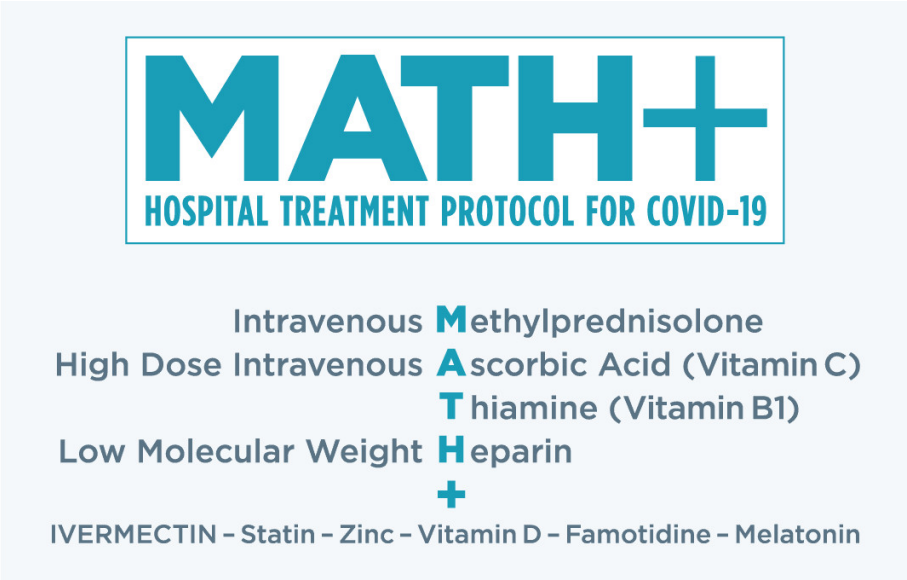
An overview of the MATH+, I-MASK+ and I-RECOVER Protocols

A Guide to the Management of COVID-19

Developed and updated by Paul Marik, MD, FCP (SA), FRCP (C), FCCP, FCCM for the COVID-19 Critical Care Alliance (FLCCC Alliance).

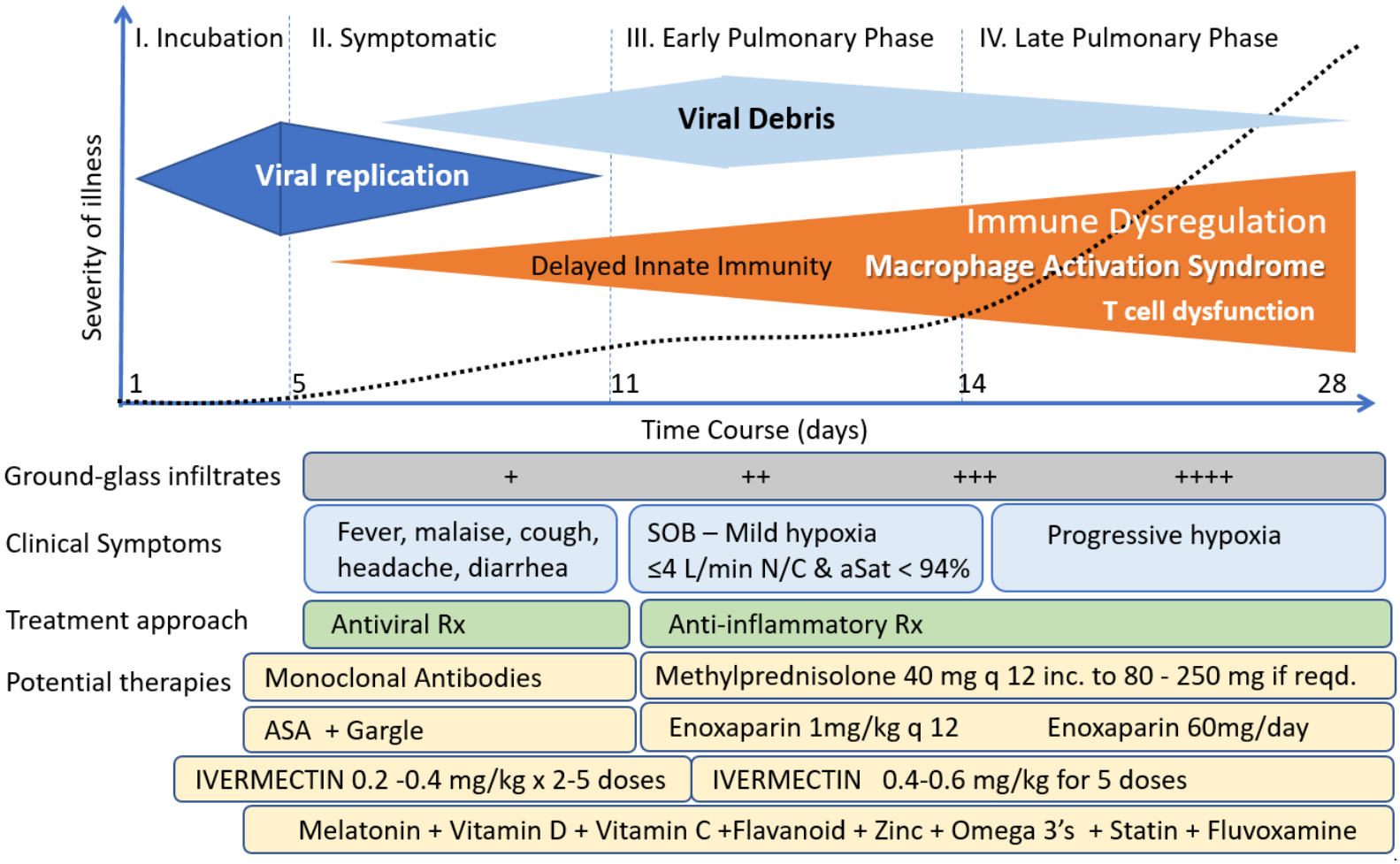
This is our recommended approach to COVID-19 based on the best (and most recent) literature. This is a highly dynamic topic; therefore, we will be updating the guideline as new information emerges. Please check on the FLCCC Alliance website for updated versions of this protocol. www.flccc.net



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

The FLCCC Alliance™ is registered as a 501(c)(3) non-profit organization.

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



THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL-

Not too early Not too late.

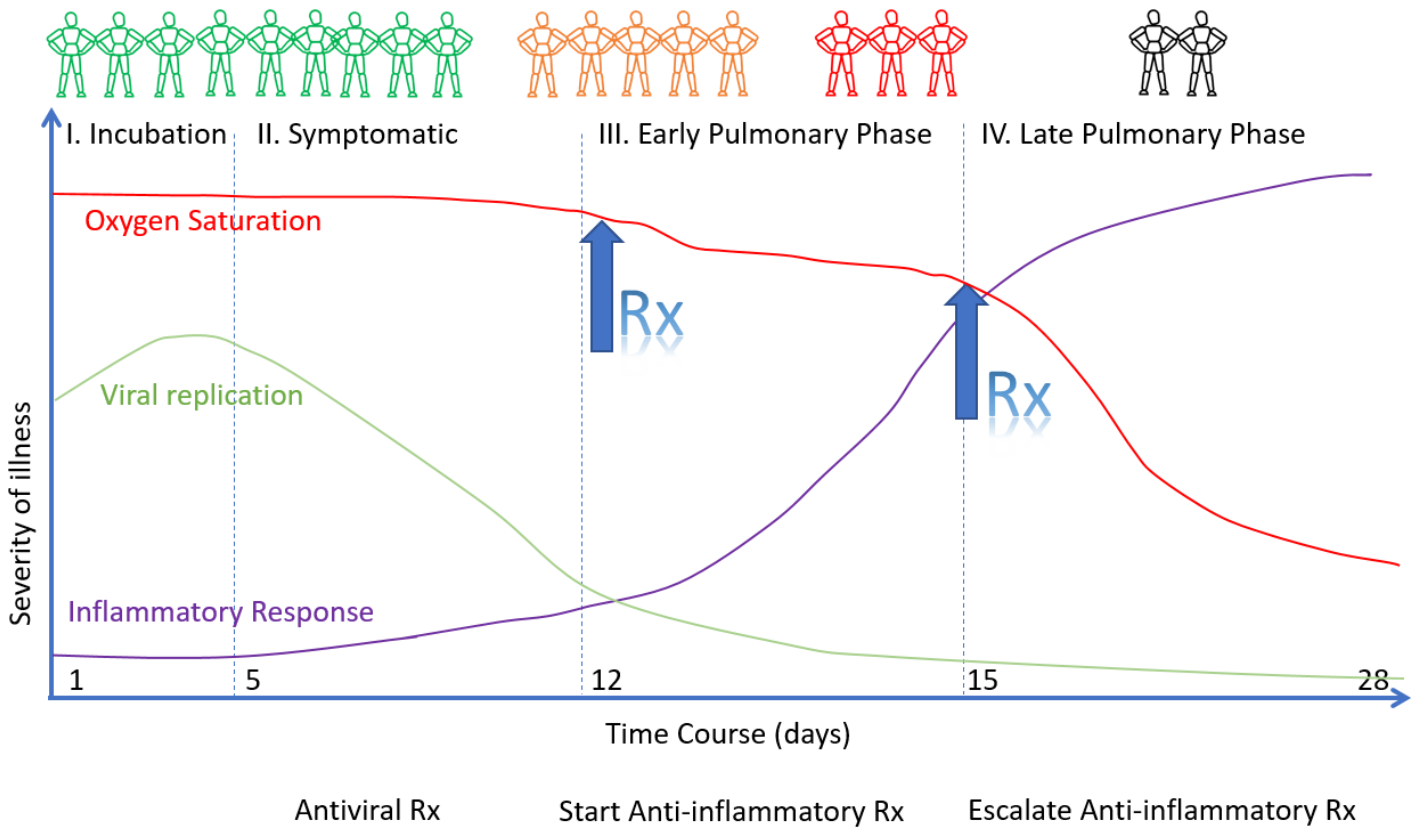
Table 1. Pharmacological therapy for COVID by stage of illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	?? Benefit	Unclear benefit	?Trend to harm
Remdesivir	n/a	No Benefit	Reduced time to recovery? No mortality benefit
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ? Benefit	No benefit	Harm
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	No Benefit
Monoclonal Abs	BENEFIT	Marginal Benefit	Harm
Colchicine	n/a	Unclear benefit	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
LMWH	n/a	n/a	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Anti-androgen Rx	?? Benefit	BENEFIT	BENEFIT

*Based on randomized controlled trials (see supporting information below)
?? based on observational data

Randomized Controlled Trials

Figure 2. Timing of the initiation of anti-inflammatory therapy



Note: Viral Replication in Figures 2 and 3 are typical for the original Wuhan SARS-CoV-2 virus. SARS-CoV-2 delta and gamma (P1) variants may present prolonged duration of viral replication. Furthermore, the time course from incubation to symptom onset and to the pulmonary phase may be shortened.

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

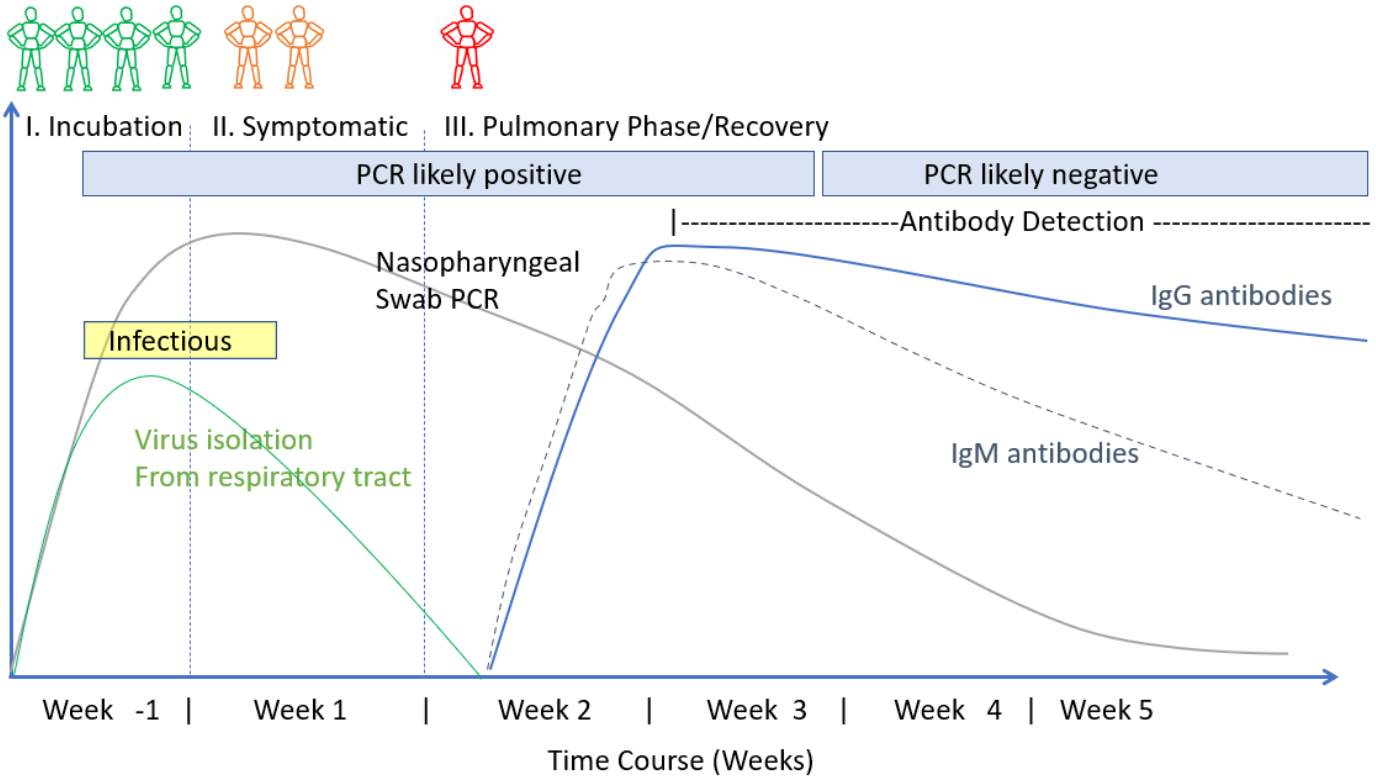
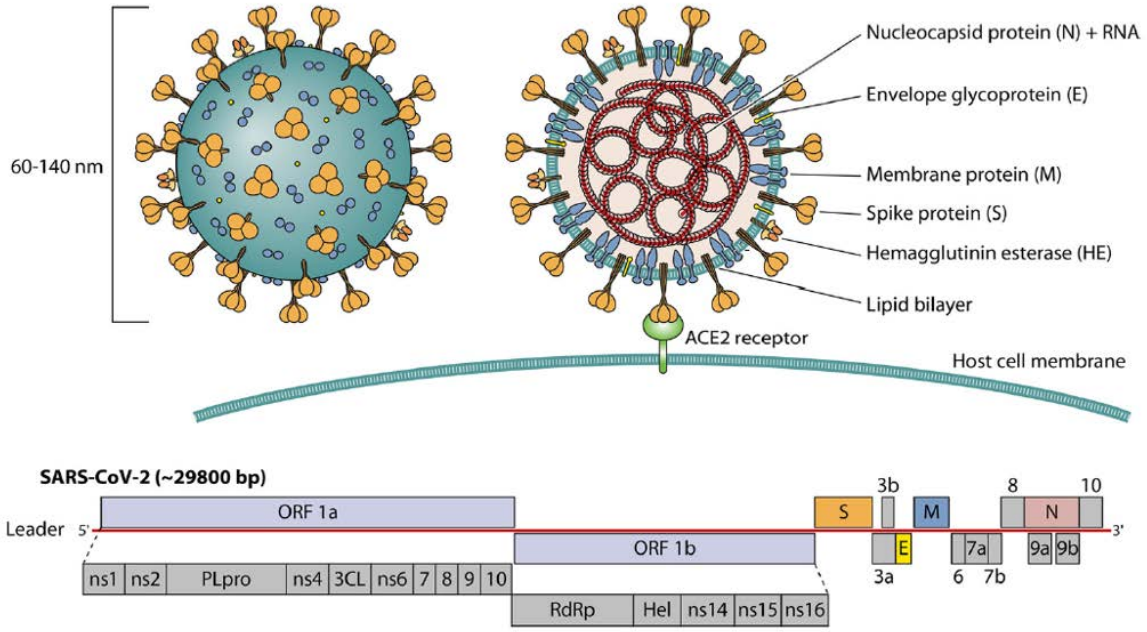


Figure 4. SARS-Co-V-2 Structure and RNA genome



While there is **no cure or "Magic-bullet"** for COVID-19, recently, a number of therapeutic agents have shown great promise for both the prevention and treatment of this disease including Ivermectin, Vitamin D, quercetin, melatonin, Vitamin C, fluvoxamine and corticosteroids. It is likely that no single drug will be effective in treating this complex disease and that multiple drugs with different mechanisms of action used in specific phases of the disease will be required. Furthermore, a growing body of evidence suggests that many of these agents may act synergistically in various phases of the disease. [1-3]

As the pandemic has played out over the last year over four million patients have died world-wide, and the pandemic shows no signs of abating. Most countries across the globe have limited resources to manage this humanitarian crisis. We developed the **MATH+ protocol** to provide guidance for the treatment of the pulmonary phase of this disease with the goal of reducing the hospital mortality from this devastating disease. However, it soon became obvious that our emphasis needed to shift to the prevention and early (home) treatment of this catastrophic disease to prevent patients progressing to the pulmonary phase and requiring hospitalization (see Figure 5). Hence, we developed the **I-MASK+ and the Test and Treat protocols.** While we strongly believe that such an approach can mitigate the development and progression of this disease, limit deaths, and allow the economy to re-open, "Health-Care authorities" across the globe have been silent in this regard, including the WHO, CDC, NIH, etc (see NIH Guidance, Figure 6a and 6b). While vaccination is part of the solution, it will take many months if not years to vaccinate 70-85% of the world's population of 7.8 billion people required for "herd immunity". We believe that the **I-MASK+** protocol provides a bridge to universal vaccination. Furthermore, we have developed the **I-MASS protocol** for a MASS Distribution campaign to lessen the impact of COVID-19 in resource-poor countries. Mutant strains of SARS-CoV-2 have recently appeared, these stains have demonstrated increased transmissibility.[4,5] [6] Many of these mutations involve the spike protein (against which almost all of the vaccines have targeted), raising the real possibility that the vaccines may become less effective against the mutating strains of SARS-CoV-2.[5,7,8] And, finally the Post-COVID syndrome or "long-hauler syndrome" has emerged as a common and disabling disorder its pathophysiology of which is poorly understood. We offer the **I-RECOVER** protocol to help treat this disabling disorder. Recently, the post-vaccination syndrome has emerged as a problematic entity; we believe that the **I-RECOVER** protocol has utility in treating this syndrome.

Figure 5. Treatment Phases of COVID-19

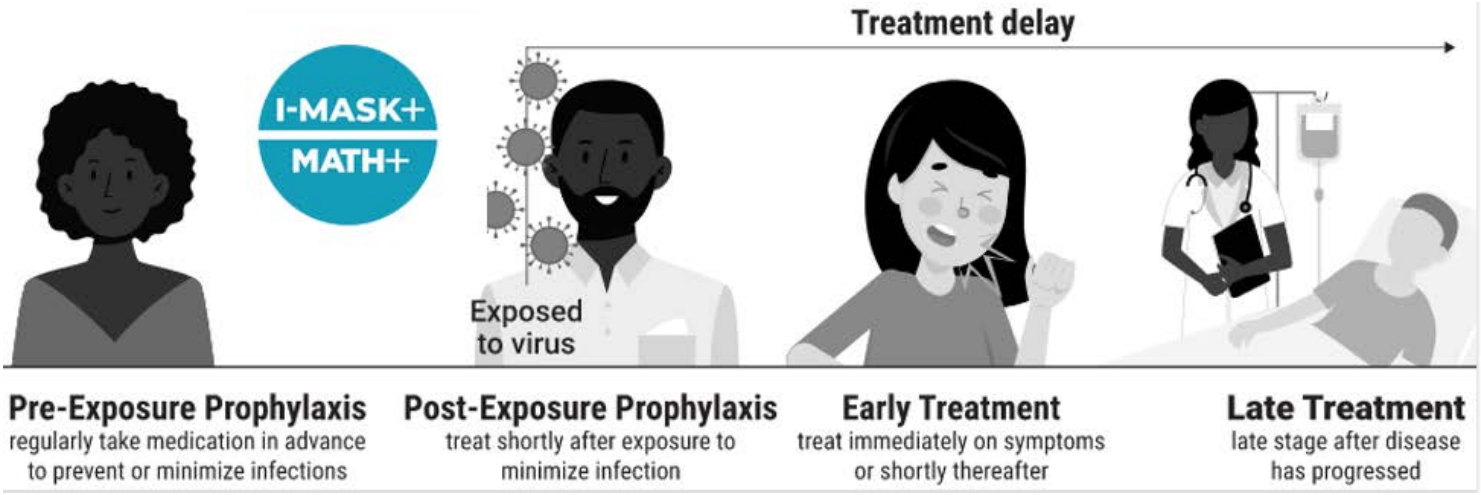


Figure 6a. NIH Recommendations for the Treatment of COVID-19 across the stages of the disease.

Clinical Management Summary

Last Updated: July 8, 2021

NIH | COVID-19 Treatment Guidelines

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(BIIa)**

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

Figure 6b. NIH Recommendations for the prevention and prophylaxis of COVID-19.

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: July 8, 2021

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines **(AI)**.
- The Panel **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**.
- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**.
- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**.

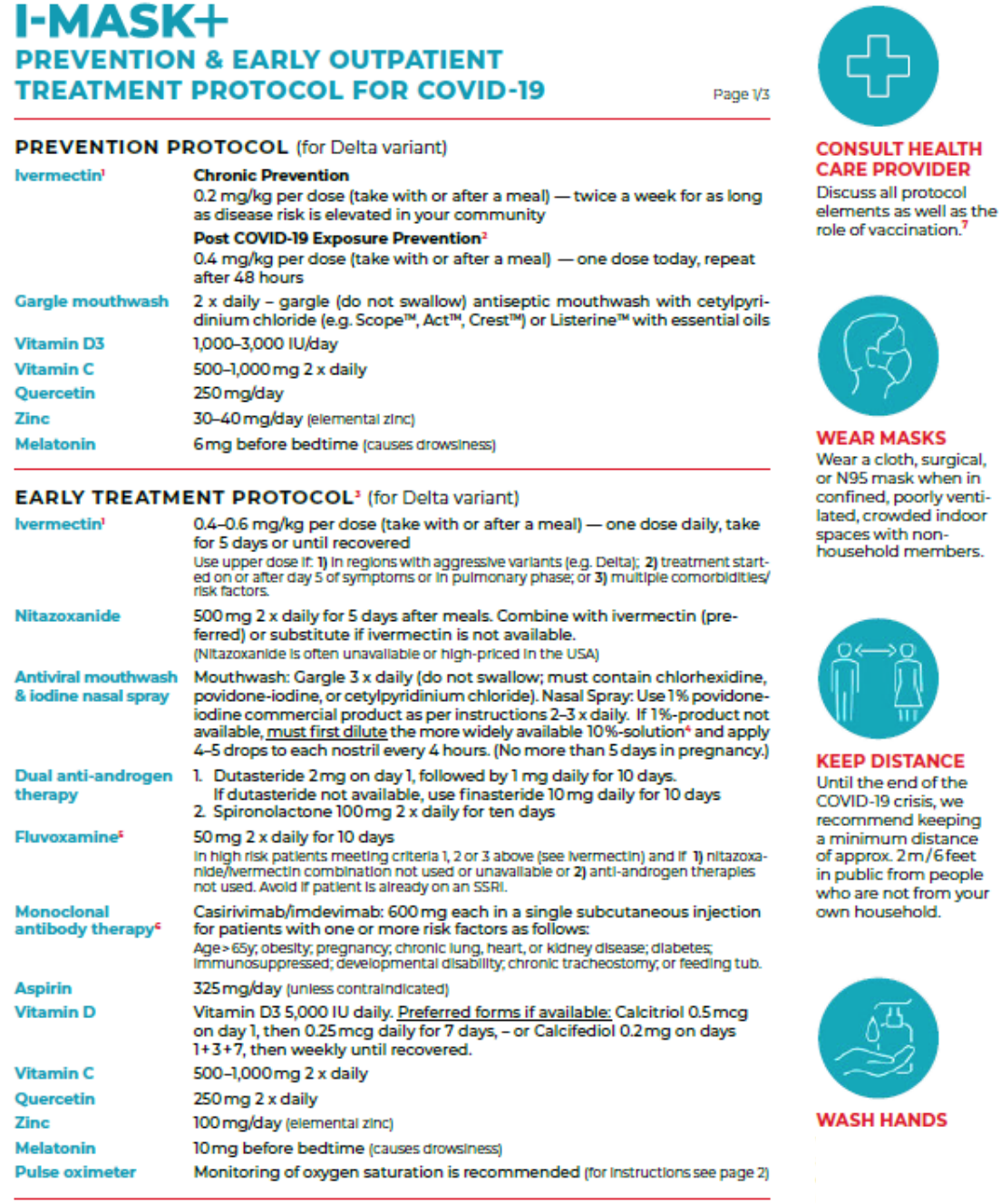
Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Pre and Postexposure Prophylaxis (The I-MASK+ protocol)

The components of the I-MASK Prophylaxis and Early Treatment protocol are illustrated in Figures 7. Recent data suggests that ivermectin, melatonin as well as the combination of quercetin (or mixed flavonoids) and vitamin C may play an important role in both pre-exposure and postexposure prophylaxis. [2,9] The evidence supporting the use of Ivermectin for the prophylaxis of COVID-19 is provided by the comprehensive review by Kory et al. [10] It is important to emphasize that ALL of the medications included in our prophylactic regimen are inexpensive, safe, and widely available. The I-MASK + protocol MUST be part of an overall strategy which includes common sense public health measures, i.e., masks, social distancing, and avoidance of large groups of people.[11]

Figure 7. The I-MASK prophylactic and Early Treatment Protocol.



I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

Page 1/3

PREVENTION PROTOCOL (for Delta variant)

Ivermectin[1]	**Chronic Prevention** 0.2 mg/kg per dose (take with or after a meal) — twice a week for as long as disease risk is elevated in your community **Post COVID-19 Exposure Prevention**[2] 0.4 mg/kg per dose (take with or after a meal) — one dose today, repeat after 48 hours
Gargle mouthwash	2 x daily – gargle (do not swallow) antiseptic mouthwash with cetylpyridinium chloride (e.g. Scope™, Act™, Crest™) or Listerine™ with essential oils
Vitamin D3	1,000–3,000 IU/day
Vitamin C	500–1,000 mg 2 x daily
Quercetin	250 mg/day
Zinc	30–40 mg/day (elemental zinc)
Melatonin	6 mg before bedtime (causes drowsiness)

EARLY TREATMENT PROTOCOL[3] (for Delta variant)

Ivermectin[1]	0.4–0.6 mg/kg per dose (take with or after a meal) — one dose daily, take for 5 days or until recovered Use upper dose if: **1)** in regions with aggressive variants (e.g. Delta); **2)** treatment started on or after day 5 of symptoms or in pulmonary phase; or **3)** multiple comorbidities/risk factors.
Nitazoxanide	500 mg 2 x daily for 5 days after meals. Combine with ivermectin (preferred) or substitute if ivermectin is not available. (Nitazoxanide is often unavailable or high-priced in the USA)
Antiviral mouthwash & iodine nasal spray	Mouthwash: Gargle 3 x daily (do not swallow; must contain chlorhexidine, povidone-iodine, or cetylpyridinium chloride). Nasal Spray: Use 1% povidone-iodine commercial product as per instructions 2–3 x daily. If 1%-product not available, must first dilute the more widely available 10%-solution[4] and apply 4–5 drops to each nostril every 4 hours. (No more than 5 days in pregnancy.)
Dual anti-androgen therapy	1. Dutasteride 2 mg on day 1, followed by 1 mg daily for 10 days. If dutasteride not available, use finasteride 10 mg daily for 10 days 2. Spironolactone 100 mg 2 x daily for ten days
Fluvoxamine[5]	50 mg 2 x daily for 10 days In high risk patients meeting criteria 1, 2 or 3 above (see Ivermectin) and if **1)** nitazoxanide/ivermectin combination not used or unavailable or **2)** anti-androgen therapies not used. Avoid if patient is already on an SSRI.
Monoclonal antibody therapy[6]	Casirivimab/imdevimab: 600 mg each in a single subcutaneous injection for patients with one or more risk factors as follows: Age > 65y; obesity; pregnancy; chronic lung, heart, or kidney disease; diabetes; immunosuppressed; developmental disability; chronic tracheostomy; or feeding tub.
Aspirin	325 mg/day (unless contraindicated)
Vitamin D	Vitamin D3 5,000 IU daily. Preferred forms if available: Calcitriol 0.5 mcg on day 1, then 0.25 mcg daily for 7 days, – or Calcifediol 0.2 mg on days 1+3+7, then weekly until recovered.
Vitamin C	500–1,000 mg 2 x daily
Quercetin	250 mg 2 x daily
Zinc	100 mg/day (elemental zinc)
Melatonin	10 mg before bedtime (causes drowsiness)
Pulse oximeter	Monitoring of oxygen saturation is recommended (for instructions see page 2)

CONSULT HEALTH CARE PROVIDER
Discuss all protocol elements as well as the role of vaccination.[7]

WEAR MASKS
Wear a cloth, surgical, or N95 mask when in confined, poorly ventilated, crowded indoor spaces with non-household members.

KEEP DISTANCE
Until the end of the COVID-19 crisis, we recommend keeping a minimum distance of approx. 2 m / 6 feet in public from people who are not from your own household.

WASH HANDS

Components of the I-MASK Prophylactic Protocol

- Ivermectin for postexposure prophylaxis (see ClinTrials.gov NCT04422561). 0.4 mg/kg immediately then repeat 2nd dose in 48 hours. Ivermectin is best taken with a meal or just following a meal (greater absorption). [12] Oropharyngeal sanitation also suggested (see section on home treatment below).
- Ivermectin for pre-exposure prophylaxis (in HCW) and for prophylaxis in high-risk individuals (> 60 years with co-morbidities, morbid obesity, long term care facilities, etc). 0.2 mg/kg per dose - start treatment with one dose, 2nd dose 48 hours later, then 1 dose every 7 days (i.e. weekly).[13-18] For those at high risk of contracting COVID-19 we now recommend twice weekly dosing. See dosing Table below. Ivermectin has a number of potentially serious drug-drug interactions; please check for potential drug interactions at Ivermectin Drug Interactions - Drugs.com (also see below) . The most important drug-drug interactions occur with cyclosporin, tacrolimus, anti-retroviral drugs, and certain antifungal drugs. While ivermectin has a remarkable safety record, [19] fixed drug eruptions (diffuse rash) and Stevens Johnson Syndrome have rarely been reported. [20,21] While hepatitis is commonly quoted as a side effect, we are aware of one published case report of reversible hepatitis.[22] The safety of ivermectin in pregnancy has not been determined. [23] Ivermectin may increase the risk of congenital malformations particularly when used in the first trimester. [23] US Food and Drug Administration (FDA) has classified ivermectin as pregnancy category C—i.e, "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks". In pregnant patients with symptomatic COVID-19 infections the risk and benefits of ivermectin should be discussed with the patient, and informed consent obtained from the patient should the drug be prescribed. Additionally, women should be counselled that low concentrations of ivermectin are present in breast milk; the implications of this finding are unclear. [24]
- Vitamin D3 1000–3000 IU/day (25-75 mcg). An alternative strategy is 40 000 IU weekly. Note RDA (Recommended Daily Allowance) is 800–1000 IU/day. The safe upper-dose daily limit is likely < 4000 IU/day. Vitamin D insufficiency has been associated with an increased risk of acquiring COVID-19 and from dying from the disease. [25-49] Vitamin D supplementation may therefore prove to be an effective and cheap intervention to lessen the impact of this disease, particularly in vulnerable populations, i.e., the elderly, those of color, obese and those living > 45° latitude. [31-46,49] It is likely that the greatest benefit from vitamin D supplementation will occur in vitamin D insufficient individuals who take vitamin D prophylactically; once vitamin D insufficient individuals develop COVID-19 the benefits will likely be significantly less. [50] This concept is supported by a recent study which demonstrated that residents of a long-term care facility who took vitamin D supplementation had a much lower risk of dying from COVID-19. [47]
- Vitamin C 500 – 1000 mg BID (twice daily) and Quercetin 250 mg daily. [51-63] Due to the possible drug interaction between quercetin and ivermectin (see below) these drugs should not be taken simultaneously (i.e. should be staggered morning and night). Vitamin C has important anti-inflammatory, antioxidant, and immune enhancing properties, including increased synthesis of type I interferons.[54,64,65] Quercetin has direct virucidal properties against a range of viruses, including SARS-CoV-2, and is a potent antioxidant and anti-inflammatory agent. [52,57,62,62,66-74] Quercetin is a potent inhibitor of inflammasome activation, which believed to play a major role in the pathophysiology of the COVID-19 immune dysfunction.[74] In addition, quercetin acts as a zinc ionophore. [75] It is likely that vitamin C and quercetin have synergistic prophylactic benefit. [2] A mixed flavonoid supplement containing quercetin, green tea catechins and anthrocyanins (from berries) may be preferable to a quercetin supplement alone; [76-80] this may further minimize the risk of quercetin related side-effects. It should be

noted that *in vitro* studies have demonstrated that quercetin and other flavonoids interfere with thyroid hormone synthesis at multiple steps in the synthetic pathway. [81-84] The use of quercetin has rarely been associated with hypothyroidism. The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with subclinical thyroidism.[85] In women high consumption of soya was associated with elevated TSH concentrations.[86] The effect on thyroid function may be dose dependent, hence for chronic prophylactic use we suggest that the lowest dose be taken. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored. It should also be noted quercetin may have important drug-drug interactions; the most important drug-drug interaction is with cyclosporin and tacrolimus. [87] In patients taking these drugs it is best to avoid quercetin; if quercetin is taken cyclosporin and tacrolimus levels must be closely monitored.

- Melatonin (slow release): Begin with 0.3 mg and increase as tolerated to 6 mg at night. [1,9,88-94]. Melatonin has anti-inflammatory, antioxidant, immunomodulating and metabolic effects that are likely important in the mitigation of COVID-19 disease.[95-97] A recent large retrospective study demonstrated that the use of melatonin in intubated patients with COVID-19 significantly reduced the risk of death (HR 0.1; p=0.0000000715).[96] It is intriguing to recognize that bats, the natural reservoir of coronavirus, have exceptionally high levels of melatonin, which may protect these animals from developing symptomatic disease. [98] The slow release (extended release) formulation of melatonin is preferred as it more closely replicates the normal circadian rhythm. [88] There is marked inter-individual variation in the metabolism of melatonin (first pass metabolism) hence the dose must be individualized.[88] High serum levels are associated with hyper-REM sleep and bad dreams. Rapid release melatonin (usual over the counter formulation) results in early high peaks that do not replicate the normal circadian pattern; hence it is important to take the slow release/extended release formulation.
- Zinc 30–50 mg/day (elemental zinc). [58,60,61,99-103] Zinc is essential for innate and adaptive immunity.[101] In addition, Zinc inhibits RNA dependent RNA polymerase *in vitro* against SARS-CoV-2 virus.[100] Due to competitive binding with the same gut transporter, prolonged high dose zinc (> 50mg day) should be avoided as this is associated with copper deficiency. [104] Commercial zinc supplements contain 7 to 80 mg of elemental zinc, and are commonly formulated as zinc oxide or salts with acetate, gluconate, and sulfate. 220 mg zinc sulfate contains 50 mg elemental zinc.
- B complex vitamins [105-109].
- Oropharyngeal hygiene with twice daily antiviral mouthwash/gargle (see below).
- Monoclonal antibodies for postexposure prophylaxis. A single subcutaneous injection of REG-COV2 (a combination of the monoclonal antibodies casirivimab and imdevimab) has been demonstrated to reduce the risk of symptomatic COVID-19 infection in close contacts by 92.6% (7.8% to 1.5%). [110] Monoclonal antibodies are recommended in high risk individuals, namely; > 65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunosuppressed, coronary heart disease, etc. See infusioncenter.org and call 1-877-332-6585 In USA for eligibility and location.
- *Optional:* Famotidine 20–40 mg/day [111-117]. Low level evidence suggests that famotidine may reduce disease severity and mortality. However, the findings of some studies are contradictory. While it was postulated that famotidine inhibits the SARS-CoV-2 papain-like protease (PLpro) as well as the main protease (3CLpro) this mechanism has been disputed. [114] Furthermore, a number of studies have demonstrated an association between the use of proton pump inhibitors (PPI's) with an increased risk of contracting COVID-19 and with worse outcomes. [118,119] This data suggest that famotidine may be the drug of choice when acid suppressive therapy is required.

Disclaimer: The safety of ivermectin in pregnancy has not been established. Particularly the use in the 1st trimester should be discussed with your doctor beforehand.

Ivermectin dosing: 200 ug/kg (0.2mg/kg) or fixed dose of 12 mg (≤ 80kg) or 18 mg (≥ 80kg).[120] Depending on the manufacturer ivermectin is supplied as 3mg, 6 mg or 12 mg tablets.

50-64.9 kg - 12mg
65-79.9 kg - 15mg
80-94.9 kg - 18mg
95-109.9 kg - 21mg
≥ 110 kg - 24mg

Drug Interactions with Ivermectin

Drug Interactions. (From Medscape).
https://reference.medscape.com/drug/stromectol-ivermectin-342657#3
Patents taking any of these medications should discuss with their treating physicians.

DRUG INTERACTIONS WITH IVERMECTIN			
SERIOUS (4) Use Alternative	MONITOR CLOSELY (possible) (49) Especially those with (*)		
Erdafitinib	Amiodarone	Glecaprevir/Pibrentasvir	Phenytoin
Lasmiditan	Atorvastatin	Indinavir	Ponatinib
Quinidine	Berotralstat	Istradefylline	Quercetin (**)
Tepotinib	Bosutinib	Itraconazole (*)	Ranolazine
	Clarithromycin (*)	Ivacaftor	Rifampin (*)
	Clotrimazole	Ketoconazole (*)	Ritonavir (*)
	Dronedarone	Lapatinib	Sarecycline
	Elagolix	Lomitapide	Simvastatin
	Eliglustat	Lonafarnib	Sirolimus (*)
	Erythromycin base	Loratadine	St John's Wort
	Erythromycin ethylsuccinate (*)	Lovastatin	Stiripentol
	Erythromycin lactobionate (*)	Nefazodone	Tacrolimus (*)
	Erythromycin stearate (*)	Nicardipine	Tolvaptan
	Felodipine	Nifedipine	Trazodone
	Fosphenytoin	Nilotinib	Tucatinib
	Fostamatinib	Phenobarbital	Verapamil (*)
			Warfarin (*)

(**) Not clear. May increase ivermectin levels

Symptomatic patients at home (I-MASK+ EARLY Treatment Protocol)

- Ivermectin 0.4- 0.6 mg/kg – one dose daily for 5 days or until recovered. [15,19,25-28,121-136]. Higher doses (0.6 mg/kg) often required in a) regions with more aggressive variants, b) treatment started on or after 5 days of symptoms or c) in patients in pulmonary phase, d) extensive CT involvement or e) extensive comorbidities/risk factors (older age, obesity, diabetes). Ivermectin is best taken with a meal or just following a meal (greater absorption). See drug-drug interactions above. It should be noted that multiday treatment has been shown to be more clinically effective than single-day dosing.
- Nitazoxanide (NTZ) 600 mg BID for 5 days was shown to reduce disease progression, hospitalization and death when used early in outpatients with mild to moderate disease.[137] The combination of NTZ and ivermectin has been shown to reduce viral clearance and symptom progression in outpatients with COVID-19. [138,139] NTZ is an oral antiparasitic drug having activity against many protozoa and helminths, and similar to Ivermectin has been shown to have antiviral and immune-modulatory effects.[140,141] Like ivermectin NTZ has broad spectrum antiviral activity that includes SARS-CoV-2.[141-144] Furthermore, as NTZ and ivermectin have differing modes of action it is likely that these two drugs have synergistic antiviral and anti-inflammatory effects.[139,142,145] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
- Oropharyngeal sanitization. [146] Inhaled steam supplemented with antimicrobial essential oils (e.g VapoRub™ inhalations) has been demonstrated to have virucidal activity. [147] Antiseptic-antimicrobial mouthwashes (chlorhexidine, povidone-iodine, cetylpyridinium chloride and the combination of eucalyptus, menthol and thymol [Listerine™]) have been shown to inhibit SARS-CoV-2 replication and to reduce viral load in research studies. [148-155] A mouthwash containing cetylpyridinium chloride (CPC) has broad antimicrobial properties and has been shown to be effective in controlling gingivitis and gingival plaque.[155-157] An *in-vitro* study demonstrated that CPC was highly viricidal against a human coronavirus.[158] In a primary prophylaxis study, a povidone-iodine throat spray administered three times daily proved to be highly effective in reducing the risk of laboratory confirmed SARS-CoV-2 infection. In patients with symptomatic disease treated at home with a 1% povidone iodine mouthwash/gargle together with nasal and eye drops resulted in a dramatic reduction in morbidly, hospitalization and death. [159] A nasal spray with 1% povidone-iodine (for example Immune Mist ™) administered 2-3 times per day is recommended in postexposure prophylaxis and in symptomatic patients (early phase of COVID-19 infection).[150] Due to low level systemic absorption povidone-iodine nasal spray should not be used for longer than 5-7 days in pregnant women. While the use of an iodine containing mouth wash over a 6-month period was demonstrated to increase serum iodine levels, thyroid function tests remained unchanged. [160] Oropharyngeal sanitization will likely reduce the viral load in the upper airways, thereby reducing the risk of symptomatic disease and likely reducing disease severity. This may be particularly important with the Delta variant which replicates to achieve viral high loads in the nasopharynx/ oropharynx.
- Anti-androgen therapy. Androgens augment SARS-CoV-2 infectivity by promoting the expression of transmembrane protease (TMPRSS2) that primes the spike viral entry protein.[161] In addition androgens are pro-inflammatory.[162]. 5-alpha reductase inhibitors such as dutasteride and finasteride block the conversion of testosterone to the biologically more active hormone dihydrotestosterone. Finasteride has a very short half-life of 6 hours, compared to 5 weeks for dutasteride. [163,164] Proxalutamide is a potent antiandrogen that block the androgen receptor. The mineralocorticoid receptor antagonist spironolactone is a known androgen receptor antagonist. Both spironolactone and dutasteride decrease expression of

TMPRSS2.[165] Multiple clinical studies support the notion that androgens exacerbate COVID-19 anti-androgen therapy consistently demonstrate a dramatic improvement in clinical outcomes. The anti-androgens dutasteride, proxalutamide and spironolactone have been demonstrated to reduce time to viral clearance, improved time to recovery and reduced hospitalization (outpatients) as well as reduced mortality (hospitalized patients) in both men and women. [166-172] Dutasteride has been used in women with alopecia and reported to be safe. [173,174] However, this agent **MUST** be avoided in pregnant women. We therefore recommend dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. The optimal anti-androgenic dose of spironolactone appears to be 100 mg BID. It should be noted that spironolactone has a favorable effect on the renin-angiotensin-aldosterone-system (RAAS).[175,176] It should be noted that proxalutamide is not currently available in most countries.

- Fluvoxamine 50 – 100 mg BID. [177-181] This SSRI is recommended in those patients with more severe symptoms/more advanced disease. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that activates sigma-1 receptors decreasing cytokine production. [177,178] In addition, fluvoxamine reduces serotonin uptake by platelets, reduces histamine release from mast cells, interferes with lysosomal trafficking of virus and inhibits melatonin degradation.[182,183] Antidepressant medications (SSRI) deplete platelet serotonin content, thereby diminishing the release of serotonin following platelet aggregation.[184-186] The use of antidepressants has be associated with a lower risk of intubation and death in patients hospitalized with COVID-19. [180,181] Fluoxetine (Prozac; 20-40mg daily), has activity against the sigma-1 receptor and is an alternative should fluvoxamine not be available. [187]
- Vitamin C 500 – 1000 mg BID and Quercetin 250 mg BID (or mixed flavonoid supplement). Due to the possible drug interaction between quercetin and ivermectin (see above) these drugs ***should not be taken simultaneously*** (i.e., should be staggered morning and night).
- Zinc 75–100 mg/day (elemental zinc)
- Melatonin 10 mg at night (the optimal dose is unknown) [94-97] The slow release/extended-release preparation is preferred as it minimizes the risk of bad dreams.
- Vitamin D 3 5000 IU daily (125 mcg). Calcitriol 0.25 ug/day or Calcifediol 0.2 mg day 1, day 3 and day 7 then weekly are alternative options,[188] however availability and cost may be an issue . In the acute setting calcifediol appears to be more effective than vitamin D3.[189] Calcifediol is more efficiently absorbed, achieves 25-OH vitamin D levels quicker and is three times more potent than vitamin D3. [190,191] However, it is important to note that the optimal dose of vitamin D in the acute setting is unknown.[192,193] Very high doses may paradoxically block the vitamin D receptor.
- ASA 325 mg/day (unless contraindicated). ASA has anti-inflammatory, antithrombotic, immunomodulatory, and antiviral effects.[194-196] Platelet activation plays a major role in propagating the prothrombotic state associated with COVID-19. [197-199]
- Monoclonal antibodies *for early outpatient treatment*. In the REG-COV2 outpatient study 4057 patients with at least one risk factor for severe COVID were randomized to a single intravenous infusion of REG-COV2 (a combination of the monoclonal antibodies casirivimab and imdevimab) or placebo.[200] In this study the median duration of symptoms prior to enrollment was 3 days. The composite endpoint of hospitalization and death was reduced by 71% (4.6 % to 1.3%). While not reported in the publication, the mortality rate was not significantly different between groups!!! [200] The duration of symptoms was 4 days shorter in the REG-COV2 group. Monoclonal antibodies are recommended in high-risk individuals, namely, > 65 years, obesity, pregnancy, chronic kidney disease, diabetes mellitus, immunosuppressed, coronary heart disease, etc. See infusioncenter.org and call 1-877-332-6585 In USA for eligibility and location.
- *B complex vitamins*

- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed. Omega-3 fatty acids have anti-inflammatory properties and play an important role in the resolution of inflammation. Omega-3 fatty acids reprogram macrophages/monocytes from a M1 phenotype to a M2 phenotype.[201-203] As discussed later this is critical in the management of COVID-19. In addition, omega-3 fatty acids may have antiviral properties. [60,204-207]
- *Optional:* Maraviroc 300 mg BID for 10 days. Maraviroc is a C-C- chemokine 5 receptor blocker (CCR5). Genomic and proteomic data have demonstrated that the CCR5 axis plays a major role in the pathophysiology of coronavirus infection, largely by recruiting activated monocytes to the lung. [208-210] Preliminary data demonstrated that disruption of the CCR5 axis with monoclonal antibodies was associated with an improved outcomes in patients with COVID-19. [211-213] Maraviroc is a CCR5 blocker that has been extensively used in patients with HIV, with an good safety record. [214-216] Emerging data suggests that maraviroc may be useful as an adjunctive agent in both acute COVID-19 infection and in the long-haul syndrome. Due to the very low risk of hepatotoxicity monitoring LFT's are recommended. Price and availability may however be an issue.
- *Optional:* Famotidine 40 mg BID (reduce dose in patients with renal dysfunction*) [111-117].*
- *Optional*: Interferon-α/β nasal spray, inhalation or s/c injection. [217-221] It should be noted that Zinc potentiates the effects of interferon.[222,223]
- In symptomatic patients, monitoring with home pulse oximetry is recommended (due to asymptomatic hypoxia). The limitations of home pulse oximeters should be recognized, and validated devices are preferred.[224] Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous.[224] Baseline or ambulatory desaturation < 94% should prompt hospital admission. [225] The following guidance is suggested: [224]
    - Use the index or middle finger
    - Only accept values associated with a strong pulse signal
    - Observe readings for 30–60 seconds to identify the most common value
    - Remove nail polish from the finger on which measurements are made
    - Warm cold extremities prior to measurement
- *Unclear benefit: Inhaled corticosteroids (budesonide).* Two recent RCTs have demonstrated more rapid symptomatic improvement in ambulatory patients with COVID-19 treated with inhaled budesonide, however, there with no difference in the rate of hospitalization.[226,227] It should be noted that both these studies were open label (no placebo in the control arm) and that the primary end-point was subjective (time to symptom resolution). Corticosteroids downregulate the expression of interferons (hosts primary antiviral defenses) and downregulate ACE-2 expression (harmful). Furthermore, two population level studies suggest that inhaled corticosteroids may increase the risk of death in patients with COVID-19. [228,229] Based on these data the role of inhaled corticosteroids in the early phase of COVID-19 is unclear.
- *Unclear benefit (best avoided).* Colchicine 0.6mg BID for 3 days then reduce to 0.6mg daily for a total of 30 days. In the COLCORONA study colchicine reduced the need for hospitalization (4.5 vs 5.7%) in high risk patients. [230] Colchicine was associated with an increased risk of side effects most notably diarrhea and pulmonary embolism. It should be noted that in the RECOVERY trial colchicine failed to demonstrate a survival benefit in hospitalized patients. Due to potentially serious drug interactions with ivermectin (and other CYP 3A4 and p-glycoprotein inhibitors) as well as with statins, [231] together with its marginal benefit colchicine is best avoided.
- *Not recommended: Systemic corticosteroids.* In the early symptomatic (viral replicative phase), corticosteroids may increase viral replication and disease severity.[232]

- *Unclear benefit.* Hydroxychloroquine (HCQ). The use of HCQ is highly controversial.[233] Observational studies have demonstrated a benefit of HCQ in postexposure prophylaxis and early treatment. However, randomized controlled trials have failed to demonstrate a benefit of this drug for post exposure prophylaxis, the early symptomatic phase and in hospitalized patients.[234-255] Very high dosages were used in many of the RCTs'. Furthermore, HCQ is a ZINC ionophore and it is noteworthy that none of the RCTs included zinc in the treatment protocol. The use of HCQ is further complicated by the drugs unique pharmacokinetic properties (it takes 5–10 days to achieve adequate plasma and lung concentrations).[244,256-258] In addition, SARS-CoV-2 ejects its genome directly into the cell avoiding being trapped in endosomes/lysosome.[259].Disruption of lysosomes is the main mechanism that HCQ is postulated to have antiviral effects.[259] Finally, it should be recognized that many of the observational studies are severely methodologically flawed.[260-263]
- *Not recommended:* Prophylactic azithromycin, as well as doxycycline, or quinolone antibiotics are of little benefit in patients with COVID-19. [264-266]

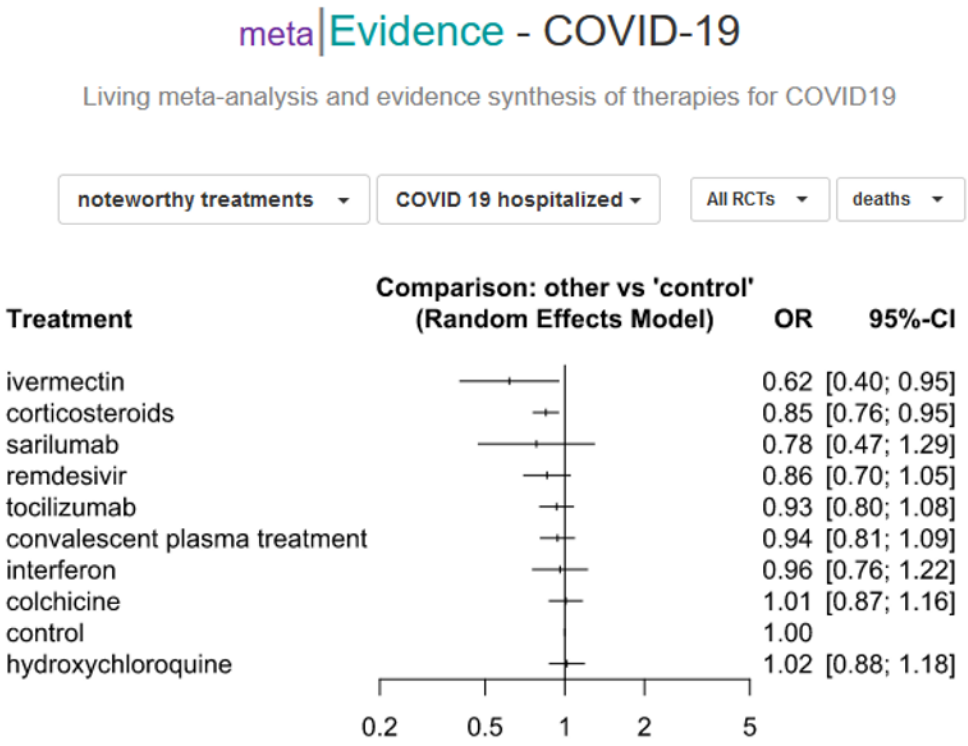
Mildly Symptomatic patients (on floor/ward in hospital).

- It is important to note that ivermectin and corticosteroids form the foundation of care for the hospitalized patient. Multiple RCTs have demonstrated that both of these drugs reduce the mortality of patients hospitalized with COVID-19 (See independent meta-analysis Figure 8).
- Ivermectin 0.4 – 0.6 mg/kg daily for 5 days or until recovered. A higher dose may be required in patients with more severe disease and in those in whom treatment is delayed. [15,19,25-28,121-130,132,134-136]. While ivermectin retains full efficacy against the variants (as best we know), the Delta variant results in very high viral loads and may take longer to eradicate. Ivermectin is best taken with a meal or just following a meal (greater absorption). It should be noted that ivermectin has potent anti-inflammatory properties apart from its antiviral properties.[267-270] See drug-drug interactions above.
- Nitazoxanide (NTZ) 600 mg BID for 7 days.[271] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
- Methylprednisolone 80 mg bolus followed by 40 mg q 12 hourly (alternative: 80 mg bolus followed by 80 mg/240 ml normal saline IV infusion at 10 ml/hr); increase to 80 mg and then 125 mg q 12 hourly in patients with progressive symptoms and increasing CRP. There is now overwhelming and irrefutable evidence that corticosteroids reduce the risk of death in patients with the pulmonary phase of COVID-19 i.e., those requiring supplemental oxygen or higher levels of support. [272-284] We believe that the use of low-fixed dose dexamethasone is inappropriate for the treatment of the pulmonary phase of COVID-19. The role of inhaled corticosteroids (budesonide) is unclear and appears to be rather limited (as reviewed above). While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/counties where it is not available the following (in order of preference) may be substituted for methylprednisolone (dose adjusted according to methylprednisolone dosages), 2) prednisolone, 3) prednisone, 4) hydrocortisone, and 5) LASTLY dexamethasone.
- Enoxaparin 1mg/kg 12 hourly (see dosage adjustments and Xa monitoring below). The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a significant reduction of the primary end point (composite of organ support days and hospital mortality) regardless of D-Dimer levels.[285]
- Vitamin C 500–1000 mg q 6 hourly and Quercetin 250–500 mg BID (if available)
- Zinc 75–100 mg/day (elemental zinc)
- Melatonin 10 mg at night (the optimal dose is unknown) [94]

- Calcifediol 0.2 mg day 1, day 3 and day 7 then weekly. [188] Calcitriol 0.25 ug/day is the active form of vitamin D3 and is another option depending on availability and price. Vitamin D3 20,000–60,000 IU single oral dose is another option; this should be followed by 20,000 IU D3 weekly until discharged from hospital. In the acute setting calcifediol/calcitriol appears to be more effective than vitamin D3. [189]
- ASA 325 mg (if not contraindicated). Moderate-severe COVID infection results in profound platelet activation contributing to the pro-thrombotic state and increasing the inflammatory response.[198,199,286,287]
- B complex vitamins
- Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40mg daily is an alternative.
- Atorvastatin 40- 80 mg/day (reduce dose to 40 mg if taken with ivermectin due to possible drug-drug interaction). Statins have pleiotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. Statins reprogram macrophages/monocytes from a M1 phenotype to a M2 phenotype. [288,289] As discussed later this is critical in the management of COVID-19. In addition, statins decrease expression of PAI-1. Simvastatin has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. [290] Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[291-295] **Due to numerous drug-drug interactions (including ivermectin) simvastatin should be avoided.**
- Anti-androgen therapy (both men and women). Dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. **AVOID IN PREGNANCY**. [166-168] Spironolactone 100 mg BID for 10 days.
- *Optional.* Losartan 50- 100 mg q day (reduce to 25 -50 mg with impaired renal function) or telmisartan 40-80 mg BID (reduce to 40 mg q day /BID with impaired renal function). [296-298] SARS -CoV-2 binds the ACE-2 receptor with internalization of the receptor and decreased ACE-2 activity. This results in increased circulating levels of angiotensin II with decreased levels of the vasodilator angiotensin 1-7. Increased angiotensin II levels have been demonstrated to be linearly associated with viral load and lung injury.[299] Observational data and those from a RCT suggest that ARB's improve the outcome of hospitalized patients with COVID-19. [296,300-302] Furthermore ARBs appear to be synergistically of benefit with statins. [302] ARBs are *contraindicated in pregnancy*.
- *Optional:* Maraviroc 300 mg BID for 10 days (see discussion above).
- *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [111-117] Famotidine may be useful for its protective effect on gastric mucosa, its anti-viral properties and histamine blocking properties.
- *Optional:* JAK inhibitors ruxolitinib or baricitinib. JAK inhibitors target JAK1, JAK2, JAK3, and whose inhibition downregulates the JAK/STAT signaling pathway decreasing cytokine concentrations.[303] These drugs have been shown to decrease the use of mechanical ventilation and the risk of death. [304] However the role of these drugs is unclear, and they should not be used in combination with corticosteroids. [305]
- *Optional:* The anti-serotonin agent, cyproheptadine 4–8 mg PO q 6 hour should be considered in patients with more severe disease. [306,307] Patients with COVID-19 have increased circulating levels of serotonin likely the result of increased platelet activation and decreased removal by the pulmonary circulation due to an extensive microcirculatory vasculopathy. [306,308-310] 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. [311-314] Furthermore, serotonin itself enhances platelet aggregation creating a propagating immuno-thrombotic cycle.[315] In addition, serotonin receptor blockade may reduce progression to pulmonary fibrosis. [316]

- *Optional:* Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. [317] *Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed*
- *Optional:* Remdesivir 200 mg IV loading dose D1, followed by 100mg day IV for 9 days. [318,319] This agent has been reported to reduce time to recovery (based on an ordinal scale) in patients requiring low levels of supplemental oxygen. [319,320] The recently published SOLIDARITY trial demonstrated no mortality benefit of this agent in the entire treatment cohort or any subgroup.[321] Furthermore, the recent VA study showed no mortality benefit with Remdesivir and a longer length of hospital stay.[322] Considering the high cost of this agent and the lack of benefit on patient centered outcomes the role of this drug seems very limited. An *in vitro* study demonstrated marked synergy between Remdesivir and Ivermectin. [323] Considering the broad antiviral and anti-inflammatory effects of ivermectin, together with its remarkable safety record, this finding suggest that ivermectin should be prescribed in all patients receiving Remdesivir. However, Remdesivir should only be prescribed in the early viral replicative phase of COVID-19.
- *Not recommended:* Hydroxychloroquine, azithromycin, doxycycline, or quinolone antibiotics. [172,173]
- *Not recommended:* Colchicine. Recruitment to the colchicine arm of the RECOVERY trial has been closed as no mortality benefit was noted with colchicine (Mortality 20% colchicine, 19% standard of care). In addition, potentially serious drug-drug interactions exist with the use of colchicine and CYP 3A4 and p-glycoprotein inhibitors (ivermectin, macrolide antibiotics, cyclosporin, etc) as well as with the use of statins. [231]
- N/C 2L/min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use “Spinhaler” or MDI and spacer if required.
- T/f EARLY to the ICU for increasing respiratory signs/symptoms, increasing oxygen requirements and arterial desaturation.

Figure 8. Network meta-analysis of various interventions on hospital mortality.



MATH + PROTOCOL (for patients admitted to the ICU) [324,325]

1. ***Methylprednisolone*** 80 mg loading dose followed by 40 mg q 12 hourly for at least 7 days and until transferred out of ICU (alternative: 80 mg bolus followed by 80 mg/240 ml normal saline IV infusion at 10 ml/hr). In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 12 hourly (then 125 mg q 12 hourly), then titrate down as appropriate. [272-284] Pulse methylprednisolone 250–500 mg mg/day for 3 days (followed by taper) may be required.[282] We suggest that all patients admitted to the ICU have a chest CT scan on admission to allow risk stratification based on the extent of the disease; those with extensive disease should be initiated on high dose corticosteroids (see section below on severe COVID). As depicted in Table 2, methylprednisolone is the corticosteroid of choice. Observational and randomized studies have clearly demonstrated the superiority of methylprednisolone over low dose dexamethasone.[326,327] These clinical findings are supported by a genomic study.[196] Methylprednisolone should be weaned slowly over two weeks once oxygen is discontinued to prevent relapse/recurrence (20mg twice daily once of oxygen, then 20 mg/day for 5 days, then 10 mg/day for 5 days). While 1) methylprednisolone is the corticosteroid of choice (see below) in those regions/countries where it is not available the following (in order of preference) may be substituted for methylprednisolone (dose adjusted according to methylprednisolone dosages), 2) prednisolone, 3) prednisone, 4) hydrocortisone, and 5) LASTLY dexamethasone.
2. ***Ascorbic acid (Vitamin C***) 50 mg/kg (or 3000 mg) IV q 6 hourly for at least 7 days and/or until transferred out of ICU.[55,64,65,328-338]. *Mega-dose vitamin C* should be considered in severely ill patients, those with progressive respiratory failure and as salvage therapy: 25 g vitamin C in 200-500 cc saline over 4-6 hours every 12 hourly for 3-5 days, then 3g IV q 6 hourly for total of 7-10 days of treatment [339] (also see https://www.youtube.com/watch?v=Au-mp6RZjCQ). Mega-dose Vitamin C appears safe in patients with ARF and ESRD. In patients with CRF a dose of 12.5 g q 12 hourly may be an adequate compromise.[340] In the study by Lankadeva et al, mega-dose vitamin C increased renal cortical blood flow and renal cortical pO2; oxalate crystals were not detected.[339] Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport and it is difficult to achieve adequate levels with PO administration. However, should IV Vitamin C not be available, it would be acceptable to administer PO vitamin C at a dose of 1g every 4–6 hours.
3. ***Anticoagulation***: The ATTACC, ACTIV-4a & REMAP-CAP trials demonstrated a marginally increased mortality in ICU patients treated with full anti-coagulation (35.3% vs. 32.6%).[285] Critically ill COVID-19 patients frequently have impaired renal and it is likely that in the absence of Xa monitoring patients were over-anticoagulated. However, full anti-coagulation should be continued on floor patients transitioned to the ICU who have normal renal function. In all other patients we would suggest intermediate dose enoxaparin i.e 60 mg/day (enhanced thromboprophylaxis) or 0.5 mg/kg q 12 hourly.[341] 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.[64,65] 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). [342-344] The use of the novel oral anticoagulants (NOAC/DOAC) is not recommended. [345]

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

4. Highly recommended: Ivermectin 0.6 – 1.0 mg/kg day orally for 5 days or until recovered [19,25-27,121,124-131,267-269,346-352]. A higher dose (0.6mg/kg) is suggested in patients with severe disease and/or those with delayed initiation of therapy. Note that ivermectin has potent antiviral and anti-inflammatory effects. As noted above clinical outcomes are superior with multiday as opposed to single day dosing. Furthermore, as indicated above, higher dosages and a longer treatment course are suggested with the Delta variant.
5. Nitazoxanide (NTZ) 600 mg BID for 7 days.[271] NTZ should therefore considered as an alternative to ivermectin, or as part of a multi-drug combination that includes ivermectin. It should be noted that while NTZ is relatively cheap in most of the world it is very expensive in the USA???
6. Melatonin 10 mg at night (the optimal dose is unknown).[95-97]
7. Calcifediol 0.2–0.5 mg (25-OH Vitamin D). [188] This should be followed by 0.2 mg calcifediol weekly until discharged from hospital. Calcitriol 0.25 ug/day is the active form of vitamin D3 and is another option depending on availability and price. Should calcifediol/calcitriol not be available, supplement with vitamin D3 (cholecalciferol) 20,000–60,000 IU single oral dose, followed by 20,000 IU D3 weekly until discharged from hospital. In the acute setting calcifediol/calcitriol appears to be more effective than vitamin D3. [189] Vitamin D3 takes many days to be converted to 25OH vitamin D; [353] this may explain the lack of benefit of vitamin D3 in patients hospitalized with severe COVID-19. [50]
8. Thiamine 200 mg IV q 12 hourly for 3-5 days then 200mg daily [354-359] Thiamine may play a role in dampening the cytokine storm. [355,360]
9. ASA 325 mg. COVID infection results in profound platelet activation contributing to the severe pro-thrombotic state and increasing the inflammatory response.[198,199,286,287] As the risk of significant bleeding is increased in patients receiving both ASA and heparin, ASA should therefore not be used in patients at high risk of bleeding. In addition (as noted below) patients should receive famotidine concurrently.
10. The anti-serotonin agent, cyproheptadine. Platelet activation results in the release of serotonin, which may contribute to the immune and vascular dysfunction associated with COVID-19. [215-219] Therefore, the serotonin receptor blocker cyproheptadine 4–8 mg PO q 6 hours should be considered.
11. B complex vitamins.
12. Fluvoxamine 50 -100 mg BID. Fluoxetine 20-40mg daily is an alternative.
13. Vascepa (Ethyl eicosapentaenoic acid) 4g daily or Lovaza (EPA/DHA) 4g daily; alternative DHA/EPA 4g daily. Vascepa and Lovaza tablets must be swallowed and cannot be crushed, dissolved, or chewed.
14. 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.*
15. Losartan 50- 100 mg q day (reduce to 25 -50 mg with impaired renal function) or telmisartan 40-80 mg BID (reduce to 40 mg q day /BID with impaired renal function). [296-298]
16. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.2 mmol/l. [108] Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc). [361-363]
17. Anti-androgen therapy (both men and women). Dutasteride 2 mg day 1, followed by 1.0 mg for 10 days. Finasteride 10 mg is an alternative (dutasteride cannot be crushed).[164] [364] **AVOID IN PREGNANCY**. [167,168] Spironolactone 100 mg BID for 10 days. Flutamide 250 mg PO q 8 hourly is an option in critically ill men and women. Tis dose flutamide has been shown to be safe in women. [365]

18. *Optional:* Famotidine 40 mg BID (20–40 mg/day in renal impairment). [111-117].
19. *Optional:* Maraviroc 300 mg BID for 10 days (see discussion above).
20. *Optional:* JAK inhibitors ruxolitinib or baricitinib.
21. *Unclear benefit.* CCR5 antagonists, including Maraviroc. [213] CCR5 is a chemokine that activates macrophages/monocytes and whose circulating levels are significantly increased in COVID-19.[210,366] Blocking the CCR5 receptor (CCR5R) repolarizes macrophages/monocytes and decreases the production of proinflammatory cytokines (see section on repolarizing macrophages/monocytes).
22. *Not recommended:* The best information to date suggests that prophylactic azithromycin as well as doxycycline and quinolone antibiotics are of little benefit in patients with COVID-19.[264,367,368] Patients with COVID-19 are at an increased risk of developing bacterial superinfections and prophylactic antibiotics may increase the risk of infection with multi-resistant organisms.
23. *Not recommended:* Remdesivir. This drug has no benefit at this stage of the disease.
24. *Not recommended.* Convalescent serum [369-374] nor monoclonal antibodies. [375] However, convalescent serum/ monoclonal antibodies may have a role in patients with hematologic malignancies.[376]
25. *Not recommended.* Colchicine (see above).
26. *Not recommended.* Tocilizumab. Five RCTS have now failed to demonstrate a clinical benefit from tocilizumab. [377-381] Considering the effect of IL-6 inhibitors on the profile of dysregulated inflammatory mediators this finding is not surprising. [323] Tocilizumab may have of benefit in patients receiving an inadequate dose of corticosteroids.[382] In patients who receive an adequate therapeutic dose of corticosteroid the role of this drug appears limited.
27. 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. [383-385] Patients with non-resolving fever, increasing WBC count and progressive pulmonary infiltrates should be screened for COVID-19-associated pulmonary aspergillosis (CAPA). [386] 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.
28. 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.
29. 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.
30. 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
    d. Trial of inhaled Flolan (epoprostenol)

e. Attempt proning (cooperative repositioning-proning) [387-390]
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.[391] HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

Table 2: Comparison of Methylprednisolone, Dexamethasone and Hydrocortisone- Number Need to Treat (NNT)

PUBLISHED RCT's/COHORT STUDIES OF CORTICOSTEROID THERAPY IN COVID-19		ABSOLUTE DIFFERENCE IN MORTALITY RATE (Rx Group vs. Control Group)	ESTIMATED NUMBER NEEDED TO TREAT TO SAVE ONE LIFE
METHYLPREDNISONE – HOSPITAL PATIENTS (Edalatifard et al, Iran)		5.9% vs. 42.9%	2.7
METHYLPREDNISONE – ICU PATIENTS (Salton et al, Italy)		7.2% vs. 23.3%	6.2
METHLPREDNISONE – HOSPITAL PATIENTS, (Fadel et al, USA)		13.6% vs. 26.3%	7.8
METHYLPREDNISONE- ARDS PATIENTS (Wu C et al- China)		46.0% vs. 61.8%	6.3
METHYLPREDNISONE - Pts on oxygen – (Fernandez-Cruz, Spain)		13.9% vs. 23.9%	10.0
CoDEX –DEXAMETHASONE - MECHANICAL VENTILATION		56.3% vs 61.5%	19.2
RECOVERY TRIAL (DEXAMATHASONE)	PTS ON OXYGEN	23.3% vs. 26.2%	28.6
	PTS ON MV	29.3% vs. 41.4%	8.4
HYDROCORTISONE -CAPE-COVID – ICU Patients (Dequin et al France)		14.7% vs 27.4%	7.9
HYDROCORTISONE –REMAP-CAP – ICU patients		28%% vs 33%	20.0

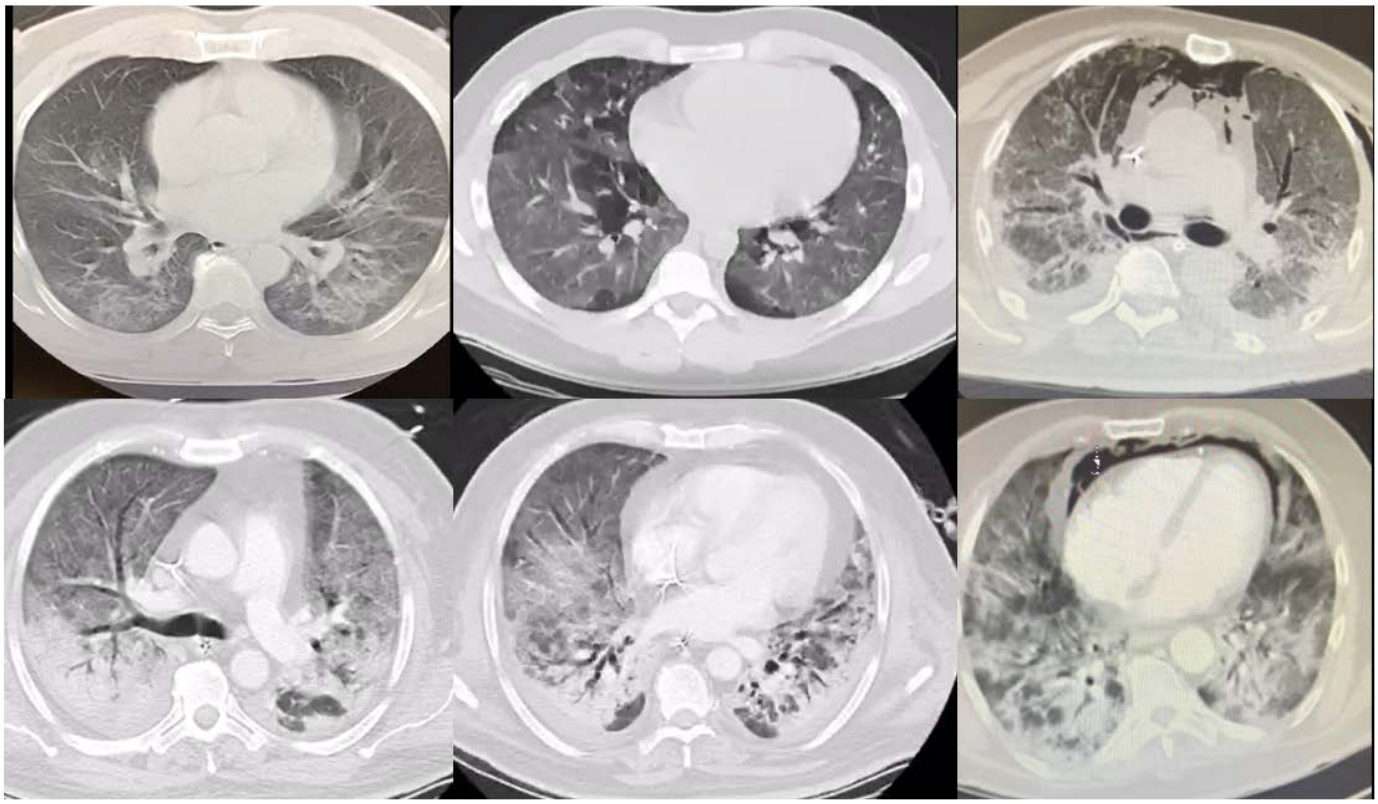
An Approach to the patient with SEVERE Life threatening COVID-19 Organizing Pneumonia

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

a) The length of time that has elapsed since the onset of symptoms. Early aggressive treatment is critical to prevent disease progression. With each day the disease becomes more difficult to reverse. The 'traditional' approach of supportive care alone is simply unacceptable.
b) The level of inflammatory biomarkers particularly the CRP. In general the CRP tracks the level of pulmonary inflammation.[392] 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.[393] The extent of the pulmonary involvement may be determined qualitatively or preferably quantitatively (see Figure 9).[392,394-400] The Ichikado CT Score is a useful quantitative score to evaluate the extent of lung involvement with COVID-19.[401,402] 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.[392] 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.

Figure 9. "Typical" progression of Chest CT findings.



The FULL "MONTY" for SEVERE COVID Pulmonary disease

I. Methylprednisolone 250-500 mg q 12 hourly for at least 3 days then titrate guided by clinical status and CRP.
II. Ivermectin 0.6 mg/kg for 5 days
III. Vitamin C 3 g 6 hourly to 25g q 12 hourly
IV. Cyproheptadine 4–8 mg PO q 6 hourly
V. Melatonin 10 mg PO at night
VI. 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).
VII. Fluvoxamine 50- 100 mg BID
VIII. Atorvastatin 80 mg/day (reduce dose to 40mg if taken with ivermectin due to possible drug-drug interaction)
IX. Losartan 50- 100 mg q day (reduce to 25 -50 mg with impaired renal function) or telmisartan 40-80 mg BID (reduce to 40 mg q day /BID with impaired renal function).
X. Losartan 25 mg BID (reduce to 25mg with renal impairment)
XI. Omega-3 fatty acids 4g/day
XII. Famotidine 40 mg BID
XIII. Thiamine 200 mg q 12 hourly
XIV. Finasteride 5-10 mg daily or dutasteride 2mg day 1 then 1mg daily together with spironolactone 100 mg BID and flutamide 250 mg PO q 8 hourly.
XV. Consider plasma exchange on admission to the ICU.

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

Salvage Treatments

- High dose bolus corticosteroids; 500–1000 mg/day methylprednisolone for 3 days then taper. [280,282]
- Plasma exchange [403-409]. 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".
- Mega-dose vitamin C should be considered in severely ill patients and as salvage therapy: 25g vitamin C in 200-500 cc saline over 4-6 hours, 12 hourly for 3-5 days, then 3g IV q 6 hourly for total of 7-10 days of treatment.[339,340] (also see https://www.youtube.com/watch?v=Au-mp6RZjCQ)
- 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; 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation.[410,411]
- Etoposide IV once per week at 50 mg/m2 until improved. [412,413] Severe-COVID pneumonia/organizing pneumonia is in essence caused by the "pulmonary macrophage activation syndrome". [414,415] Similar to the treatment of macrophage activation syndrome and HLH, etoposide may reduce macrophage numbers and improve outcome.[416-418] Etoposide is a chemotherapeutic agent and the risk/benefits should be considered in consultation with a hematologist. Furthermore, the changes in the hematological profile should be closely monitored.
- 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". [419-422]
- ECMO [423-425]. 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. [426]
- Lung transplantation. [427]

Salvage treatments of unproven/no benefit.

- Convalescent serum/monoclonal antibodies: Four RCT's failed to demonstrate a clinical benefit with the use of convalescent serum. [369-371,373,374] Eli Lilly suspended the ACTIV-33 clinical trial as their monoclonal antibody failed to demonstrate a clinical benefit in hospitalized patients.[428] It is noteworthy that the only RCT demonstrating efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever. [211] Furthermore, giving antibodies directed against SARS-CoV-2 appears pointless when the virus is already DEAD (pulmonary phase). In addition, IgG is a large protein

which penetrates tissues poorly, and is unlikely to achieve submucosal concentrations required for mucosal immunity.[429] And lastly, COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum. [430]
- In patients hospitalized with severe COVID-19, Canakinumab, an anti‑interleukin-1 β antibody failed to improve any outcome measure. [431]
- In patients with progressive fibrosis the combination of anti-fibrotic therapy with corticosteroids should be considered. [432-435] 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 [436,437] This treatment strategy appears to have an extremely limited role.

Treatment of Macrophage Activation Syndrome (MAS)

- Severe-COVID pneumonia/organizing pneumonia is in essence caused by the "pulmonary macrophage activation syndrome" and the distinction between severe COVID and MAS is unclear (see below). [414,415]
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multisystem organ failure.[416]
- "*High dose corticosteroids*." Methylprednisolone 500-1000 mg daily for three days and then wean according to Ferritin, CRP, AST/ALT. Ferritin should decrease by at least 15% before weaning corticosteroids.
- Similar to the treatment of macrophage activation syndrome and HLH, etoposide may reduce macrophage numbers and improve outcome (see above).[416-418] The combination of high dose corticosteroids and "low-dose" etoposide is an effective treatment for MAS.
- Consider plasma exchange.

Approach to the DELTA/P1 Variant

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

Monitoring

- On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg. CRP and D-dimer are important prognostic markers.[438] A PCT is essential to rule out coexisting bacterial pneumonia.[439]
- 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.[401,440] 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. [441]
- 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. [442,443]
- ECHO as clinically indicated; Patients may develop a severe "septic" cardiomyopathy and/or COVID-19 myocarditis. [444,445]

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

a. Patients have an increased risk of thromboembolic events post-discharge. [446,447] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include:[448]
    i. Increased D dimer (> 3 times ULN)
    ii. Increased CRP (> 2 times ULN) [449]
    iii. Age > 60
    iv. Prolonged immobilization
b. 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).
c. Patients should continue to receive vitamin C, melatonin, omega-3 fatty acids and a statin. These agents may reduce this risk of developing the post-COVID syndrome.
d. Patients should be followed/monitored for developing the post-COVID/long hauler syndrome.

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

The pathophysiology of COVID-19

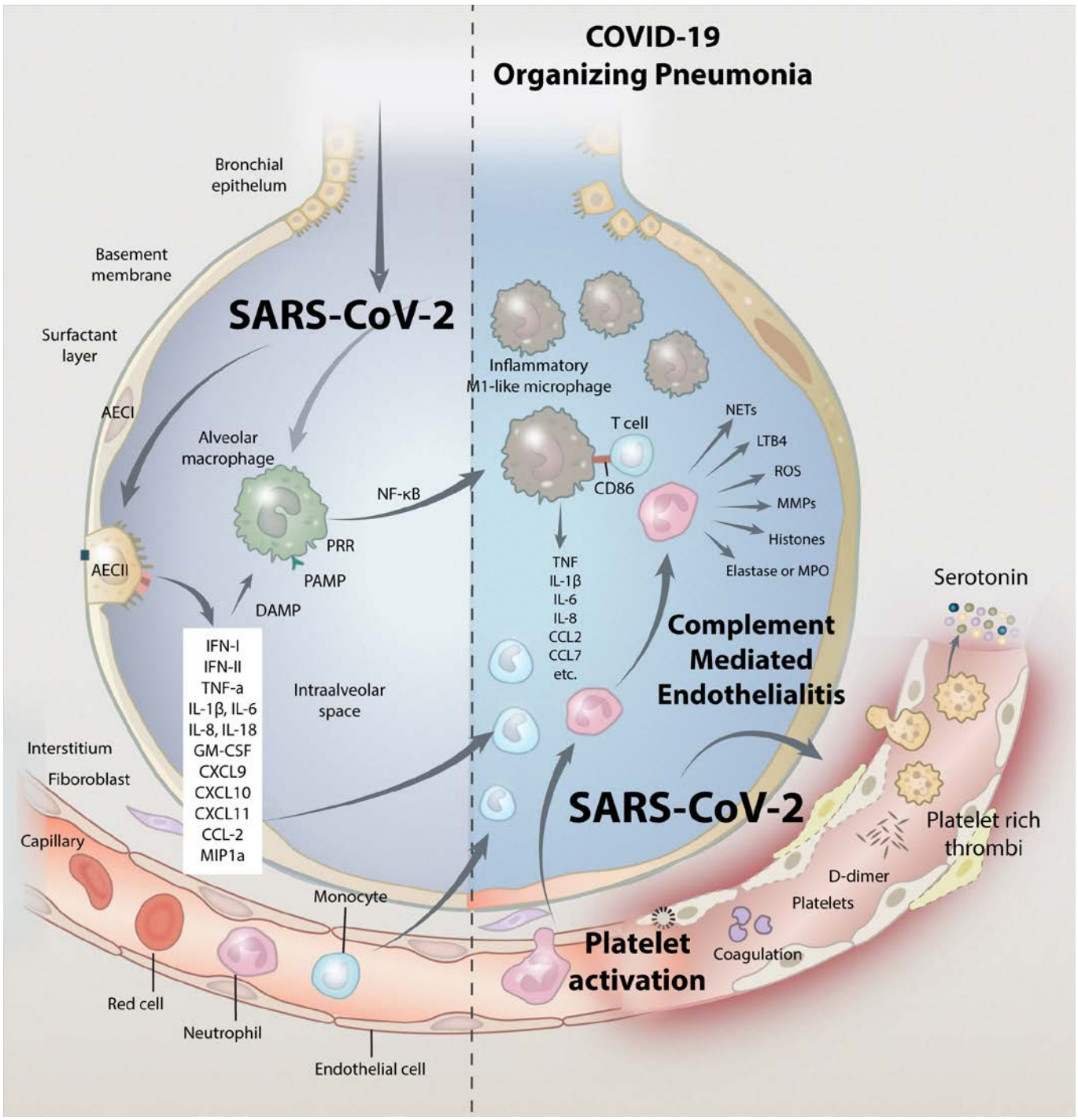
- Pulmonary Macrophage Activation Syndrome
    - Severe hyperinflammatory status
- Microvascular endothelialitis and thrombosis
    - Activation of clotting esp. platelet thrombi in lung and brain
    - High circulating serotonin
        - Arterial vasoconstriction
        - V/Q mismatch
    - Organ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

Based on clinical, proteomic, and genomic studies as well as autopsy data severe COVID-19 disease can be considered to be the connection of three basic pathologic processes, namely a pulmonary macrophage activation syndrome with excess production of cytokines and chemokines and uncontrolled inflammation, a complement mediated endothelialitis together with a procoagulant state with a thrombotic microangiopathy (see figure 10). In addition, platelet activation with the release of serotonin and the activation and degranulation of mast cells contributes to the hyper-inflammatory state. Autoantibodies have been demonstrated in a large number of hospitalized patients which adds to the end-organ damage and prothrombotic state. However, activated M1 macrophages appear to be the major driver of severe COVID-19 infection. Similarly, recent data suggests that the Long Haul Covid Syndrome (LHCS) results due to increased circulating levels of activated monocytes with ongoing cytokine production.[366] Interestingly, these monocytes contain high levels of the spike protein.[450] Both activated macrophages and activated monocytes express the same surface activation markers (CD14+, CD16+). This suggests that treatment aimed at repolarizing the macrophage/monocyte should have an important adjunctive role in the treatment of both acute COVID and the LHCS. Those interventions that have been demonstrated to repolarize macrophages/monocytes (from M1 to M2 phenotype) are listed below.

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

- Corticosteroids [451]
- Statins [288,289]
- Omega-3 fatty acids [201-203]
- Melatonin [452]
- Vitamin C

Figure 10. Pathogenetic mechanism of severe COVID-19 disease



The Long Haul COVID syndrome (post-COVID syndrome)

The Long Haul COVID Syndrome (LHCS) is characterized by prolonged malaise, headaches, generalized fatigue, sleep difficulties, hair loss, smell disorder, decreased appetite, painful joints, dyspnea, chest pain and cognitive dysfunction.[453-464] Up to 80% of patients experience prolonged illness after Covid-19. LHCS is not only seen after the COVID infection but it is being observed in some people that have received vaccines (likely due to monocyte activation by the spike protein from the vaccine). LHCS may persist for months after the acute infection and almost half of patients report reduced quality of life. Patients may suffer prolonged neuropsychological symptoms, including multiple domains of cognition.[462,465] A puzzling feature of the LHCS syndrome is that it is not predicted by initial disease severity; post-COVID-19 frequently affects mild-to-moderate cases and younger adults that did not require respiratory support or intensive care. [464] The symptom set of LHCS is in majority of the cases very similar to the chronic inflammatory response syndrome (CIRS)/ myalgic encephalomyelitis/chronic fatigue syndrome.[464] An important differentiating factor from CIRS is the observation that LHCS continues to improve on its own albeit slowly in majority of the cases. Another important observation is that LHCS includes more young people compared to severe COVID that affects older people or persons with comorbidities. Furthermore, the similarity between the mast cell activation syndrome and LHCS has been observed, and many consider post-COVID to be a variant of the mast cell activation syndrome.[466]

The LHCS syndrome is highly heterogeneous and likely results from a variety of pathogenetic mechanisms Furthermore, it is likely that delayed treatment (with ivermectin) in the early symptomatic phase will results in a high viral load which increase the risk and severity of LHCS. The following theories have been postulated to explain LHCS: [464]

1. Ongoing respiratory symptoms (SOB, cough, reduced effort tolerance) may be related to unresolved organizing pneumonia (activate pulmonary macrophages).
2. Monocyte activation syndrome. Persistence of viral debris in monocytes results in an ongoing immune response in an attempt by the immune system to clear the offending protein(s) and viral RNA fragments.
3. The neurological symptoms may be related micro- and/or macrovascular thrombotic disease which appears to be common in severe COVID-19 disease.[467] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [468] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [469] as well as severe cerebral vasoconstriction. [470] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirions" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[471].
4. An unmasking of mast cell activation syndrome (MCAS), or triggering of mast cell activation syndrome. Mast cells are present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for corticotropin releasing hormone.[472] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation.[472] The "brain-fog", cognitive impairment and general fatigue reported in long-COVID may be due to mast cell related neurovascular inflammation.

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

1. Respiratory: shortness of breath, congestion, persistent cough, etc.
2. Neurological/psychiatric: brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus/concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.

3. Musculoskeletal: myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life (ADL's).
4. Cardiovascular: Palpitations, arrhythmias, Raynaud like syndrome, hypotension, and tachycardia on exertion.
5. Autonomic: Postural tachycardia syndrome (POTs), abnormal sweating.
6. Gastrointestinal disturbance: Anorexia, diarrhea, bloating, vomiting, nausea, etc.
7. Dermatologic: Itching, rashes, dermatographia
8. Mucus membranes: Running nose, sneezing, Burning and itchy eyes.

Approach to Treatment:

The treatment approach should be individualized according to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g**.** ivermectin) during the acute symptomatic phase and adequate anti-inflammatory/macrophage repolarization therapy (e.g. corticosteroids, statins, omega-3 fatty acids, fluvoxamine, ivermectin, etc.) during the acute phase of COVID-19 are much more likely to develop the Post-COVID-19 Syndrome. In patients with ongoing respiratory symptoms chest imaging is suggested (preferably a chest CT scan). Those with unresolved pulmonary inflammation (organizing pneumonia) should be treated with a course of corticosteroids (prednisone) and closely followed. A CRP should be measured, and extended corticosteroids (titrated to the CRP) offered to these patients. Similar to patients who have recovered from septic shock, [473] a prolonged (many months) immune disturbance with elevated pro- and anti-inflammatory cytokines may contribute to the LHCS. This is likely the consequence of monocyte activation syndrome and monocyte repolarization therapy is therefore indicated. In addition, a cytokine panel may allow targeted anti-inflammatory therapy (Maraviroc in patients with high CCR5 levels) . It should be noted that much like omega-3 fatty acids, corticosteroids have been demonstrated to increase expression of pro-resolving lipids including Protectin D1 and Resolvin D4.[474] An unknown number of patients who have recovered from COVID-19 organizing pneumonia will develop pulmonary fibrosis with associated limitation of activity. Pulmonary function testing demonstrates a restrictive type pattern with decreased residual volume and DLCO.[459] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [432-435] however additional data is required before this therapy can be more generally recommended. As discussed above, the serotonin receptor blocker cyproheptadine may reduce the risk of pulmonary fibrosis. [316]

I-RECOVER: The **I-RECOVER Protocol** for the treatment of the "Long-haul COVID Syndrome".

Although numerous reports describe the epidemiology and clinical features of LHCS, [453-463] studies evaluating treatment options are glaringly sparse.[312] Indeed, the NICE guideline for managing the long-term effects of COVID-19 provide no specific pharmacologic treatment recommendations.[475] In general, while the treatment of 'Long COVID" should be individualized, the following treatments may have a role in the treatment of this disorder. In addition, the I-RECOVER protocol may have a role in the treatment of post-vaccination syndrome.

- Ivermectin has been reported to have a role in the treatment of post-COVID-19 syndrome. [312] A dose of 0.2-0.4 mg/kg day for 3-5 days, followed by once or twice weekly dosing for ongoing symptoms for up to 4 weeks. A repeat course is recommended in those who respond poorly or relapse once the treatment is stopped. The anti-inflammatory properties of ivermectin may mediate this benefit.
- Prednisone if inadequate response to ivermectin. Prednisone 0.5mg/kg daily for 5 days, 0.25mg/kg for 5 days followed by 0.12 mg/kg for 5 days. Patients with persistent organizing pneumonia may require higher doses for a more prolonged period of time.
- Vitamin C 500 mg BID (vitamin C inhibits histamine and repolarizes monocytes).[64]
- Omega-3 fatty acids: Vascepa, Lovaza or DHA/EPA 4 g day. Omega-3 fatty acids play an important role in the resolution of inflammation by inducing resolvin production. [206,207]
- Melatonin 2- 10 mg at night (slow release/extended release) with attention to sleep hygiene. Increase dose from 2mg as tolerated (may cause severe nightmares at high dosages)
- Vitamin D3 1000-3000 u/day
- Atorvastatin 40 mg daily (increase resolvin synthesis and repolarized macrophages) [408]
- Functional rehabilitation with light aerobic exercise paced according to individual capacity.[464]
- Behavioral modification, mindfulness therapy [476]and psychological support may help improve survivors' overall well-being and mental health. [464]
- *Optional:* Luteolin 100-200 mg day or quercetin 250 mg day (or mixed flavonoids). Luteolin and quercetin have broad spectrum anti-inflammatory properties. These natural flavonoids inhibit mast cells,[472,477-480] and have been demonstrated to reduce neuroinflammation. [481]
- *Optional:* Famotidine 20-40 mg day (histamine-2 blocker for Mast Cell Activation syndrome). [466]
- *Optional:* Fluvoxamine, especially in those with neurocognitive issues. Start at 25 mg daily, Increase slowly to 50 -100 mg per day. Monitor response closely as some patients will respond poorly to this medication. Teens and young adults who are prescribed fluvoxamine can experience acute anxiety which needs to be monitored for and treated by the prescribing clinician to prevent rare escalation to suicidal or violent behavior.
- *Optional:* Maraviroc in patients with high CCR5 levels.
- *Optional:* H1 receptor blockers (for mast cell activation syndrome). Loratadine 10mg daily, Cetirizine 5-10mg daily, Fexofenadine 180mg daily.
- *Optional:* H2 receptor blockers (for mast cell activation syndrome). Famotidine 20 mg, or Nizatidine 150 mg – twice daily as tolerated.
- *Optional:* montelukast 10 mg/day (for mast cell activation syndrome). Caution as may cause depression is some patients.

I-RECOVER

Management Protocol for Long-haul COVID Syndrome (LHCS)

The approach outlined below is a simplified, consensus protocol based on a collaboration led by Dr. Mobeen Syed ("Dr. Been"), Dr. Ram Yogendra, Dr. Bruce Patterson, Dr. Tina Peers, and the FLCCC Alliance. Given the lack of clinical treatment trials of Long-haul Covid Syndrome, these recommendations are based on the pathophysiologic mechanisms of COVID and post-viral illnesses along with our collective experience observing profound and sustained clinical responses achieved with the treatment approaches below.

This protocol has also been used to treat post-vaccine inflammatory syndromes with similar success. As with all FLCCC Alliance protocols, the components, doses, and durations will evolve as more clinical data accumulates. Several members of this collaboration employ various adjunctive therapies they have found beneficial. Info on these approaches can be found on page 3.

Initial therapy of Long-haul Covid Syndrome:

IVERMECTIN

0.2–0.4 mg/kg dose once daily with meals* for 3–5 days (higher doses are sometimes needed in ansomia).

* Take on empty stomach if presenting with nausea/diarrhea/anorexia.

After 3–5 days, change to once or twice weekly depending on the time to symptom recurrence/persistence.

Discontinue after 2–4 weeks if all symptoms have resolved and do not recur.

Relative Contraindications:
- Patients on Warfarin require close monitoring and dose adjustment.
- Pregnant or lactating women require a more in-depth risk/benefit assessment.

If not all symptoms resolve with ivermectin:

CORTICOSTEROID THERAPY

A tapering dose of **prednisone** as follows:

1. 0.5 mg/kg daily for 5 days
2. 0.25 mg/kg daily for 5 days
3. 0.12 mg/kg daily for 5 days

Take in morning to lessen impact on sleep.

Side effects may include: Increased appetite, mood changes, insomnia, raised blood glucose, dyspepsia.

Recommended to support the LHCS therapy:

SUPPLEMENTS

- Vitamin C: 500 mg twice daily.
- Vitamin D3: 2,000–4,000 IU daily.
- Melatonin: 2–10 mg nightly – start with low dose, increase as tolerated in absence of sleep disturbance.

If presenting with neurologic symptoms, i.e. poor concentration, forgetfulness, mood distrubance:

FLUVOXAMINE

50 mg – twice daily for 15 days.

Reduce dose or discontinue if side effects develop. Doses as low as 9 mg twice daily have shown efficacy.

If presenting with shortness of breath or low oxygen levels:

PULMONARY EVALUATION

Refer to lung specialist if available, otherwise perform chest imaging (CT preferred) to assess for secondary organizing Pneumonia (OP).

If findings consistent with secondary OP found, initiate **Corticosteroid Therapy** as below. May need to repeat or prolong course of treatment if symptoms or oxygen needs persist.

If symptoms still unresolved or recur after ivermectin and corticosteroid regimens:

TREATMENT OF SUSPECTED MAST CELL ACTIVATION

Choose a Type I and Type II antihistamine along with a mast cell stabilizer – for example, Loratidine, Famotidine, and Rupatadine. Change medicines if poor response. US FDA approved doses of many of the below medicines are daily, but can increase to three times daily with caution and close monitoring if poor response.

First-line Therapy
- Low histamine diet

Type I antihistamines:
- Use up to TDS: Loratadine 10 mg, or Cetirizine 10 mg, or Fexofenadine 180 mg

Type II antihistamines:
- twice daily: Famotidine 20 mg, or Nizatidine 150 mg

Mast cells stabilizers:
- Rupatadine 10 mg, or Ketotifen 1 mg, plus or minus
- Sodium Cromoglycate 200 mg TDS (increase slowly) or Quercetin 500 mg TDS

Second-line Therapy
- Montelukast 10 mg (beware depression in some)
- Low Dose Naltrexone (LDN; avoid if taking opiates), start with 0.5 mg daily increasing by 0.5 mg weekly up to 4.5 mg daily
- Diazepam 0.5-1 mg twice daily
- SSRIs

BID	twice daily	mg/kg	dose in mg per kg body weight
CT	computed tomography scan	OP	organizing pneumonia
GIT	gastrointestinal tract	RDA	recommended dietary allowances
IU	international units	TDS	3 times daily

Please regard our disclaimer on page 3.

For more information on the treatment protocols of the FLCCC Alliance please see: flccc.net

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

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

1. It is important to focus on the totality of the evidence and not just on RCTs (see figure 11). We are in the midst of a global pandemic and the use of cheap, effective, and safe repurposed drugs has and will continue to have a major role in the prevention and treatment of this disease.
2. Patients transition through a number of different phases (clinical stages). The treatment of each phase is distinct ... this is critically important (see Figures 1 & 2).
3. Antiviral therapy is likely to be effective only during the viral replicative phase whereas anti-inflammatory therapy is expected to be effective during the pulmonary phase and possibly the post-COVID-19 phase. While Remdesivir is a non-specific antiviral agent that targets RNA viruses, it is likely that agents specifically designed to target SARS-CoV-2 will be developed.
4. The SARS-CoV-2 PCR remains positive for at least 2 weeks following detection of whole virus (by culture, See figure 3). Patients who progress to the pulmonary phase are usually PCR positive despite cessation of viral replication (and are therefore less likely to be infectious).
5. Due to the imperfect sensitivity of the PCR test as many as 20% of patients who progress to the pulmonary phase will be PCR negative (even on repeat testing). At symptom onset PCR will be positive in approximately 60% of patients; maximal positivity rate is on day 8 (post infection) when 80% of patients will be positive (see Figure3). [482] COVID-19 is essentially a clinical diagnosis supported by laboratory tests.
6. Symptomatic patients are likely to be infectious during a narrow window starting 2–3 days before the onset of symptoms and to up to 6 days after the onset of symptoms (see Figure 3).[483]
7. It is important to recognize that COVID-19 patients present with a variety of phenotypes, likely dependent on inoculum size and viral load, SARS-CoV-2 variant, genetic heterogeneity mutations and polymorphisms, biotypes, blood type, sex and androgen status, age, race, BMI (obesity), immunological and nutritional status, and co-morbidities.[275,484-494] 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. [495]
8. The pulmonary phase is characterized by immune dysregulation, [467,487,496-509] a pulmonary microvascular injury (vasculopathy),[467,509-512] with activation of clotting and a procoagulant state together with the characteristics of an organizing pneumonia. [393,513]
9. Endothelial damage and an imbalance of both innate and adaptive immune responses, with aberrant macrophage activation, plays a central role in the pathogenesis of the severe COVID-19 Disease. [467]
10. As patients, progress down the pulmonary cascade the disease becomes more difficult to reverse. The implications of this are twofold.
    a. Early treatment (of the pulmonary phase) is ESSENTIAL to a good outcome.
    b. Treatment in the late pulmonary phase may require escalation of the dose of corticosteroids as well as the use of salvage methods (i.e., plasma exchange). However, patients who present in the late pulmonary phase may have progressed to the irreversible pulmonary fibroproliferative phase.
11. The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to "supportive care" alone. Furthermore, it is unlikely that there will be a single "silver bullet" to treat severe COVID-19 disease. Rather, patients will require treatment with multiple drugs/interventions that have synergistic and overlapping biological effects. Repurposed FDA

approved drugs that are safe, inexpensive, and "readily" available are likely to have a major therapeutic effect on this disease. The impact of COVID-19 on middle- and low-income countries is enormous; these countries are not able to afford expensive propriety "designer" molecules.

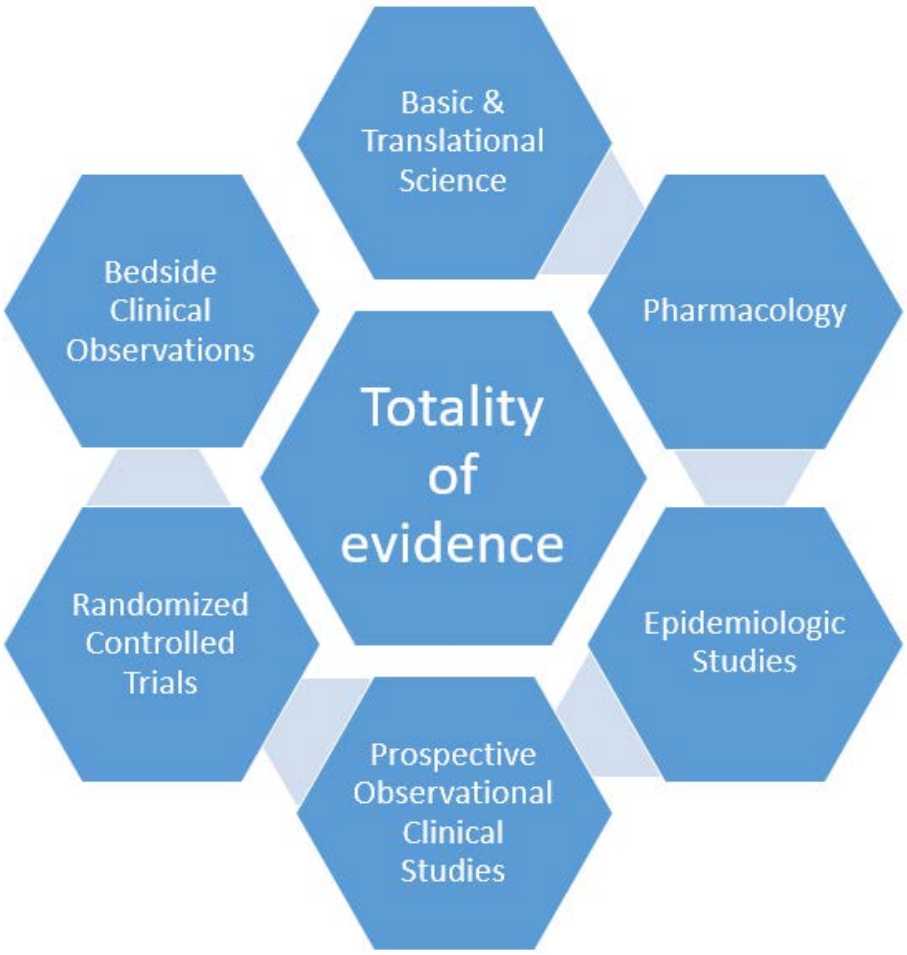
12. The radiographic and pathological findings of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [393,514,515]
13. THIS is NOT ARDS (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS.[516-518] The ground glass infiltrates are peripheral and patchy, [514] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS".[519] Extravascular lung water index (EVLWI) is normal or only slightly increased; this by definition excludes non-cardiogenic pulmonary edema (ARDS). Lung compliance is normal (this excludes ARDS). Patients are PEEP unresponsive. Treating patients as if they ARDS is an extremely dangerous approach. The hypoxia is due to an organizing pneumonia with severe ventilation/perfusion mismatch likely due to the microvascular narrowing, thrombosis and vasoplegia.
14. The core principles of the pulmonary phase (MATH+) is the use of anti-inflammatory agents to dampen the "cytokine storms" together with anticoagulation to limit the microvascular and macrovascular clotting and supplemental oxygen to help overcome the hypoxia.
15. Ivermectin has emerged as a highly effective drug for the prophylaxis and treatment COVID-19. Ivermectin inhibits viral replication and has potent anti-inflammatory properties. Emerging clinical data (including RCT's) 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. [19,25-27,121,124-130,267-269,346-352,520] In the recommended dosages, Ivermectin is remarkably safe and effective against SARS-CoV-2. However, as noted above there is the potential for serious drug-drug interaction.
16. The pulmonary phase of COVID-19 is characterized by PROLONGED immune dysregulation that may last weeks or even months. The early and abrupt termination of anti-inflammatory agents will likely result in rebound inflammation. [521]
17. SARS-CoV-2 as compared to all other respiratory viruses, upregulates cytokines and chemokines while at the same time down regulating the expression of Interferon alpha (the hosts primary antiviral defence mechanism). [131,155] Low innate antiviral defenses and high pro-inflammatory mediators contribute to ongoing and progressive lung injury.
18. An unknown percentage of patients with COVID-19 present with "silent hypoxia" with a blunted respiratory response. This phenomenon may be related to involvement of chemoreceptors of the carotid bodies and/or brain stem dysfunction,[522,523] and necessitates pulse oximetry in symptomatic patients managed at home (as discussed above).
19. It should be recognized that LWMH has non-anticoagulant properties that are likely beneficial in patients with COVID-19, these include anti-inflammatory effects and inhibition of histones.[524] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[525,526] as well as viral replication [129,527]. Most importantly LWWH inhibits heparanase (HPSE).[528] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[528] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [529] Due to the ease of administration, greater anti-Xa activity and better safety profile we prefer low molecular weight heparin (LMWH) to unfractionated heparin (UFH).
20. The combination of steroids and ascorbic acid (vitamin C) is essential. Both have powerful synergistic anti-inflammatory actions. [330,335] Vitamin C protects the endothelium from oxidative injury.[64,530-532] Furthermore, vitamin C Increases the expression of interferon-alpha [54] while corticosteroids (alone) decrease expression of this important protein. [533-536] 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. [277,537] It is likely that heparin (LMWH) acts synergistically with corticosteroids and vitamin C to protect the endothelium and treat the endothelialitis of severe COVID-19 disease.

21. Notwithstanding the particularly important and impressive results of the Recovery-Dexamethasone study, methylprednisolone is the corticosteroid of choice for the pulmonary phase of COVID-19. This is based on pharmacokinetic data (better lung penetration),[538] genomic data specific for SARS-CoV-2,[196] and a long track record of successful use in inflammatory lung diseases (see Table 2).
22. It should be noted that animal studies have demonstrated that ivermectin has immunostimulatory effects.[539,540] For this reason patients taking ivermectin do not need to stop taking ivermectin when vaccinated. Indeed, ivermectin may boost the immune response to the vaccine.

And finally: "If what you are doing ain't working, change what you are doing"

Figure 11. Evaluating the totality of evidence.



References

1. Fatima S, Zaidi SS, Alsharidah AS et al. Possible prophylactic approach for SARS-CoV-2 infection by combination of melatonin, Vitamin C and Zinc in animals. Fronteirs in Veterinary Science 2020; 7:585789.
2. Arslan B, Ergun NU, Topuz S et al. Synergistic effect of quercetin and vitamin C against COVID-19: Is a possible guard for front liners? ssrn 2020.
3. Ahmed AK, Albalawi YS, Shora HA et al. Effects of quadruple therapy: Zinc, Quercetin, Bromelain and Vitamin C on clinical outcomes of patients infected with COVID-19. Rea Int Jou of End and Dia 2020; 1:1005.
4. Leung K, Shum MMH, Leung GM et al. Early empirical assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. medRxiv 2020.
5. Tegally H, Wilkinson E, Giovanetti M et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spke mutations in South Africa. medRxiv 2020.
6. Li B, Deng A, Li K et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 delta variant. medRxiv 2021.
7. Fratev F. The SARS-CoV-2 S1 spike mutation N501Y alters the protein interactions with both hACE2 and human derived antibody: A free energy of perturbation study. bioRxiv 2020.
8. Nonaka CK, Franco MM, Graf T et al. Genomic evidence of a SARS-C0V-2 reinfection case with E484K spike mutation in Brazil. Preprints 2021.
9. Jehi L, Ji X, Milinovich A et al. Individualizing risk prediction for positive COVID-19 testing. Results from 11,672 patients. Chest 2020; 158:1364-75.
10. Kory P, Meduri GU, Iglesias J et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the propphylaxis and treatment of COVID-19. ssrn 2020.
11. Guy GP, Lee FC, sunshine G et al. Association of State-Issued mask mandates and allowing on premises restaurant dining with County-levels COVID-19 case and death growth rates-United States, March 1 - December 31, 2020. MMWR 2021; 70.
12. Guzzo CA, Furtek CI, Porras AG et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol 2002; 42:1122-33.
13. Behera P, Patro BK, Singh AK et al. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study. medRxiv 2020.
14. Carvallo H, Hirsch RR, Alkis P et al. Study of the efficacy and safety of topical ivermectin + Iota-carrageenan in the prophylaxis against COVID-19 in health personnel. Journal of Biomedical Research and Clinical Investigation 2020; 2.
15. Kory P, Meduri GU, Iglesias J 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.
16. Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administraion of ivermectin. Int J Antimicrob Agents 2020.
17. Morgenstern J, Redondo JN, Olavarria A et al. Retrospective cohort study of Ivermectin as a SARS-CoV-2 pre-exposure prophylaxis method in Healthcare Workers. medRxiv 2021.
18. Chahla RE, Medina Ruiz L, Mena T et al. Ivermectin reproposing for COVID-19 treatment outpatients in mild stage in primary health centers. medRxiv 2021.
19. Kircik LH, Del Rosso JQ, Layton AM et al. Over 25 years of clinical experience with Ivermectin: An overview of safety for an increasing number of indications. J Drugs Dermatol 2016; 15:325-32.
20. Aroke D, Tchouakam DN, Awungia AT et al. Ivermectin induced Steven-Johnsons syndrome: case report. BMC Research Notes 2017; 10:179.
21. Ngwasiri CA, Abanda MH, Aminde LN. Ivermectin-induced fixed drug eruption in an elderly Cameroonian: a case report. Journal of Medical Case Reports 2018; 12:254.
22. Veit O, Beck B, Steuerwald M et al. First case of ivermectin-induced severe hepatitis. Trans R Soc Trop Med Hyg 2021; 100:795-97.
23. Nicolas P, Maia MF, Bassat Q et al. Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. Lancet Glob Health 2020; 8:e92-e100.
24. Canga AG, Sahagun Prieto AM, Diez Liebana MJ et al. The pharmacokinetics and interactions of Ivermectin in humans-A mini-review. The AAPS Journal 2007; 10:42-46.

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

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

76. Nieman DC, Simonson A, Sakaguchi CA et al. Acute Ingestion of a Mixed Flavonoid and Caffeine Supplement Increases Energy Expenditure and Fat Oxidation in Adult Women: A Randomized, Crossover Clinical Trial. Nutrients 2019; 11.
77. Nieman DC, Kay CD, Rathore AS et al. Increased Plasma Levels of Gut-Derived Phenolics Linked to Walking and Running Following Two Weeks of Flavonoid Supplementation. Nutrients 2018; 10.
78. Nieman DC, Ramamoorthy S, Kay CD et al. Influence of Ingesting a Flavonoid-Rich Supplement on the Metabolome and Concentration of Urine Phenolics in Overweight/Obese Women. Journal of Proteome Research 2017; 16:2924-35.
79. Cialdella-Kam L, Ghosh S, Meaney MP et al. Quercetin and Green Tea Extract Supplementation Downregulates Genes Related to Tissue Inflammatory Responses to a 12-Week High Fat-Diet in Mice. Nutrients 2017; 9.
80. Ohgitani E, Shin-Ya M, Ichitani M et al. Rapid inactivation in vitro of SARS-CoV-2 in saliva by black tea and green tea. bioRxiv 2021.
81. Giuliani C, Bucci I, Di Santo S et al. The flavonoid quercetin in hibits thyroid-restricted genes expression and thyroid function. Food and Chemical Toxicology 2014; 66:23-29.
82. de Souza dos Santos MC, Goncalves CF, Vaisman M et al. Impact of flavonoids on thyroid function. Food and Chemical Toxicology 2011; 49:2495-502.
83. Chandra AK, De N. Catechin induced modulation in the activities of thyroid hormone synthesizing enzymes leading to hypothyroidism. Mol Cell Biochem 2013; 374:37-48.
84. Pistollato F, Masias M, Agudo P et al. Effects of phytochemicals on thyroid function and their possible role in thyroid disease. Ann N Y Acad Sci 2019; 1433:3-9.
85. Sathyapalan T, Manuchehri AM, Thatcher NJ et al. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: A randomized, double-blind, crossover study. J Clin Endocrinol Metab 2020; 96:1422-49.
86. Tonstad S, Jaceldo-Siegl K, Messina M et al. The association between soya consumption and serum thyroid-stimulating hormone in the Adventist Health Study-2. Public Health Nutr 2016; 19:1464-70.
87. Colombo D, Lunardon L, Bellia G. Cyclosporine and herbal supplement interactions. Journal of Toxicology 2014; 2014:145325.
88. Colunga Biancatelli RM, Berrill M, Mohammed YH et al. Melatonin for the treatment of sepsis: the scientific rationale. J Thorac Dis 2020; 12 (Suppl 1):S54-S65.
89. Reiter RJ, Abreu-Gonzalez P, Marik PE et al. Therapeutic algorithm for use of melatonin in patients with COVID-19. Front Med 2020; 7:226.
90. Reiter RJ, Sharma R, Ma Q et al. Melatonin inhibits COVID-19-induced cytokine storm by reversing aerobic glycolysis in immune cells: A mechanistic analysis. Medicine in Drug Discovery 2020; 6:100044.
91. Zhang R, Wang X, Ni L et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci 2020; 250:117583.
92. Kleszczynski K, Slominski AT, Steinbrink K et al. Clinical trials for use of melatonin to fight COVID-19 are urgently needed. Nutrients 2020; 12.
93. Coto-Montes A, Boga JA. ER stress and autophagy induced by SARS-CoV-2: The targer for melatonin treatment. Melatonin Res 2020; 3:346-61.
94. Gandolfi JV, Di Bernardo AP, Chanes DA et al. The effects of melatonin supplementation on sleep quality and assessment of the serum melatonin in ICU patients: A randomized controlled trial. Crit Care Med 2020.
95. Castillo RR, Quizon GR, Juco MJ et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. Melatonin Res 2021; 3:297-310.
96. Ramiall V, Zucker J, Tatonetti N. Melatonin is significantly associated with survival of intubated COVID-19 patients. medRxiv 2021.
97. Farnoosh G, Akbaariqomi M, Badri T et al. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: A randomized, double-blind clinical trial. medRxiv 2021.
98. Shneider A, Kudriavtsev A, Vakhusheva A. Can melatonin reduce the severity of COVID-19 pandemic. medRxiv 2020.
99. Vogel-Gonzalez M, Tallo-Parra M, Herrera-Fernandez V et al. Low zinc levels at admission associates with poor clinical outcomes in SARS-CoV-2 infection. Nutrients 2021; 13:562.

100. te Velthuis AJ, van den Worm SH, Sims AC et al. Zn2+ inhibits Coronavirus and Arterivirus RNA polymerase activity In Vitro and Zinc ionophores block the replication of these viruses in cell culture. PLos Pathog 2010; 6:e1001176.
101. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. Nutrients 2017; 9.
102. Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. J Royal Soc Med Open 2017; 8:1-7.
103. Hoeger J, Simon TP, Beeker T et al. Persistent low serum zinc is associated with recurrent sepsis in critically ill patients - A pilot study. PloS ONE 2017; 12:e0176069.
104. Willis MS, Monaghan SA, Miller ML et al. Zinc-induced copper deficiency. A report of three cases initially recognized on bone marrow examination. Am J Clin Pathol 2005; 123:125-31.
105. Shakoor H, Freehan J, Mikkelsen K et al. Be well: A potential role for vitamin B in COVID-19. Maturitas 2020.
106. dos Santos LM. Can vitamin B12 be an adjuvant to COVID-19 treatment? GSC Biological and Pharmaceutical Sciences 2020; 11.
107. Kandeel M, Al-Nazawi M. Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci 2020; 251:117627.
108. Tan CW, Ho LP, Kalimuddin S et al. Cohort study to evaluate effect of vitamin D, magnesium, and vitamin b12 in combination on severe outcome progression in older patients with coronavirus (COVID-19). Nutrition 2020; 80:111017.
109. Zhang P, Tsuchiya K, Kinoshita T et al. Vitamin B6 prevents IL-1B protein production by inhibiting NLRP3 inflammasome activation. J Biol Chem 2020; 291:24517-27.
110. O'Brien MP, Forleo-Neto E, Musser BJ et al. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. N Engl J Med 2021.
111. Freedberg DE, Conigliaro J, Sobieszczyk ME et al. Famotidine use is associated with impoved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. medRxiv 2020.
112. Janowitz T, Baglenz E, Pattinson D et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series. Gut 2020; 69:1592-97.
113. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients. Am J Gastroenterol 2020.
114. Malone RW, Tisdall P, Fremont-Smith P et al. COVID-19: Famotidine, Histamine, Mast Cells, and mechanisms. Research Square 2020.
115. Sethia R, Prasad M, Mahapatra SJ et al. Efficacy of famotidine for COVID-19: A systematic review and meta-analysis. medRxiv 2020.
116. Shoaibi A, Fortin S, Weinstein R et al. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. medRxiv 2020.
117. Yeramaneni S, Doshi P, Sands K et al. Famotidine use is not associated with 30-day mortality: A coarsened exact match study in 7158 hospitalized COVID-19 patients from a large healthcare system. medRxiv 2020.
118. Almario CV, Chey WD, Spiegel BM. Increased risk of COVID-19 among users of proton pump inhibitors. Am J Gastroenterol 2020.
119. Lee SW, Ha EK, Moon SY et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut 2021; 70:76-84.
120. Munoz J, Ballester MR, Antonijoan RM et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18 mg tablet in healthy adult volunteers. PLoS Neglected Tropical Diseases 2018; 12:e0006020.
121. Hashim HA, Maulood MF, rasheed AM et al. Controlled randomized clinical triaal on using Ivermectin with Doxycycline for treating COVID-19 patients in Bagdad, Iraq. medRxiv 2020.
122. Alam MT, Murshed R, Bhiuyan E et al. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. Bangladesh Coll Phys Surg 2020; 38:10-15.
123. Chowdhury AT, Shahabz M, Karim MR et al. A randomized trial of ivermectin-doxycycline and hydrochloroquine-azithromycin therapy on COVID-19 patients. Research Square 2020.
124. Chamie J. Real-World evidence: The case of Peru, casuality between Ivermectin and COVID-19 infection fatality rate. ResearchGate 2020.
125. Caly L, Druce JD, Catton MG et al. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020.

126. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. In Vivo 2020; 34:3023-26.
127. 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.
128. Yang SN, Atkinson SC, Wang C et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. Antiviral Res 2020; 177:104760.
129. Dayer MR. Coronavirus (2019-nCoV) deactivation via spike glycoprotein shielding by old drugs, bioinformatic study. Preprints 2020.
130. 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.
131. Kalfas S, Visvanathan K, Chan K et al. The therapeutic potential of ivermectin for COVID-19: A systematic review of mechanisms and evidence. medRxiv 2020.
132. 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.
133. Wehbe Z, Wehbe M, Iratni R et al. Repurposing Ivermectin for COVID-19: Molecular aspects and therapeutic possibilities. Front Immunol 2021; 12:663586.
134. Hazan S, Dave S, Gunaratne AW et al. Effectiveness of ivermectin-based multidrug therrapy in severe hypoxic ambulatory COVID-19 patients. medRxiv 2021.
135. Bryant A, Lawrie TA, Dowswell T et al. Ivermectin for the prevention and treatment of COVID-19 infection: a systematic review and meta-analysis. Lancet 2021.
136. Hill A, Garratt A, Levi J et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infectious Diseases 2021.
137. Rossignol JF, Bardin MC, Oaks JB et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. medRxiv 2021.
138. Cadegiani FA, Goren A, Wambier CG et al. Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly reduced symptoms compared to known outcomes in untreated patients. New Microbes and New Infections 2021; 43:100915.
139. Elalfy H, Besheer T, El-Mesery A et al. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. J Med Virol 2021; 93:3176-83.
140. Hong SK, Kim HJ, Song CS et al. Nitazoxanide suppresses IL-6 production in LPS-stimulated mouse macrophages and TG-injected mice. International Immunopharmacology 2012; 13:23-27.
141. Rossignol JF. Nitazoxanide: A first-in-class broad-spectrum antiviral agent. Antiviral Res 2014; 110:94-103.
142. Padmanabhan S, Padmanabhan K. The devil is in the dosing- targeting the interferon pathway by repositioning Nitazoxanide against COVID-19. Research Square 2021.
143. Cao J, Forrest CJ, Zhang X. A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs. Antiviral Res 2015; 114:1-10.
144. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. Journal of Infection and Public Health 2016; 9:227-30.
145. Piacentini S, La Frazia S, Riccio A et al. Nitazoxanide inhibits paramyxovirus replication by targeting the Fusion protein folding: role of glycoprotein-specific thiol oxireductase ERp57. Scientific Reports 2018; 8:10425.
146. Merchant HA. CoViD-19: An early intervention therapeutic strategy to prevent developing a severe disease as an alternative approach to control the pandemic. medRxiv 2021.
147. da Silva JK, Figueirdo PL, Byler KG et al. Essential oils as antiviral agents, potential of essential oils to treat SARS-CoV-2 infection: an In-Silico investigation. Int J Mol Sci 2020; 21:3426.
148. Seet RC, Quek AM, Ooi DS et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: an open-label randomized trial. Int J Infect DIs 2021.
149. Vergara-Buenaventura A, Castro-ruiz C. Use of mouthwashes against COVID-19 in dentistry. British Journal of Oral and Maxillofacial Surgery 2020; 58:924-27.
150. Baxter AL, Schwartz KR, Johnson RW et al. Rapid initiation of nasal saline irrigation: hospitalizations in COVID-19 patients randomized to alkalinization or povidone-iodine compared to a national dataset. medRxiv 2021.

151. Seneviratne CJ, Balan P, Ki KK et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: Randomized controlled trial in Singapore. Infection 2020; 49:305-11.
152. Frank S, Brown SM, Capriotti JA et al. In vitro efficacy of a providone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. JAMA Otolaryngol Head Neck Surg 2020; 146:1054-58.
153. Burton MJ, Clarkson JE, Goulao B et al. Antimicrobial mouthwashes (gargling) and nasal sprays to protect healthcare workers when undertaking aerosol-generating procedures (AGPs) on patients withou suspected or conformed COVID-19 infection (Review). Cochrane Database of Syst Rev 2020; 9:CD013628.
154. Meister TL, Briggemann Y, Todt D et al. Virucidal efficacy of different oral rinses against severe acute respiratory syndrome coronavirus 2. J Infect Dis 2020; 222:1289-92.
155. Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. Dermatology 2002; 204 (suppl 1):37-41.
156. Teng F, He T, Huang S et al. Cetylpyridinium chloride mouth rinses alleviate experimental gingivitis by inhibiting dental plaque maturation. Journal of Oral Science 2016; 8:182-90.
157. Rosing CK, Cavagni J, Gaio EJ et al. Efficacy of two mouthwashes with cetylpyridinium chloride: a controlled randomized clinical trial. Braz Oral res 2017; 31:e47.
158. Green A, Roberts G, Tobery T et al. In vitro assessment of the virucidal activity of four mouthwashes containing Cetyylpyridinium Chloride, ethanol, zinc and a mix of enzymes and proteins against human coronavirus. bioRxiv 2021.
159. Choudhury IM, Shabnam N, Ahsan T et al. Effect of 1% povidone iodine mouthwash/gargle, nasal and eye drop in COVID-19 patient. Bioresearch Communications 2021; 7.
160. Ader AW, Paul TL, Reinhardt W et al. Effect of mouth rinsing with two polyvinylpyrrolidine-iodine mixtures on iodine absorption and thyroid function. J Clin Endocrinol Metab 2021; 66:632-35.
161. Lucas JM, Heinlein C, Kim T et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 2020; 4:1310-1325.
162. Marik PE, DePerrior SE, Ahmad Q et al. Gender-based disparities in COVID-19 patient outcomes. Journal of Investigative Medicine 2021; 69:814-18.
163. Wambier CG, de Pina Almeida Prado Junior B, Pereira CS et al. Brazilian blood donation eligibility criteria for dermatologic patients. An Bras Dermatol 2021; 87:590-595.
164. Zarehoseinzade E, Allami A, Ahmadi M et al. Finasteride in hospitalized adult males with COVID-19: A risk factor for severity of the disease or an adjunct treatment: A randomized controlled clinical trial. Medical Journal of the Islamic Republic of Iran 2021; 35:30.
165. Samuel RM, Majd H, Richter MN et al. Androgen signaling regulates SARS-CoV-2 receptor levels and is associated with severe COVID-19 symptoms in men. Cell Stem Cell 2020; 27:876-89.
166. Cadegiani FA, McCoy J, Wambier CG et al. Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to remission in males with COVID-19: A randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV Trial- Biochemical). Cureus 2021.
167. McCoy J, Goren A, Cadegiani FA et al. Proxalutamide reduces the rates of hospitalization for COVID-19 male outpatients: A randomized double-blinded placebo-controlled trial. Front Med 2021; 8:668698.
168. Cadegiani FA, McCoy J, Zimerman A et al. Efficacy of proxalutamide in hospitalized COVID-19 patients: A randomized, double-blind, placebo-controlled, parallel-design clinical trial. medRxiv 2021.
169. Wambier CG, Lin EM, Cadegiani FA et al. Accelerated viral clearance and symptom resolution in symptomatic COVID-19 outpatients treated with antiandrogens. medRxiv 2021.
170. Cadegiani FA, Goren A, Wambier CG et al. An open-label prospective observational study of antiandrogen and non-antiandrogen early pharmacological approaches in females with mild-to-moderate COVID-19. The PreAndroCoV Female trial. medRxiv 2021.
171. McCoy J, Cadegiani FA, Wambler CG et al. 5-alpha-reductase inhibitors are associated with reduced frequency of COVID-19 symptoms in males with androgenic alopecia. JEADV 2021; 35:e243-e246.
172. Goren A, Wambler CG, Herrera S et al. Anti-androgens may protect against severe COVID-19 outcomes: results form a prospective cohort of 77 hospitalized men. JEADV 2021; 35:e13-e15.
173. van Zuuren EJ, Fedorowicz Z, Schoones J. Interventions for female pattern hair loss (Review). Cochrane Database of Syst Rev 2016; 5:CD007628.
174. Seale LR, Eglini AN, McMichael AJ. Side effects related to 5 alpha-reductase inhibitor treatment of hair loss in women: A review. J Drugs Dermatol 2016; 15:414-19.

175. Cadegiani FA, Wambier CG, Goren A. Spironolactone: An anti-androgenic and anti-hypertensive drug that may provide protection against the novel Coronavirus (SARS-CoV-2) induced acute respiratory distress syndrome (ARDS) in COVID-19. Fronteirs in Medicine 2020; 7:453.
176. Cadegiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARA-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS). Medical Hypotheses 2020; 143:110112.
177. Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs placebo and clinical deterioration in outpatietns with symptomatic COVID-19. A randomized clinical trial. JAMA 2020.
178. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of COVID-19. Open Forum Infectious Diseases 2021.
179. Hamed MG, Hagaga RS. The possible immunoreulatory and anti-inflammatory effects of selective serotonin reuptake inhibitors in coronavirus disease patients. Medical Hypotheses 2020; 144:110140.
180. Hoertel N, Sanchez-Rico M, Vernet R et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVId-19: results from an observational study. Molecular Psychiatry 2021.
181. Zimering MB, Razzaki T, Tsang T et al. Inverse association between serotonin 2A receptor antagonist medication use and mortality in severe COVID-19 infection. Endocrinol Diabetes Metab J 2020; 4:1-5.
182. Sukhatme VP, Reiersen AM, Vayttaden SJ et al. Fluvoxamine: A review of its mechanism of action and its role in COVID-19. Fronteirs in Pharmacology 2021; 12:652688.
183. Hartter S, Wang X, Weigmann H et al. Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. J Clin Psychopharmacology 2021; 21:167-74.
184. Maurer-Spurej E, Pittendreigh C, Solomons K. The influence of selective serotonin reuptake inhibitors on human platelet serotonin. Thromb Haemost 2004; 91:119-28.
185. Bismuth-Evenzal Y, Gonopolsky Y, gurwitz D et al. Decreased serotonin content and reduced agonist-induced aggregation in platelets of chronically medicated with SSRI drugs. Journal of Affective Disorders 2012; 136:99-103.
186. Javors MA, Houston JP, Tekell JL et al. Reduction of platelet serotonin content in depressed patients treated with either paroxetine or desipramine. International Journal of Neuropsychopharmacology 2000; 3:229-35.
187. Ishima T, Fujita Y, Hashimoto K. Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells. Eur J Pharmacol 2014; 727:167-73.
188. Castillo ME, Costa LM, Barrios JM et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol 2020; 203:105751.
189. Loucera C, Pena-Chilet M, Esteban-Medina M et al. Real world evidence of calcifediol use and mortality rate of COVID-19 hospitalized in a large cohort of 16,401 Adalusian patients. medRxiv 2021.
190. Quesada-Gomez JJ, Bouillon R. Is calcifediol better than cholecalciferol for vitamin D supplementation? Osteoporosis International 2018; 29:1697-711.
191. Cesareo R, Falchetti A, Attanasio R et al. Hypovitaminosis D: Is it time to consider the use of calcifediol? Nutrients 2019; 11:1016.
192. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med 2019; 381:2529-40.
193. Amrein K, Martucci G, McNAlly JD. When not to use meta-analysis: Analysing the meta-analysis on vitamin D in critical care. Clin Nutr 2017; 36:1729-30.
194. Bianconi V, Violi F, Fallarino F et al. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? Drugs 2020.
195. Muller C, Karl N, Ziebuhr J et al. D,L-lysine acetylsalicylate + glycine impairs coronavirus replication. J Antivir Antiretovir 2020.
196. Draghici S, Nguyen TM, Sonna LA et al. COVID-19: disease pathways and gene expression chnages predict methylprednisolone can improve outcome in severe cases. Bioinformatics 2020.
197. Varatharajah N. COVID-19 CLOT: What is it? Why in the lungs? Extracellular histone, "auto-activation" of prothrombin, emperipolesis, megakaryocytes, "self-association" of Von Willebrand factor and beyond. Preprints 2020.
198. Cloutier N, Allaeys I, Marcoux G et al. Platelets release pathogenic serotonin and return to circulation after immune complex-mediated sequestration. PNAS 2018;E1550-E1559.

199. Hottz ED, Azevedo-Quintanilha Ig, Palhinha L et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020; 136:1330-1341.
200. Weinreich DM, Sivapalasingam S, Norton T et al. REGEN-CoV antibody cocktail clinical outcomes study in Covid-19 outpatients. medRxiv 2021.
201. Gutierrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. Int J Mol Sci 2019; 20:5028.
202. Titos E, Rius B, Gonzalez-Periz A et al. Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. J Immunol 2021; 187:5408-18.
203. Yoshihara T, Shimada K, Fukao K et al. Omega 3 polyunsaturated fatyy acids suppress the development of aortic aneurysms through the inhibition of macrophage-mediated inflammation. Circ J 2015; 79:1470-1478.
204. Hammock BD, Wang W, Gilligan MM et al. Eicosanoids. The overlooked storm in Coronavirus Disease 2019 (COVID-19)? Am J Pathol 2020.
205. Das UN. Can bioactive lipids inactivate coronavirus (COVID-19)? Arch Med Res 2020; 51:282-86.
206. Lee CR, Zeldin DC. Resolvin infectious inflammation by targeting the host response. N Engl J Med 2015; 373:2183-85.
207. Serhan CN. Novel pro-resolving lipid mediators in inflammation are leads for resolution physiology. Nature 2014; 510:92-101.
208. Law HK, Cheng CY, Ng HY et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood 2005; 105:2366-74.
209. Baranova A, Cao H, Zhang F. Unraveling risk genes of COVID-19 by multi-omics integrative analysis. Fronteirs in Medicine 2021.
210. Li S, Jiang L, Li X et al. Clinical and pathological investigation of patients with severe COVID-19. JCI Insight 2020; 5:e138070.
211. Yang B, Fulcher JA, Ahn J et al. Clinical characteristics and outcomes of COVID-19 patients receiving compassionate use Leronlimab. Clin Infect Dis 2021.
212. Patterson BK, seethamraju H, Dhody K et al. Disruption of the CCL5/RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. medRxiv 2020.
213. Patterson BK, seethamraju H, Dhody K 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.
214. Gulick RM, Fatkenheuer G, Burnside R et al. Five-year safety evaluation of Maraviroc in HIV-1-infected treatment-experienced patients. J Acquir Immune Defic Syndr 2014; 65:78-81.
215. Ayoub A, Alston S, Goodrich J et al. Hepatic safety and tolerability in the maraviroc clinical development program. AIDS 2010; 24:2743-55.
216. Giaquinto C, Mawela MP, Chokephaibutkit K et al. Pharmacokinetics, safety and efficacy of Maraviroc in treatment-experienced pediatric patients infected with CCR5=tropic HIV-1. Pediatr Infect Dis 2018; 37:459-65.
217. Idelsis Esquivel-Moynelo I, Perez-Escribano J, Duncan-Roberts Y et al. Effect of combination of interferon alpha-2b and interferon-gamma or interferon alpha 2b alone for elimination of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv 2020.
218. Davoudi-Monfarad E, Rahmani H, Khalili H et al. Efficacy and safety of interferon B-1a in treatment of severe COVID-19: A randomized clinical trial. medRxiv 2020.
219. Wang N, Zhan Y, Zhu L et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host & Microbe 2020;ePub.
220. Meng Z, Wang T, Chen L et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent COVID-19 in medical staff in an epidemic area. medRxiv 2020.
221. Feld JJ, Kandel C, Biondi MJ et al. Peginterferon lamda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Resp Med 2021.
222. Berg K, Bolt G, Andersen H et al. Zinc potentiates the antiviral action of human IFN-alpha tenfold. J Interferon Cytokine Res 2001; 21:471-74.
223. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. J Interferon Cytokine Res 1997; 17:469-72.

224. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home: Potential pitfalls and practical guidance. Ann Thorac Med 2020.
225. Jouffroy R, Jost D, Prunet B. Prehospital pulse oximetry: a red flag for early detection of silent hypoxemia in COVID-19 patients. Crit Care 2020; 24:313.
226. Yu LM, Bafadhel M, Doeward J et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyes from the PRINCIPLE trial. Lancet 2021.
227. Ramakrishnan S, Nicolau DV, Langford B et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Resp Med 2021.
228. Schultze A, Walker AJ, MacKenna B et al. Inhaled corticosteroids use and the risk of COVID-19 related death among 966,461 patients with COPD or asthma: An OpenSAFELY analysis. medRxiv 2020.
229. Aveyard P, Gao M, Lindson N et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. Lancet Resp Med 2021.
230. Tardif JC, Bouabdallaoui N, L'Allier PL et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. Lancet Resp Med 2021.
231. Finkelstein Y, Aks SE, Hutson JR et al. Colchicine poisoning: the dark side of an acient drug. Clinical Toxicology 2010; 48:407-14.
232. Effect of Dexamethasone in hospitalized patients with COVID-19-Preliminary report. N Engl J Med 2020.
233. Risch HA. Early outpatient treatment of symptomatic, High-Risk Covid-19 patients that should be ramped-up immediately as key to the pandemic crisis. Am J Epidemiol 2020; 189:1218-26.
234. Borba MG, Val FF, Sampaio S. Effect of High vs Low Doses of chloroquine diphosphate as adjunctive therapy for patietns hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A randomized clinical trial. JAMA Network Open 2020.
235. Boulware DR, Pullen MF, Bangdiwala AS et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020.
236. Barnabas RV, Brown ER, Bershteyn A et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection. Ann Intern Med 2020.
237. Mitja O, Corbacho-Monne M, Ubals M et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: A randomized-controlled trial. Clin Infect Dis 2020.
238. Mitja O, Ubals M, Corbach-Monne M et al. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. N Engl J Med 2020.
239. Cavalcanti AB, Zampieri FG, Rosa RG et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 2020; 383:2041-52.
240. Skipper CP, Pastick KA, Engen NW. Hydroxychlooquine in nonhospitalized adults with early COVID-19. Ann Intern Med 2020; 173:623-31.
241. Rosenberg ES, Dufort EM, Udo T et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323:2493-502.
242. Geleris J, Sun Y, Platt J et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020.
243. Magagnoli J, Narendran S, Pereira F. Outcomes of hydroxychloroquine usage in United states veterans hospitalized with COVID-19. medRxiv 2020.
244. Lopez A, Duclos G, Pastene B et al. Effects of hydroxychloroquine on Covid-19 in Intensive Care Unit Patients: Preliminary Results. Int J Antimicrob Agents 2020.
245. Mahevas M, Tran VT, Roumier M et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. medRxiv 2020.
246. Elsawah HK, Elsokary MA, Elrazzaz MG et al. Hydroxychloroquine for treatment of non-severe COVID-19 patients: systematic review and meta-analysis of controlled clinical trials. medRxiv 2020.
247. Axfors C, Schmitt AM, Janiaud P et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials. medRxiv 2020.
248. Sbidian E, Josse J, Lemaitre G et al. Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France. medrx 2020.
249. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020; 383:2030-2040.
250. Abd-Elsalam S, Esmail ES, Khalaf M et al. Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study. Am J Trop Med Hyg 2020; 103:1635-39.

251. Rajasingham R, Bangdiwala AS, Nicol MR et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. medRxiv 2020.
252. Self WE, Semler MW, Leither Lm et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19. a randomized clinical trial. JAMA 2020.
253. Johnston C, Brown ER, Stewart J et al. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial. EClinicalMedicine 2021.
254. Reis G, Silva EA, Silva DC et al. Effect of early treatment with hydroxychloroquine or Lopinavir and Ritonavir on risk of hospitalization among patients with COVID-19. The TOGETHER randomized clinical trial. JAMA Network Open 2021; 4:e216468.
255. Dubee V, Roy PM, Vielle B et al. Hydroxychloroquine in mild-to moderate COVID-19: a placebo-controlled double blind trial. Clinical Microbiology and Infection 2021.
256. Tett SE, Cutler DJ, Day RO et al. Bioavailability of hydroxychloroquine tablets in healthy volunteers. Br J Clin Pharmac 1989; 27:771-79.
257. MacGowan A, Hamilton F, Bayliss M et al. Hydroxychloroquine serum concentrations in non-critical care patients infected with SARS-CoV-2. medRxiv 2020.
258. Nicol MR, Joshi A, Rizk ML et al. Pharmacokinetic and pharmacological properties of chloroquine and hydroxychloroquine in the context of COVID-19 infection. medRxiv 2020.
259. Scudellari M. How the coronavirus infects our cells. Nature 2021; 595:640-644.
260. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020.
261. Lagier JC, Million M, Gautret P et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Travel Medicine and Infectious Disease 2020.
262. Million M, Gautret P, Colson P et al. Clinical efficacy of chloroquine derivatives in COVID-19 infection: Comparative meta-analysis between big data and the real world. New Microbes and New Infections 2020.
263. Morgan A, Stevens J. Does Bacopa monnieri improve memoy performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. J Altern Complement Med 2010; 16:753-59.
264. Azithromycin in hospitalized patients with COVID-19 (RECOVERY) a randomised, controlled, open-label, platform trial. medRxiv 2020.
265. Rosenthal N, Zhun Cao Z, Gundrum J et al. Risk factors associated with in-hospital mortality in a US National Sample of patients with COVID-19. JAMA Network Open 2020; 3:e2029058.
266. Butler CC, Yu LM, Dorward J et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet Resp Med 2021.
267. Zhang X, Song Y, Ci X et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res 2008; 57:524-29.
268. Ci X, Li H, Yu Q et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen activated protein kinase pathway. Fundamental & Clinical Pharmacology 2009; 23:449-55.
269. 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.
270. 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.
271. Blum VF, Cimerman S, Huneter JR et al. Nitazoxanide superioroty to placebo to treat moderate COVID-19 - A pilot prove of concept randomized double-blind clinical trial. EClinicalMedicine 2021; 37:100981.
272. Villar J, Confalonieri M, Pastores SM et al. Rationale for prolonged corticosteroid tratment in the acute respiratory distress syndrome (ARDS) caused by COVID-19. Crit Care Expl 2020; 2:e0111.
273. Fadel R, Morrison AR, Vahia A et al. Early course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020; 71:2114-20.
274. Chroboczek T, Lacoste M, Wackenheim C et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. medRxiv 2020.
275. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan,China. JAMA Intern Med 2020.

276. Cruz AF, Ruiz-Antoran B, Gomez AM et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. medRxiv 2020.
277. Liu J, Zheng X, Huang Y et al. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol 2020.
278. Meduri GU, Bridges L, Shih MC et al. 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; 42:829-40.
279. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. A meta-analysis. JAMA 2020.
280. Ruiz-Irastorza G, Pijoan JI, Bereciatua E et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. medRxiv 2020.
281. Tomazini BM, Maia IS, Cavalcanti AB et al. 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; 324:1307-16.
282. Edalatifard M, Akhtari M, Salehi M et al. Intravenous methylprednisolone pulse as a treatment for hospitalized severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020.
283. 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.
284. Dequin PF, Heming N, Meziani F et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. A randomized Clinical trial. JAMA 2020.
285. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med 2021; 389:790-802.
286. Barrett TJ, Lee AH, Xia Y et al. Platelet and vascular biomarkers associate with thrombosis and death in coronavirus disease. Circulation Research 2020; 127:945-47.
287. Zhang S, Liu Y, Wang X et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. Journal of hematology & oncology 2020; 13:120.
288. Kauerova S, Bartuskova H, Muffova B et al. Statins directly influence the polarization of adipose tissue macrophages: A role in chronic inflammation. Biomedicines 2021; 9:211.
289. van der Meij E, Koning GG, Vriens PW et al. A clinical evaluation of statin pleiotrophy: Statins selectively and dose-dependently reduce vascular inflammation. PloS ONE 2013; 8:e53882.
290. Calfee CS, Delucchi KL, Sinha P et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Resp Med 2018; 6:691-98.
291. Zhang XJ, Qin JJ, Cheng X et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metabolism 2020.
292. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA et al. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care 2020; 24:429.
293. Gupta A, Madhavan MV, Poterucha TJ et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Research Square 2020.
294. Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. Am J Cardiol 2020.
295. Tan WY, Young BE, Lye DC et al. Statin use is assocaited with lower disease severity in COVID-19 infection. Nature Research 2020.
296. Duarte M, Pelorosso F, Nicolosi L et al. Telmisartan for treatment of COVID-19 patients: an open multicenter randomized clinical trial. EClinicalMedicine 2021; 37:100962.
297. Rothlin RP, Vetulli HM, Duarte M et al. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. Drug Dev Res 2020; 81:768-70.
298. Nejat R, Sadr AS, Freitas BT et al. Losartan inhibits SARS-CoV-2 replication in vitro. J Pharm Pharm Sci 2021; 24:390-399.
299. Liu Y, Yang Y, Zhang C et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020; 63:364-74.

300. Nunez-gil IJ, Olier I, Feltes G et al. Renin-angiotensin system inhibitors effect before and during hospitalization in COVID-19 outcomes: final analysis of the international HOPE COVID-19 (Health Outcome Predictive evaluation for COVID-19) Registry. Am Heart Journal 2021.
301. Zhang P, Zhu L, Cai J et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020; 126:1671-81.
302. Byttebier G, Belmans L, Alexander M et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and/or ARBs. Human vaccines & Immunotherapeutics 2021.
303. 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.
304. Chen CX, Wang JJ, Li H et al. JAK-inhibitors for coronavirus disease-2019 (COVID): a meta-analysis. Leukemia 2021.
305. Calabrese LH, Calabrese C. Baricitinib and dexamethasone for hospitalized patients with COID-19. Cleve Clin J Med 2021.
306. Jalali F, Rezaie S, Rola P et al. COVID-19 pathophysiology: Are platelets and serotonin hiding in plain sight? ssrn 2021.
307. Lin OA, Karim ZA, Vemana HP et al. The antidepressant 5-HT2a receptor antagonists Pizotifen and cyproheptadine inhibit serotonin-enhanced platelet function. PloS ONE 2014; 9:e87026.
308. Zaid Y, Guessous F, Puhm F et al. Platelet reactivity to thrombin differs between patients with COVID-19 and those with ARDS unrelated to COVID-19. Blood Advances 2021; 5:635-39.
309. Zaid Y, Puhm F, Allaeys I et al. Platelets can associate with SARS-CoV-2 RNA and are hyperactivated in COVID-19. Circ Res 2020; 127:1404-18.
310. Dawson C, Christensen CW, Rickaby DA et al. Lung damage and pulmonary uptake of serotonin in intact dogs. J Appl Physiol 1985; 58:1761-66.
311. MacLean MR, Herve P, Eddahibi S et al. 5-hydroxytryptamine and the pulmonary circulation: receptors, transporters and the relevance to pulmonary arterial hypertension. Br J Pharmacol 2000; 131:161-68.
312. 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.
313. Watchorn J, Hang DY, Joslin J et al. Critically ill COVID-19 patients with acute kidney injury have reduced renal blood flow and perfusion despite preserved cardiac function: A case-control study using contrast enhanced ultrasound. Lancet Resp Med 2021.
314. McGoon MD, Vanhoutte PM. Aggregating platelets contract isolated canine pulmonary arteries by releasing 5-hydroxytryptamine. J Clin Invest 1984; 74:823-33.
315. Almqvist P, Skudder P, Kuenzig M et al. Effect of cyproheptadine on endotoxin-induced pulmonary platelet trapping. Am Surg 1984; 50:503-5.
316. Skurikhin EG, Andreeva TV, Khnelevskaya ES et al. Effect of antiserotonin drug on the development of lung fibrosis and blood system reactions after intratracheal administration of bleomycin. Bull Exp Biol Med 2012; 152:519-23.
317. Doaei S, Gholami S, Rastgoo S et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. J Transl Med 2021; 19:128.
318. Wang Y, Zhang D, Du G et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicenter trial. Lancet 2020; 395:1569-78.
319. Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the treatment of Covid-19-Preliminary report. N Engl J Med 2020;ePub.
320. Spinner CD, Gottlieb RL, Criner GJ et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. A randomized clinical trial. JAMA 2020.
321. Pan H, Peto R, Karim QA et al. Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial. medrx 2020.
322. Ohl ME, Miller DR, Lund BC et al. Association of remdesivir treatment with survival and length of hospital stay among US veterans hospitalized with COVID-19. JAMA Network Open 2021; 4:e2114741.
323. Jeffreys L, Pennington SH, Duggan J et al. Remdesivir-Ivermectin combination displays synergistic interactions with improved in vitro antiviral activity against SARS-CoV-2. bioRxiv 2020.
324. Marik PE, Kory P, Varon J et al. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. Exp Rev Anti Infect Ther 2020.

325. Kory P, Meduri GU, Iglesias J et al. Clinical and scientific rationale for the "MATH+" hospital treatment protocol for COVID-19. J Intensive Care Med 2020.
326. Ranjbar K, Shahriarad R, erfani A et al. Methylprednisolone or dexamethasone, which one is the superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. BMC Infect Dis 2021; 21:337.
327. Ko JJ, Wu C, Mehta N et al. A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. medRxiv 2021.
328. Fowler AA, Truwit JD, Hite D et al. Vitamin C Infusion for TReatment In Sepsis-Induced Acute Lung Injury-CITRIS-ALI: A Randomized, Placebo Controlled Clinical Trial. JAMA 2018; 322:1261-70.
329. Marik PE, Khangoora V, Rivera R et al. Hydrocortisone, Vitamin C and Thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. Chest 2017; 151:1229-38.
330. Barabutis N, Khangoora V, Marik PE et al. Hydrocortisone and Ascorbic Acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. Chest 2017; 152:954-62.
331. Cheng RZ. Can early and high-dose vitamin C prevent and treat coronavirus disease 2019 (COVID-19). Medicine in Drug Discovery 2020.
332. Wang Y, Lin H, Lin BW et al. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. Ann Intensive Care 2019; 9:58.
333. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. PharmaNutrition 2020; 12:100190.
334. Iglesias J, Vassallo AV, Patel V et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis. Chest 2020; 158:164-73.
335. 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.
336. Zhang J, Rao X, Li Y et al. High-dose vitamin C infusion for the treatment of critically ill COVID-19. Research Square 2020.
337. Kumari P, Dembra S, Dembra P et al. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020; 12:e11779.
338. Al Sulaiman K, Al Juhani O, Badreldin HA et al. Adjunctive therapy with ascorbic in critically ill patients with COVID-19: A multicenter propensity score matched study. Crit Care 2021.
339. Lankadeva YR, Peiris RM, Okazaki N et al. Reversal of the pathophysiological responses to Gram-negative sepsis by megadose Vitamin C. Crit Care Med 2020.
340. Zhang J, Rao X, Li Y et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intenisve Care 2020.
341. Lavinio A, Ercole A, Battaglini D et al. Safety profile of enhanced thromboprophylaxis strategies for critically ill COVID-19 patients during the first wave of the pandemic: observational report from 28 European intensive care units. Crit Care 2021; 25:155.
342. 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.
343. Tomassa-Irriguible TM, Lielsa-Berrocal L. COVID-19: Up to 87% critically ill patients had low vitamin C values. Research Square 2020.
344. 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.
345. Lopes RD, Furtado RH, Bronhara B et al. 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; 397:2253-63.
346. Murshed MR, Bhiuyan E, Saber S et al. A case series of 100 COVID-19 positive patients treated with combination of Ivermectin and Doxycycline. Bangladesh Coll Phys Surg 2020; 38:10-15.
347. Jans DA, Wagstaff KM. Ivermectin as a broad-spectrum host directed anti-viral: The real deal. Cells 2020; 9:2100.
348. Sharun K, Dhama K, Patel SK et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob 2020; 19:23.
349. Peralta EG, Fimia-Duarte R, Cardenas JW et al. Ivermectin, a drug to be considered for the prevention and treatment of SARS-CoV-2. Brief literature review. EC Veterinary Science 2020; 5:25-29.

350. Al-Jassim KB, Jawad AA, Al-Masoudi EA et al. Histopathological and biochemical effects of ivermectin on kidney functions, lung and the ameliorative effects of vitamin C in rabbits. Bas J Vet Res 2016; 14:110-124.
351. Mudatsir M, Yufika A, Nainu F et al. Antiviral activity of ivermectin against SARS-CoV-2: an old-fashioned dog with a new trick- Literature review. Sci Pharm 2020; 88:36.
352. Carvallo H, Hirsch R, Farinella ME. Safety and efficacy of the combined use of Ivermectin, dexamethasone, enoxaparin and aspirin against COVID-19. medRxiv 2020.
353. Heaney RP, Armas LA, Shary JR et al. 25-hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr 2008; 87:1738-42.
354. Menezes RR, Godin AM, Rodrigues FF et al. Thiamine and riboflavin inhibit production of cytokines and increase the anti-inflammatory activity of a corticosteroid in a chronic model of inflammation induced by complete Freund's adjuvant. Pharmacological Reports 2020; 69:1036-43.
355. Vatsalya V, Li F, Frimodig J et al. Therapeutic prospects for Th-17 cell immune storm syndrome and neurological symptoms in COVID-19: Thiamine efficacy and safety, In-vitro evidence and pharmacokinetic profile. medRxiv 2020.
356. Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! J Thorac Dis 2016; 8:1062-66.
357. Moskowitz A, Donnino MW. Thiamine (vitamin B1) in septic shock: a targeted therapy. J Thorac Dis 2020; 12 (suppl 1):S78-S83.
358. Woolum JA, Abner EL, Kelly A et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Crit Care Med 2018; 46:1747-52.
359. Marik PE. Thiamine: An essential component of the metabolic resuscitation protocol. Crit Care Med 2018; 46:1869-70.
360. Al Sulaiman K, Aljuhani O, Al Dossari M et al. Evaluation of thiamine as adjunctive therapy in COVID-19 critically ill patients: A multicenter propensity score matched study. Research Square 2021.
361. Lee CY, Jan WC, Tsai PS et al. Magnesium sulfate mitigates acute lung injury in endotoxemia rats. J Trauma 2011; 70:1177-85.
362. Salem M, Kasinski N, Munoz R et al. Progressive magnesium deficiency inceases mortality from endotoxin challenge:Protective effects of acute magnesium replacement therapy [abstract]. Crit Care Med 1995;A260.
363. Jiang P. Does hypomagnesemia impact on the outcome of patients admitted to the intensive care unit? A systematic review and meta-analysis. Shock 2019; 47:288-95.
364. Chen L, Jiang X, Huang L et al. Bioequivalence of a single 10-mg dose of finasteride 5-mg oral disintegrating tablets and standard tablets in healthy adult male Han Chinese volunteers: A randomized sequence, open-label, two-way crossover study. Clinical Therapeutics 2009; 31:2242-48.
365. Calaf J, Lopez E, Millet A et al. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: A 12-month, double-blind, parallel; clinical trial. J Clin Endocrinol Metab 2007; 92:3446-52.
366. Patterson BK, Guevara-Coto J, Yogendra R et al. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. Front Immunol 2021.
367. Oldenburg CE, Doan T. Azithromycin for severe COVID-19. Lancet 2020.
368. Futado RH, Berwanger O, Fonseca HA et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised trial. Lancet 2020.
369. Agarwal A, Mukherjee A, Kumar G et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020; 371:m3939.
370. Simonovich VA, Pratx LD, Scibona P et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med 2020.
371. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E et al. Convalescent plasma for COVID-19: A multicenter, randomized clinical trial. medRxiv 2020.
372. Balcells ME, Rojas L, Le Corre N et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. PLOS Med 2021; 18:e1003415.
373. Janiaud P, Axfors C, Schmitt AM et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19. A systematic review and meta-analysis. JAMA 2021.

374. Li L, Zhang W, Hu Y et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. A randomized clinical trial. JAMA 2020; 324:460-470.
375. Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? Filaria Jurnal 2003; 3 (Suppl I):S8.
376. Thompson MA, Henderson JP, Shah PK et al. Convalescent plasma and improved survival in patients with hematologic malignancies and COVID-19. medRxiv 2021.
377. Rosas IO, Brau N, Waters M et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv 2020.
378. Hermine O, Mariette X, Tharaux PL et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia.A randomized Clinical Trial. JAMA Intern Med 2020.
379. Stone JH, Frigault MJ, Sterling-Boyd NJ et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020.
380. Salvarani C, Dolci G, Massari M et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. A randomized clinical trial. JAMA Intern Med 2020.
381. Salama C, Han J, Yau L et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2020.
382. Gordon AC, Mouncey PR, Rowan KM et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19 - Preliminary report. medRxiv 2021.
383. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020.
384. Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clinical Microbiology & Infection 2021; 27:9-11.
385. Le Balc'h P, Pinceaux K, Pronier C et al. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care 2020; 24:530.
386. Koehler P, Bassetti M, Chen SC et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021.
387. Xu Q, Wang T, Quin X et al. Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19; a case series. Crit Care 2020; 24:250.
388. Elharrar X, Trigui Y, Dois AM et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA 2020.
389. Reddy MP, Subramaniam A, Afroz A et al. Prone positioning of nonintubated patients with Coronavirus Disease 2019- A systematic review and meta-analysis. Crit Care Med 2021.
390. Xin Y, Martin K, Morais CC et al. Diminishing efficacy of prone positioning with late application in evolving lung injury. Crit Care Med 2021.
391. Haymet A, Bassi GL, Fraser JF. Airborne spread of SARS-CoV-2 while using high-flow nasal cannula oxygen therapy: myth or reality. Intensive Care Med 2020; 46:2248-51.
392. Francone M, Lafrate F, Masci GM et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. European Radiology 2020; 30:6808-17.
393. 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.
394. Parry AH, Wani AH, Shah NN et al. 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.
395. Zhang J, Meng G, Li W et al. Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respiratory Research 2020; 21:180.
396. Yang R, Li X, Liu H et al. Chest CT severity score: An imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging 2020; 2:e2000047.
397. Li K, Wu J, Wu F et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Investigative Radiology 2020; 55:1-5.
398. Pan F, Ye T, Sun P et al. Time course of lung changes at Chest CT during recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2021; 295:715-21.
399. Ding X, Xu J, Zhou J et al. Chest CT findings of COVID-19 pneumonia by duration of symptoms. European Journal of Radiology 2020; 127:109009.
400. Bernheim A, Mei X, Huang M et al. Chest CT findings in Coronavirus disease 2019 (COVID-19): relationship to duration of infection. Radiology 2020; 295:685-91.
401. Ichikado K, Suga M, Muranka H et al. Prediction of prognosis for acute respiratory distress syndrome with thin-section CT: Validation in 44 cases. Radiology 2006; 238:321-29.

402. Ichikado K, Suga M, Muller NL et al. Acute interstitial pneumonia. Comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002; 165:1551-56.
403. Keith P, Day M, Perkins L et al. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care 2020.
404. Keith P, Wells AH, Hodges J et al. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: A single center experience. Crit Care 2020; 24:518.
405. Busund R, Koukline V, Utrobin U et al. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002; 28:1434-39.
406. Morath C, Weigand MA, Zeier M et al. Plasma exchange in critically ill COVID-19 patients. Crit Care 2020; 24:481.
407. Khamis F, Al-Zakwani I, Al Hashmi S et al. Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect DIs 2020.
408. Fernandez J, Gratacos-Gines J, Olivas P et al. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. Crit Care Med 2020.
409. Gucyetmez B, Atalan HK, Sertdemir I et al. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care 2020; 24:492.
410. Poor HD, Ventetuolo CE, Tolbert T et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfuncion responsive to thrombolysis. medRxiv 2020.
411. Wang J, Najizadeh N, Moore EE et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated respiratory distress syndrome (ARDS): A case series. J Thromb Haemost 2020.
412. Patel M, Dominguez E, Sacher D et al. Etoposide as salvage therapy for cytokine storm due to Coronavirus Disease 2019. Chest 2021; 159:e7-e11.
413. Hamizi K, Aouidane S, Belaaloui G. Etoposide-based therapy for severe forms of COVID-19. Medical Hypotheses 2020; 142:109826.
414. Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. Inflammation Regeneration 2020; 40:19.
415. Opoka-Winiarska V, Grywalska E, Rolinski J. Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? BMC Medicine 2020; 18:214.
416. Kyriazopoulou E, Leventogiannis K, Norrby-Teglund A et al. Macrophage activation-like syndrome: an immunological entity associated with rapid progression to death in sepsis. BMC Medicine 2017; 15:172.
417. Brisse E. Hemophagocytic lymphohistiocytosis (HLH): A heterogenous spectrum of cytokine-driven immune disorders. Cytokine Growth Factors Reviews 2015; 26:263-80.
418. Mehta R. Hemophagocytic lymphohistiocytosis (HLH) : a review of literature. Med Oncol 2013; 30:740.
419. Abou-Arab O, Huette P, Debouvries F et al. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. Crit Care 2020; 24:645.
420. Bagate F, Tuffet S, Masi P et al. Rescue thearpy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. Ann Intensive Care 2020.
421. Caplan M, Goutay J, Bignon A et al. Almitrine infusion in severe acute respiratory syndrome coronavirus-2 indued acute respiratory distress syndrome: A single-center observational study. Crit Care Med 2020.
422. Payen D. Coronavirus disease 2019 acute respiratory failure: Almitrine drug resuscitaion or resuscitating patients by almitrine? Crit Care Med 2020.
423. 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.
424. Abrams D, Lorusso R, Vincent JL et al. ECMO during the COVID-19 pandemic: when is it unjustified. Crit Care 2020; 24:507.
425. Supady A, Taccone FS, Lepper PM et al. Survival after extracorporeal membrane oxygenation in severe COVID-19 ARDS: results from an international multicenter registry. Crit Care Med 2021; 25:90.
426. Barbaro RP, MacLaren G, Boonstra PS et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020.
427. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. Lancet Resp Med 2021; 8:944-46.
428. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. N Engl J Med 2020.

429. Cerutti A, Chen K, Chorny A. Immunoglobulin responses at the mucosal interface. Annu Rev Immunol 2011; 29:273-93.
430. Jacobs JJ. Neutralizing antibodies mediate virus-immue pathology of COVID-19. Med Hypotheses 2020; 143:109884.
431. Caricchio R, Abbate A, Gordeev I et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19. A randomized clinical trial. JAMA 2021.
432. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. Medical Hypotheses 2020; 144:11005.
433. Saba A, Vaidya PJ, Chavhan VB et al. Combined pirfenidone, azithromycin and prednisolone in post-H1N1 ARDS pulmonary firbosis. Sarcoidosis Vasc Diffuse Lung Dis 2018; 35:85-90.
434. Spagnolo P, Balestro E, Aliberti S et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Resp Med 2020; 8:750-752.
435. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antibibrotic therapy. Lancet Resp Med 2020; 8:807-15.
436. Brouwer WP, Duran S, Kuijper M et al. Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study. Crit Care 2019; 23:317.
437. Villa G, Romagnoli S, De Rosa S et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. Crit Care 2020; 24:605.
438. Ahmad Q, DePerrior SE, Dodani S et al. Role of inflammatory biomarkers in the prediction of ICU admission and mortality in patients with COVID-19. Medical Research Archives 2020; 8:1-10.
439. Marik PE, Stephenson E. The ability of procalcitonin, lactate, white blood cell count and neutrophil-lymphocyte count ratio to predict blood stream infection. Analysis of a large database. J Crit Care 2020; 60:135-39.
440. Ichikado K, Muranaka H, Gushima Y et al. Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study. BMJ Open 2012; 2:e000545.
441. Tan C, Huang Y, Shi F et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020; 92:856-62.
442. 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.
443. Stephenson E, Hooper MH, Marik PE. Vitamin C and Point of Care glucose measurements: A retrospective, Observational study [Abstract]. Chest 2018; 154 (suppl.):255a.
444. Hekimian G, Kerneis M, Zeitouni M et al. COVID-19 acute myocarditis and multisystem inflanmmatory syndrome in Adult Intensive and cardiac Care Units. Chest 2020.
445. Ma KL, Liu ZH, Cao CF et al. COVID-19 myocarditis and severity factors: An adult cohort study. medRxiv 2020.
446. Brosnahan SB, Bhatt A, Berger JS et al. COVID-19 pneumonia hospitalizations followed by re-presentation for presumed thrombotic event. Chest 2020.
447. Giannis D, allen SL, Tsang J et al. Post-discharge thromboembolic outcomes and mortality of hospitalized COVID-19 patients: The CORE-19 registry. Blood 2021.
448. Spyropoulos AC, Lipardi C, Xu J et al. Modified IMPROVE VTE Risk Score and elevated D-Dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. TH Open 2020; 4:e59-e65.
449. Kunutsor SK, Seidu S, Blom AW et al. Serum C-reactive protein increases the risk of venous thromboembolism: a prospective study and meta-analysis of published prospective evidence. Eur J Epidemiol 2017; 32:657-67.
450. Patterson BK, Francisco EB, Yogendra R et al. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in post-acute sequelae of COVID-19 (PASC) up to 15 months post-infection. bioRxiv 2021.
451. Luvanda M, Posch W, Vosper J et al. Dexamethasone promotes *Aspergillus fumigatus* growth in macrophages by triggering M2 repolarization via targeting PKM2. J Fungi 2021; 7:70.
452. Reiter RJ, Sharma R, Ma Q et al. Plasticity of glucose metabolism in activated immune cells: advantages for melatonin inhibition of COVID-19 disease. Melatonin Res 2020; 3:362-79.

453. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020.
454. Prescott HC, Girard TD. Recovery from Severe COVID-19. Leveraging the lessons of survival from sepsis. JAMA 2020.
455. Greenhalgh T, Knight M, A'Court C et al. Management of post-acute Covid-19 in primary care. BMJ 2020.
456. Chopra V, Flanders SA, O'Malley M. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2020.
457. Mandal S, Barnett J, Brill SE et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalization for COVID-19. Thorax 2020.
458. Michelen M, Manoharan L, Elkheir N et al. Characterising long-term covid-19: a rapid living systematic review. medRxiv 2020.
459. Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged feom hospital: a cohort study. Lancet 2021.
460. Logue JK, Franko NM, McCulloch DJ et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Network Open 2021; 4:e210830.
461. Janiri D, Carfi A, Kotzalidis GD et al. Posttraumatic stress disorder in patients after severe COVID-19 infection. JAMA Psychiatry 2021.
462. Voruz P, Allali G, Benzakour L et al. Long COVID neuropsychological deficits after severe, moderate or mild infection. medRxiv 2021.
463. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequalae of COVID-19. Nature 2021.
464. Yong SJ. Long-haul COVID-19: Putative pathophysiology, risk factors, and treatments. medRxiv 2020.
465. Taquet M, Geddes JR, Husain M et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021.
466. Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect DIs 2020.
467. Bryce C, Grimes Z, Pujadas E 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.
468. Lu Y, Li X, Geng D et al. Cerebral micro-structutal changes in COVID-19 patients - An MRI-based 3-month follow-up study. EClinicalMedicine 2020.
469. Franke C, Ferse C, Kreye J et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Brain,Behavor, and Immunity 2021.
470. Sirous R, Taghvaei R, Hellinger JC et al. COVID-19-associated encephalopathy with fulminant cerebral vasoconstriction: CT and MRI findings. Radiology Case Reports 2020; 15:2208-12.
471. Magro CM, Mulvey JJ, Laurence J et al. Docked severe acute respiratory syndrome coronavirus 2 proteins within the cutaneous and subcutaneous microvasculature and their role in the pathogenesis of severe coronavirus disease 2019. Human Pathology 2020; 106:106-16.
472. Theoharides TT, Cholevas C, Polyzoidis K et al. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. Biofactors 2021; 47:232-41.
473. Riche F. Protracted immune disorders at one year after ICU discharge in patients with septic shock. Crit Care 2018; 22:42.
474. Andreakos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. Allergy 2020.
475. COVID-19 rapid guideline: managing the long-term effects of COVID-19. www.nice.org.uk/guidance/ng188 . 2020. National Institute for Health and Care Excellence. 4-26-2021.
476. Sanabria-Mazo JP, Montero-Marin J, Feliu-Soler A et al. Mindfulness-based program plus amygdala and inusla retraining (MAIR) for the treatment of women with fibromyalgia: A pilot ramdomized controlled trial. J Clin Med 2020; 9:3246.
477. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. Biofactors 2020; 46:306-8.
478. Bawazeer MA, Theoharides TC. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-kB, inhibited by methoxyluteolin. Eur J Pharmacol 2019; 865:172760.
479. Weng Z, Patel AB, Panagiotidou S et al. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J Allergy Clin Immunol 2015; 135:1044-52.

480. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. J Pharmacol Exp Ther 2017; 361:462-71.
481. Calis Z, Mogulkoc R, Baltaci AK. The roles of flavonols/flavonoids in neurodegeneration and neuroinflammation. Mini Rev Med Chem 2020; 20:1475-88.
482. Kurcicka L, Lauer SA, Laeyendecker O et al. Variation in false-negative rate of reverse transcriptase polmerase chain reacion-based SARS-CoV-2 tests by time since exposure. Ann Intern Med 2020; 173:262-67.
483. Cheng HY, Jian SW, Liu DP et al. 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; 180:1156-63.
484. Zhao J, Yang Y, Huang H et al. Relationship between ABO blood group and the COVID-19 susceptibility. medRxiv 2020.
485. Banerjee A, Pasea L, Harris S et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet 2020; 395:1715-25.
486. Goren A, Vamo-Galvan S, Wambier CG et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain- A potential clue to the role of androgens in COVID-19 severity. J Cosmetic Dermatol 2020.
487. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China. Lancet 2020; 395:497-506.
488. Guan W, Ni Z, Hu Y et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020.
489. von der Thusen J, van der Eerden M. Histopathology and genetic susceptibility in COVID-19 pneumonia. Eur J Clin Invest 2020.
490. Sweeney TE, Liesenfeld O, Wacker J et al. Validation of inflammopathic, adaptive, and coagulopathic sepsis endotypes in Coronavirus disease 2019. Crit Care Med 2020.
491. Tartof SY, Qian L, Hong V et al. Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. Ann Intern Med 2020.
492. Pujadas E, Chaudhry F, McBride R et al. SARS-CoV-2 viral load predictes COVID-19 mortality. Lancet Resp Med 2020.
493. Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. Science 2020; 369.
494. Zhang Q, Bastard P, Liu Z et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020.
495. Li MY, Li L, Zhang Y et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious Diseases of Poverty 2020; 9:45.
496. Zhou Y, Fu B, Zheng X et al. Pathogenic T cellls and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev 2020; 7:998-1002.
497. Blanco-Melo D, Nilsson-Payant BE, Liu WC et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020; 181:1036-45.
498. Giamarellos-Bouboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host & Microbe 2020.
499. McGonagle D, Sharif K, O'Regan A et al. The role of cytokines including interleukin-6 in COVID-19 induces pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews 2020; 19:102537.
500. Zhou F, Yu T, Du R et al. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
501. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Febratinib. J Microbiol Immunol Infect 2020.
502. Giamarellos-Bourboulis EJ, Netea MG, Rovina N et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. medRxiv 2020.
503. Mehta P, McAuley DF, Brown M et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395:1033-34.
504. Qin C, Zhou L, Hu Z et al. Dysregulation of the immune response in patiens with COID-19 in Wuhan, China. Lancet Infect Dis 2020.
505. Zhang C, Wu Z, Li JW et al. 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.

506. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the "Cytokine Storm" in COVID-19. J Infection 2020.
507. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020.
508. Tay MZ, Poh CM, Renia L et al. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews 2020; 20:363-74.
509. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med 2020; 46:1105-8.
510. Teuwen LA, Geldhof V, Pasut A et al. COVID-19: the vasculature unleashed. Nature Reviews 2020.
511. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020.
512. Ackermann M, Verleden SE, Kuehnel M et al. Pulmonary vascular endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N Engl J Med 2020; 383:120-128.
513. Torrealba JR, Fisher S, Kanne JP et al. Pathology-radiology correlation of common and uncommon computed tomographic patterns of organizing pneumonia. Human Pathology 2018; 71:30-40.
514. Kanne JP, Little BP, Chung JH et al. Essentials for radiologists on COVID-19: an Update-Radiology Scientific Expert Panel. Radiology 2020.
515. Copin MC, Parmentier E, Duburcq T et al. Time to consider histologic pattern of lung injury to treat critically ill patietns with COVID-19 infection [letter]. Intensive Care Med 2020.
516. Gattinoni L, Chiumello D, Caironi P et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med 2020; 46:1099-102.
517. Chiumello D, Cressoni M, Gattinoni L. Covid-19 does not lead to a "typical" Acute Respiratory Distress syndrome. Lancet 2020.
518. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020; 24:154.
519. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med 2005; 31:776-84.
520. Patel AN, Desai SS, Grainger DW et al. Usefulness of ivermectin in COVID-19 illness. medRxiv 2020.
521. Jeronimo CM, Farias ME, Almeida FF et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A ramdomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020.
522. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med 2020.
523. Schurink B, Roos E, Radonic T et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 2020.
524. Buijsers B, Yanginlar C, Maciej-Hulme ML et al. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. EBioMedicine 2020.
525. Kim SY, Jin W, Sood A et al. Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions. Antiviral Res 2020; 181:104873.
526. Clausen TM, Sandoval DR, Spliid CB et al. SARS-CoV-2 infection depends on cellular heparan sulphate and ACE2. bioRxiv 2020.
527. Kwon PS, Oh H, Kwon SJ et al. Sulphated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discovery 2020; 6:50.
528. Huang X, Han S, Liu x et al. Both UFH and NAH alleviate shedding of endothelial glycocalyx and coagulopathy in LPS-induced sepsis. Exp Thera Med 2020; 19:913-22.
529. Buijsers B, Yanginlar C, de Nooijer A et al. Increased plasma heparanase activity in COVID-19 patients. medRxiv 2020.
530. May JM, Qu ZC. Ascorbic acid prevents oxidant-induced increases in endothelial permeability. Biofactors 2011; 37:46-50.
531. Utoguchi N, Ikeda K, Saeki K et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. Journal of Cellular Physiology 1995; 163:393-99.
532. Han M, Pendem S, Teh SL et al. Ascorbate protects endothelial barrier function during septic insult: Role of protein phosphatase type 2A. Free Radic Biol Med 2010; 48:128-35.
533. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci 2004; 1024:138-46.
534. Shodell M, Siegal FP. Corticosteroids depress INF-alpha-producing plasmacytoid dentritic cells in human blood. J Allergy Clin Immunol 2001; 108:446-48.
535. Thomas BJ, Porritt RA, Hertzog PJ et al. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. Scientific Reports 2014; 4:7176.

536. Singanayagam A, Glanville N, Girkin JL et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nature Communications 2018; 9:2229.
537. Salton F, Confalonieri P, Santus P et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv 2020.
538. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet 1983;995-97.
539. Sajid MS, Iqbal Z, Muhammad G et al. Effects of ivermectin on the cellular and humoral immune responses of rabbits. Life Sci 2007; 80:1966-70.
540. Blakley BR, Rousseaux CG. Effect of ivermectin on the immune response in mice. Am J Vet Res 1991; 52:593-95.