use of convalescent serum. [214-216;218;219] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[269] 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. [270] Lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [271]

- In patients with progressive fibrosis, the combination of anti-fibrotic therapy with corticosteroids should be considered. [272-275] 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 [276;277] 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. [278] A PCT is essential to rule out coexisting bacterial pneumonia. [279]
- 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. [249;280] 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. [281]
- 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. [282;283]
- ECHO as clinically indicated; Patients may develop a severe “septic” cardiomyopathy and/or COVID-19 myocarditis. [284;285]

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. [286;287] Extended thromboprophylaxis (with a DOAC) should be considered in high-risk patients. Risk factors include: [288]

i. Increased D dimer (> 3 times ULN)

ii. Increased CRP (> 2 times ULN) [289]

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.

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