- 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. [461,462]
- ECHO as clinically indicated; Patients may develop a severe "septic" cardiomyopathy and/or COVID-19 myocarditis. [463,464]

13. 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

14. Post Hospital Discharge management

a. Patients have an increased risk of thromboembolic events post-discharge. [465,466] Extended thromboprophylaxis (? with a DOAC) should be considered in high-risk patients. Risk factors include:[467]
    i. Increased D dimer (> 3 times ULN)
    ii. Increased CRP (> 2 times ULN) [468]
    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.

15. Pathophysiology of COVID-19

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

The pathophysiology of COVID-19

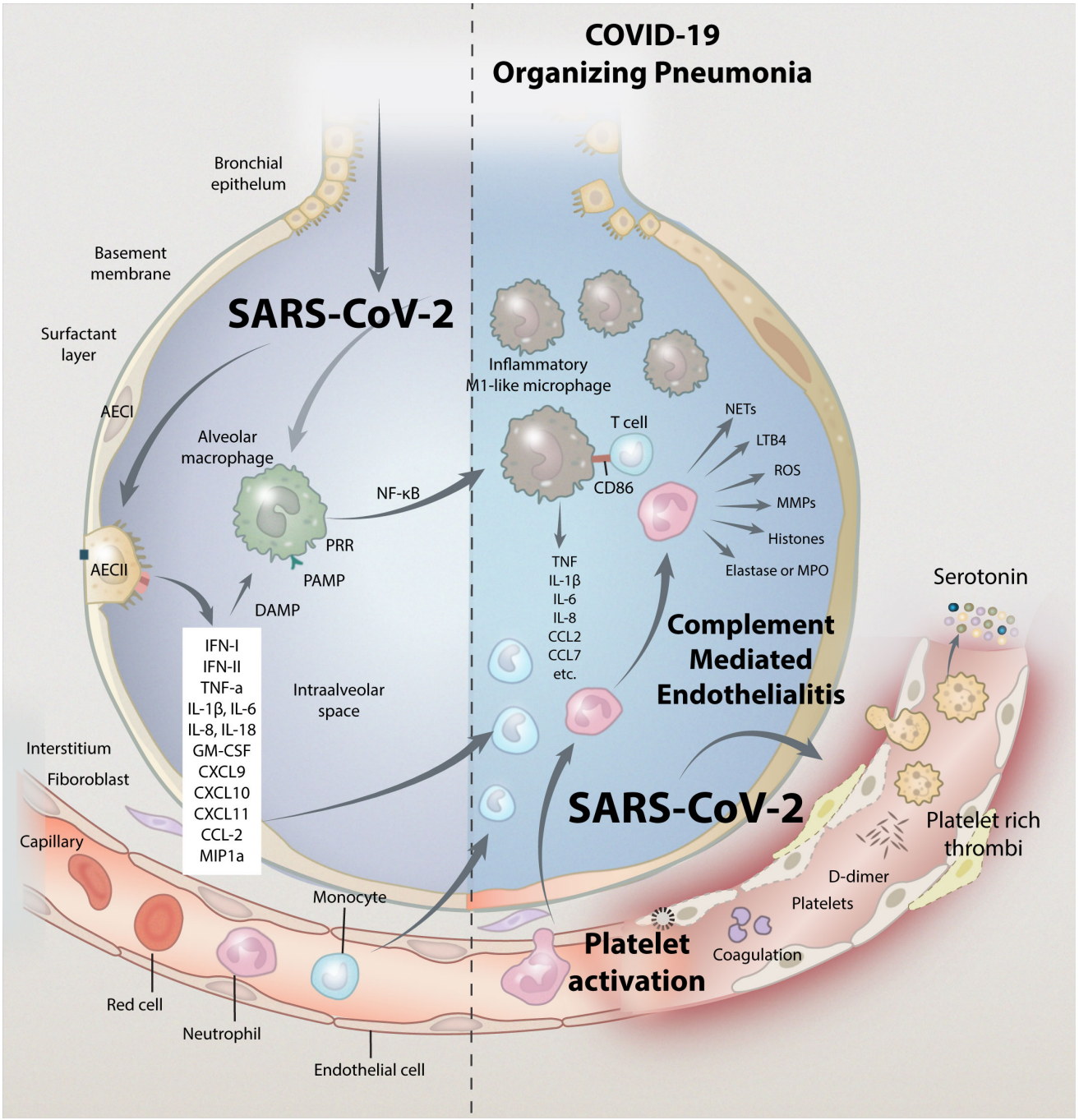
- Pulmonary Macrophage Activation Syndrome
  - Severe hyperinflammatory status
- Microvascular endothelialitis and thrombosis
  - Activation of clotting esp. platelet thrombi in lung and brain
  - High circulating serotonin
    - Arterial vasoconstriction
    - V/Q mismatch
  - Organ ischemia
- Multiple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

Based on clinical, proteomic, and genomic studies as well as autopsy data severe COVID-19 disease can be considered to be the connection of three basic pathologic processes, namely a pulmonary macrophage activation syndrome with excess production of cytokines and chemokines and uncontrolled inflammation, a complement mediated endothelialitis together with a procoagulant state with a thrombotic microangiopathy (see figure 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.[385] Interestingly, these monocytes contain high levels of the spike protein.[469] 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 [470]
- Statins [313,314]
- Omega-3 fatty acids [222-224]
- Melatonin [471]
- Vitamin C
- Anti-androgen therapy [472-474]
- Curcumin (turmeric) [48]

Figure 10. Pathogenetic mechanism of severe COVID-19 disease



16. 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.[475-486] 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.[484,487] 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. [486] 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.[486] 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.[488]

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: [486]

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.[489] Brain MRIs' 3 months post-infection demonstrated micro-structural changes in 55% of patients. [490] In addition, features of encephalopathy may be related to encephalitis and auto-reactive brain antibodies [491] as well as severe cerebral vasoconstriction. [492] The brain microvasculature expresses ACE-2 receptors and SARS-CoV-2 "pseudovirions" may bind to the microvascular endothelium causing cerebral microvascular inflammation and clotting.[493].
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.[494] Following stimulation, mast cells release proinflammatory mediators such as histamine, tryptase, chemokines and cytokines which may result in neurovascular inflammation.[494] The "brain-fog", cognitive impairment and general fatigue reported in long-COVID may be due to mast cell related neurovascular inflammation.

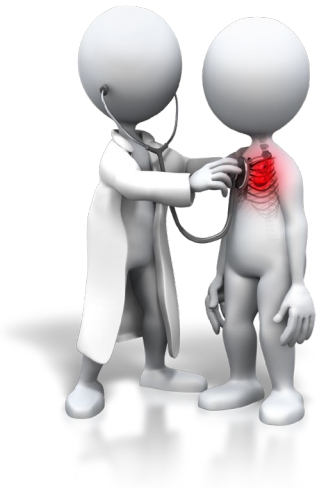
Clinical signs and symptoms can be grouped in the following clusters. The reason for this grouping is to allow organ specific targeted therapy/individualized therapy.

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.

16.1 Approach to Treatment:

The treatment approach should be individualized according to the grouping of clinical signs and symptoms. However, in general, it is likely that patients who did not receive adequate antiviral treatment (e.g**.** ivermectin) 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, [495] 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.[496] 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.[481] These patients should be referred to a pulmonologist with expertise in pulmonary fibrosis. Anti-fibrotic therapy may have a role in these patients, [451-454] 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. [334]



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

Although numerous reports describe the epidemiology and clinical features of LHCS, [475-485] 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.[497] 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).[107]
- 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. [227,228]
- 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)
- Curcumin has anti-inflammatory and immunomodulating properties and has been demonstrated to repolarize macrophages.[48]
- Kefir, probiotic yogurt and/or Bifidobacterium Probiotics (e.g., Daily Body Restore) together with Prebiotics (e.g. XOS Prebiotic, Bio Nutrition Pre-Biotic) to normalize the microbiome. Prolonged dysbiosis has been reported following COVID-19 infection. [498]
- Atorvastatin 40 mg daily (increase resolvin synthesis and repolarizes macrophages) [408]
- Functional rehabilitation with light aerobic exercise paced according to individual capacity.[486]
- Behavioral modification, mindfulness therapy [499]and psychological support may help improve survivors' overall well-being and mental health. [486]
- *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,[494,500-503] and have been demonstrated to reduce neuroinflammation. [504]
- *Optional:* Famotidine 20-40 mg day (histamine-2 blocker for Mast Cell Activation syndrome). [488]
- *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:* Antiandrogen therapy which results in macrophage repolarization. [472-474] Spironolactone 50-100 mg BID and dutasteride 1mg daily.
- *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

17. 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). [505] 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).[506]
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.[296,507-517] 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. [518]
8. The pulmonary phase is characterized by immune dysregulation, [489,510,519-532] a pulmonary microvascular injury (vasculopathy),[489,532-535] with activation of clotting and a procoagulant state together with the characteristics of an organizing pneumonia. [412,536]
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. [489]
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.

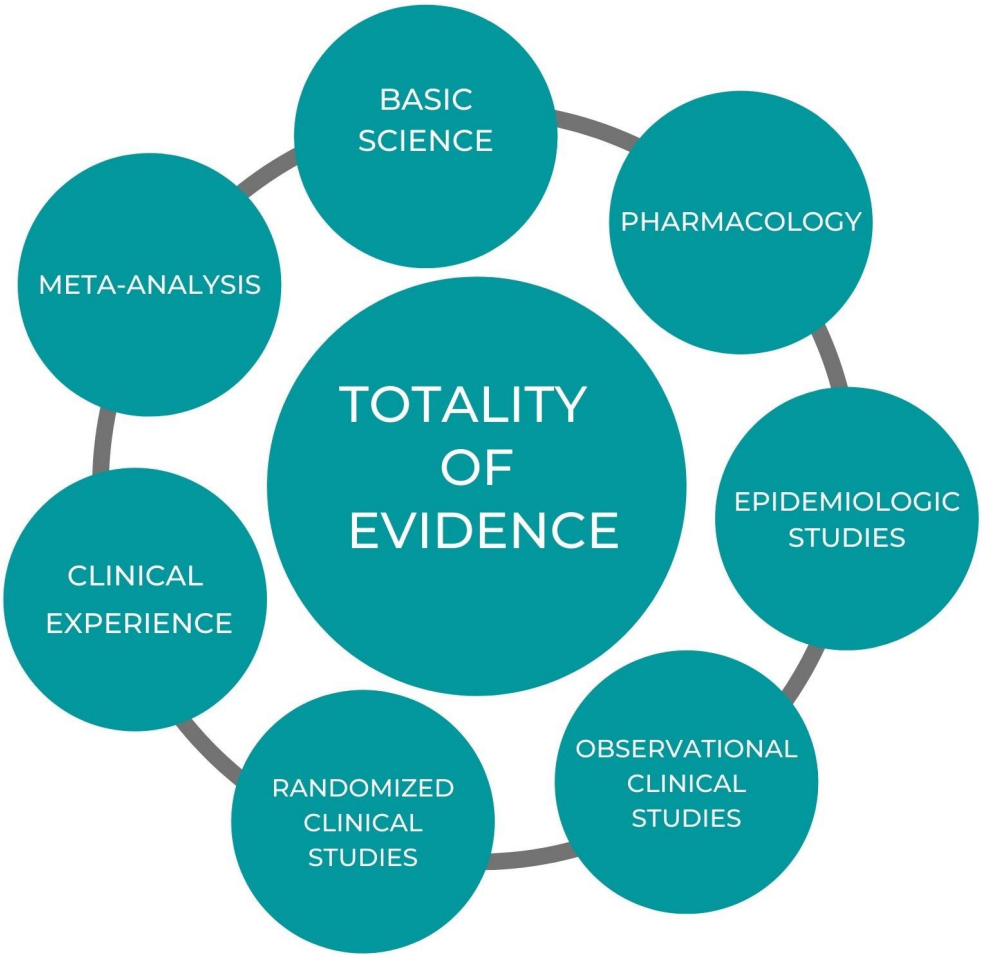
12. The radiographic and pathological findings of COVID-19 lung disease are characteristic of a Secondary Organizing Pneumonia (and not ARDS). [412,537,538]
13. THIS is NOT ARDS (at least initially), but rather an organizing pneumonia. The initial pulmonary phase neither looks like, smells like nor is ARDS.[539-541] The ground glass infiltrates are peripheral and patchy, [537] and do not resemble the dependent air space consolidation (sponge/baby lung) seen with "typical ARDS".[542] 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. [19,62-64,142,145-151,288-290,365-371,543] 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. [544]
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,[545,546] 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.[547] in addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 interaction with the ACE-2 receptor and viral entry,[548,549] as well as viral replication [150,550]. Most importantly LWWH inhibits heparanase (HPSE).[551] HSE destroys the endothelial glycocalyx increasing endothelial leakiness, activating clotting and potentiating endothelialitis.[551] HPSE levels have been reported to be increased in patients with severe COVID-19 infection. [552] 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. [349,354] Vitamin C protects the endothelium from oxidative injury.[107,553-555] Furthermore, vitamin C Increases the expression of interferon-alpha [97] while corticosteroids (alone) decrease expression of this important protein. [556-559] 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. [298,560] 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),[561] genomic data specific for SARS-CoV-2,[184] 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.[562,563] 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.



18. 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.