

Long COVID
Nutritional
Approaches

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COVID and
Immune
Health

- Stages of Infection
- The problem with ongoing inflammation
- Long Covid
- Nutritional Strategies
- Supplement support

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Fundamentals – the immune system is like an orchestra

Want an efficient anti-viral immune response (TH1)

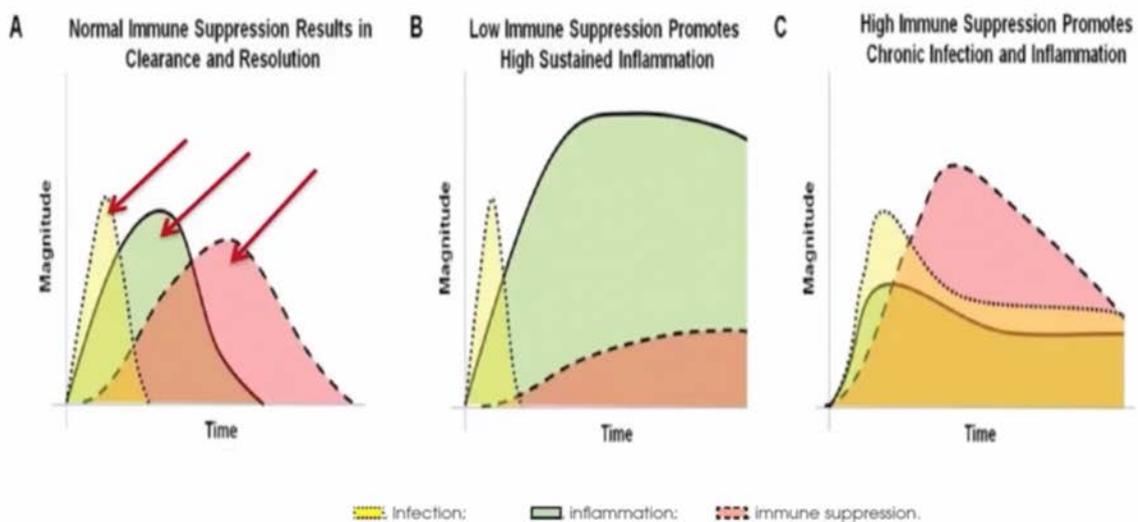
A good TH1 response can also help inhibit TH17 cells that promotes inflammation and autoimmunity

You also want to have anti-inflammatory response so that you have more room in case of an infection (and promote Treg / tolerance)

Remove inflammatory foods, stress, poor sleep, poor blood sugar etc

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A = Normally the infection should clear and inflammation calms down
B= Get the infection but you have high inflammation that persists
C= Get infection which persists which does not go away because the tolerogenic is too vigorous.



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276396/>

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Phases of COVID infection

Four Phases of COVID-19

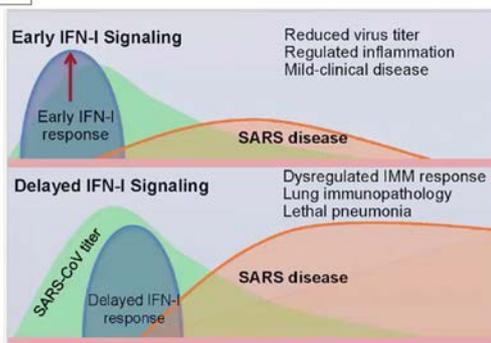
Clinicians will encounter patients in one of four phases of COVID-19, each requiring its own focus.

- **Prevention** - support is focused on immune surveillance efficiency and reduction of baseline levels of inflammation, to improve outcomes if the patient becomes infected,
- **Infection** - support emphasizes immune activity against infection,
- **Escalating Inflammation** - support is focused on anti-inflammatory measures, and
- **Recovery** - support is focused on resolving inflammation, inhibiting fibrosis and other forms of tissue damage, curtailing losses of function, and restoring and reoptimizing function.

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Getting ahead – Infectious Phase

Infection Phase

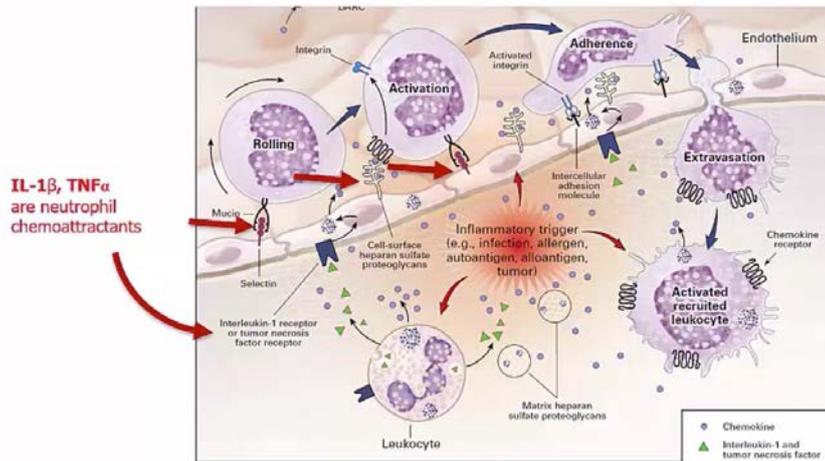


Adequate activation >> appropriate immune response
>> pathogen eradication & triggering of resolution phase chemistry >> **resolution**

Excessive activation >> epithelial & endothelial tissue damage
>> DAMPs/PAMPs >> further inflammatory cytokine generation
>> increased influx of immune elements (neutrophils, macrophages, etc.)
>> more damage >> **loop (failure of resolution)**

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Why infections lead to inflammation

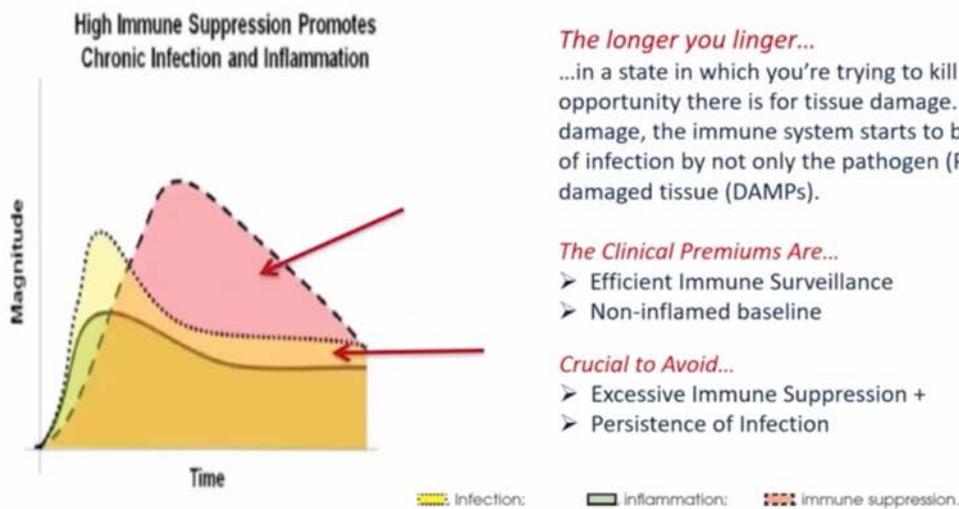


Clinical Pearl: IL-1 β and TNF α drive neutrophils into tissue. Reduce them = less inflammation...

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You want to promote resolution

- So you don't want to pump in too many anti-inflammatories in at the beginning as you will not get resolution



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Molecular Underpinnings of Severe Coronavirus Disease 2019

JAMA. 2020 Jul 24. Plenge RM.

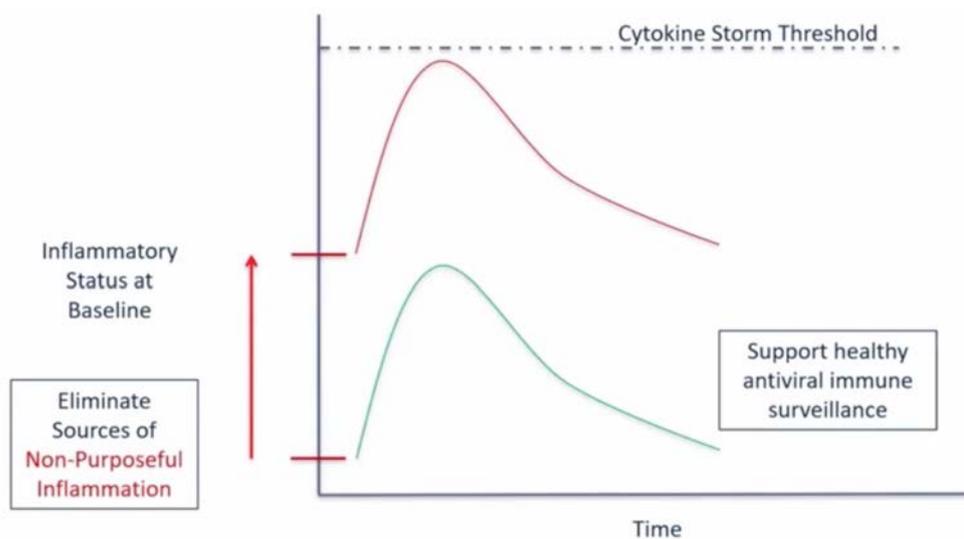
Excerpt:

"In some individuals, however, **the immune system does not clear the virus**, leading to viral replication and spread. In other individuals, an **overactive immune system** may control viral replication but result in collateral damage to neighboring tissue. Both scenarios, insufficient control of viral replication or an exuberant immune response, **may lead to severe respiratory disease, organ failure, and death**.

But this creates a therapeutic paradox: if insufficient control of viral replication is a driver of severe disease, then therapies that boost the immune system (eg, interferons) may be beneficial in clearing SARS-CoV-2, **especially early in infection**. If an overexuberant immune response is a driver of severe disease, then therapies that dampen the immune response (eg, dexamethasone) may be beneficial, **especially later in disease**."

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What is your baseline of inflammation?



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The problem with inflammation and COVID

"Nod-like receptor family, pyrin domain-containing 3 (NLRP3) regulates the secretion of proinflammatory cytokines interleukin 1 beta (IL-1 β) and IL-18. We previously showed that influenza virus M2 or encephalomyocarditis virus (EMCV) 2B proteins stimulate IL-1 β secretion following activation of the NLRP3 inflammasome. However, the mechanism by which severe acute respiratory syndrome coronavirus (SARS-CoV) activates the NLRP3 inflammasome remains unknown. **Here, we provide direct evidence that SARS-CoV 3a protein activates the NLRP3 inflammasome in lipopolysaccharide-primed macrophages.** SARS-CoV 3a was sufficient to cause the NLRP3 inflammasome activation. The ion channel activity of the 3a protein was essential for 3a-mediated IL-1 β secretion. While cells uninfected or infected with a lentivirus expressing a 3a protein defective in ion channel activity expressed NLRP3 uniformly throughout the cytoplasm, NLRP3 was redistributed to the perinuclear space in cells infected with a lentivirus expressing the 3a protein. **K⁺ efflux and mitochondrial reactive oxygen species were important for SARS-CoV 3a-induced NLRP3 inflammasome activation.** These results highlight the importance of viroporins, transmembrane pore-forming viral proteins, in virus-induced NLRP3 inflammasome activation."

<https://www.frontiersin.org/articles/10.3389/fmicb.2019.00050/full>

LOW potassium in the cell/low pH > inflammation

K⁺ efflux / mitochondrial ROS / NLRP3 inflammasome activation

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How to keep inflammation in check

- To reduce inflammasome activity you can use the following:
 - More potassium in the diet
 - Resveratrol
 - Sulforaphane
 - Quercetin
 - Berberine
 - Intermittent fasting may also help
- You don't want – elevated cholesterol, blood sugar imbalances which will aggravate inflammation

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What can happen in Recovery

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

Yanuck SF, Pizzorno J, Messler H, Fitzgerald KN. IMJC, April 2020.

“Disease sequelae, including persistent organ dysfunction, are a significant concern, particularly related to acute lung injury and fibrosis. **In SARS-CoV-1, 20% of recovered patients had fibrotic disease nine months post infection.** Given the apparent role of the NLRP3 inflammasome in COVID-19, and the role of NLRP3 in driving TGFβ-mediated fibrosis mentioned already, it becomes essential to attend to the patient’s potential need for persistent downregulation of inflammasome biology, with the goal of mitigating risk of additional consequences from **non-lethal but nonetheless life changing sequelae related to lingering inflammatory and fibrotic effects that occur in the tail of the curve** after the crescendo of disease has passed. As mentioned above, because patients have been observed to relapse into the Escalating Inflammation Phase, it is essential for clinical surveillance to continue well into what may appear to be the Recovery phase.”

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One paper, from *MedRxiv*, describes a retrospective study of 52 patients with a recent history of severe or critical COVID-19. **44% of these patients had a positive anti-nuclear antibody (ANA) and 19% had a positive rheumatoid factor (RF).** “59% of ANA patients displayed at least one other positive auto-reactive antibody test emphasizing the potential for multiple tolerance breaks across the cohort.”

Separating patients into high a low CRP groups, **more than 70% of patients in the high CRP group showed either ANA or RF elevation.** And, the authors emphasize, “all patients displaying additional autoreactivities tested positive for either **ANAs, or RF, suggesting that these two clinical tests may be valuable in efficiently screening patients for broad tolerance breaks.**”

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Long Covid

- NHS England and the Chief Medical Officer of the Scottish Government have asked NICE and SIGN to develop a guideline on the long-term effects of COVID-19.
- This UK-wide guideline is being developed collaboratively by NICE, SIGN and the RCGP.
- We acknowledge that there is still uncertainty in what is known about the long-term effects of COVID-19.
- Therefore, this guideline is being developed using a 'living' approach, which means that targeted areas of the guideline (including the case definition) will be continuously reviewed and updated in response to a developing and emerging evidence base.

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Definitions

COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline [NG188] Published date: 18 December 2020.

Acute COVID-19 infection

- Signs and symptoms of COVID-19 for up to 4 weeks.

Ongoing symptomatic COVID-19

- Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.

Post-COVID-19 syndrome

- Signs and symptoms that develop during or following an infection consistent with COVID-19, continue for more **than 12 weeks** and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body.
- Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

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Rationale for Definition

- **Clusters:** Signs and symptoms may arise from any system in the body, often overlap, and may change over time.
- This includes but is not limited to the cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, metabolic, renal, dermatological, otolaryngological, haematological and autonomic systems, in addition to psychiatric problems, generalised pain, fatigue and persisting fever.

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Is Long Covid Contagious?

- Long Covid is not contagious.
- Long Covid symptoms are caused by your body's response to the virus continuing beyond the initial illness.

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Long-Covid: Most Common Symptoms

- Fatigue
- Headaches
- IBS Symptoms
- Insomnia
- Anxiety and Depression
- Not being able to think straight or focus ('brain fog')
- Palpitations
- Chest Pains
- Low Blood Pressure
- Shortness of Breath
- Rhinitis
- Poor Exercise Tolerance
- Joint or muscle pain

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Symptoms of Long-Covid

- Persistent fatigue - 69%
- Persistent breathlessness – 53%
- Persistent cough - 34%
- Depressed – 15%
- Deteriorating chest radiograph appearance at follow-up - 9%
- Persistently elevated d-dimer - 30.1%
- Persistently elevated CRP - 9.5%

Mandal S et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2020 Nov 10;thoraxjnl-2020-215818. [Full Paper](#)

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Long Covid and Nutrition

- At least one of the papers was very dismissive of the potential value of vitamins and minerals and incorrectly stated that there was no evidence to support their use either with COVID-19 or in Long-COVID:
- “A healthy, balanced diet should be encouraged. Although two studies showed that vitamin D deficiency was over-represented in hospitalised patients with acute COVID-19, there is no current scientific evidence demonstrating that supplementation with vitamins or minerals such as vitamin D, zinc, etc. reduces the risk for COVID-19 or improves long-COVID symptoms.”

Mendelson M et al. Long-COVID: An evolving problem with an extensive impact. S Afr Med J. 2020 Nov 23;111(1):10-12. [Full Paper](#)

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Vitamin C

- **Vitamin C**
- A study from China involving 31 COVID-19 patients shows that vitamin C is, on average, deficient (11.4µmol/l), compared to healthy controls (52µmol/l) and returns into a healthy normal range (76µmol/l) with intravenous vitamin C.
- They recommend high dose intravenous vitamin C as an essential treatment to all COVID-19 patients at a dose of 100mg/kg per day. That’s 8g in an 80kg person.

Xing Y et al. Vitamin C supplementation is necessary for patients with coronavirus disease: An ultra-high-performance liquid chromatography-tandem mass spectrometry finding. J Pharm Biomed Anal. 2021 Mar 20;196:113927. doi: 10.1016/j.jpba.2021.113927. Epub 2021 Jan 27. [Full Paper](#)

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Vitamin C

- Vitamin C
- Forty-five other vitamin C-for-Covid trials are under way.
- A report from the [Florey Institute from Australia](#) documents an unexpected recovery from Covid induced sepsis with high dose vitamin C.
- A UK hospital in London is testing vitamin C with urine sticks and giving up to 6 grams a day. They have the lowest mortality.
- The Shanghai Medical Association's guidelines for doctors in China recommends high dose vitamin C for all Covid patients. You'd have to eat more than a hundred oranges to = 6 grams of vitamin C.

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Vitamin D

- Vitamin D
- Vitamin D modulates multiple mechanisms of the immune system to contain the virus that includes dampening the entry and replication of SARS-CoV-2, reduces concentration of pro-inflammatory cytokines and increases levels of anti-inflammatory cytokines, enhances the production of natural antimicrobial peptide and activates defensive cells such as macrophages that could destroy SARS-CoV-2.
- Thus, this paper provides the urgency of needed evidences through large population based randomised controlled trials and ecological studies to evaluate the potential role of vitamin D in COVID-19.

Kumar R et al. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. *Virus Res.* 2021 Jan 15; 292: 198235. Published online 2020 Nov 21. [Full Paper](#)

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Mitochondrial Involvement

- Long-Covid has resulted in the formation of a national UK consortium and the launch of the PHOSP-COVID study to investigate the long terms effects on health of this virus (see <https://www.phosp.org/>). (Mahase, 2020)
- One possible consequence of viral infection could be longer term mitochondrial dysfunction, which could lead to a variety of symptoms.
- Mitochondrial function, and their relationship to immunity, is again becoming a focus for research in the chronic fatigue syndrome, which is still not completely understood. (Anderson G, 2020)
- This has been further supported by evidence of mitochondrial dysfunction in peripheral blood mononuclear cells (PBMCs) of people with chronic fatigue syndrome. (Sweetman, 2020)

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Mast Cell Activation Syndrome (MCAS)

- Mast cells (MCs) are activated by SARS-CoV-2.
- Although only recently recognised, MC activation syndrome (MCAS), usually due to acquired MC clonality, is a chronic multisystem disorder with inflammatory and allergic themes, and an estimated prevalence of 17%.
- Hyperinflammatory cytokine storms in many severely symptomatic Covid-19 patients may be rooted in an atypical response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than a normal response by normal MCs.
- If proven, this theory has significant therapeutic and prognostic implications.

Afrin LB et al. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis.* 2020 Nov; 100: 327–332. Published online 2020 Sep 10. [Full Paper](#)

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Mast Cell Activation Syndrome (MCAS)

- Covid-19 infection causes mild to moderate symptoms in the majority of patients. However, these early data also suggest that even if symptoms are just 'mild to moderate' during the acute infection, fibrotic lung damage develops in some, potentially leading to long-term complications for a subset of patients (Spagnolo et al., 2020, Leask, 2020, Lechowicz et al., 2020, George et al., 2020).
- It is well known that over-activated MCs play a crucial role in the development of fibrotic conditions.
- Given that up to 17% of the population is generally pre-disposed to developing syndromes and diseases related to MC activation (Molderings et al., 2013), it is conceivable that people with this predisposition might have increased risk of developing the chronic respiratory, neurologic or other illnesses increasingly being seen following acute Covid-19 illness.

Afrin LB et al. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis.* 2020 Nov; 100: 327–332. Published online 2020 Sep 10. [Full Paper](#)

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Tackling MCAS

- Low histamine diet
- Drinks can block histamine breakdown
- Some foods elicit histamine release

Anti-histamine drugs

- Type 1 anti-histamine – trial and error process – “go low and slow” – 2-3 X per day
- Type 2 anti-histamine (prescribed) – 40mg per day (e.g. Famotidine)
- Mast Cell Stabiliser (leukotriene inhibitor) (prescribed)(e.g. Montelukast)

Vitamins & Minerals

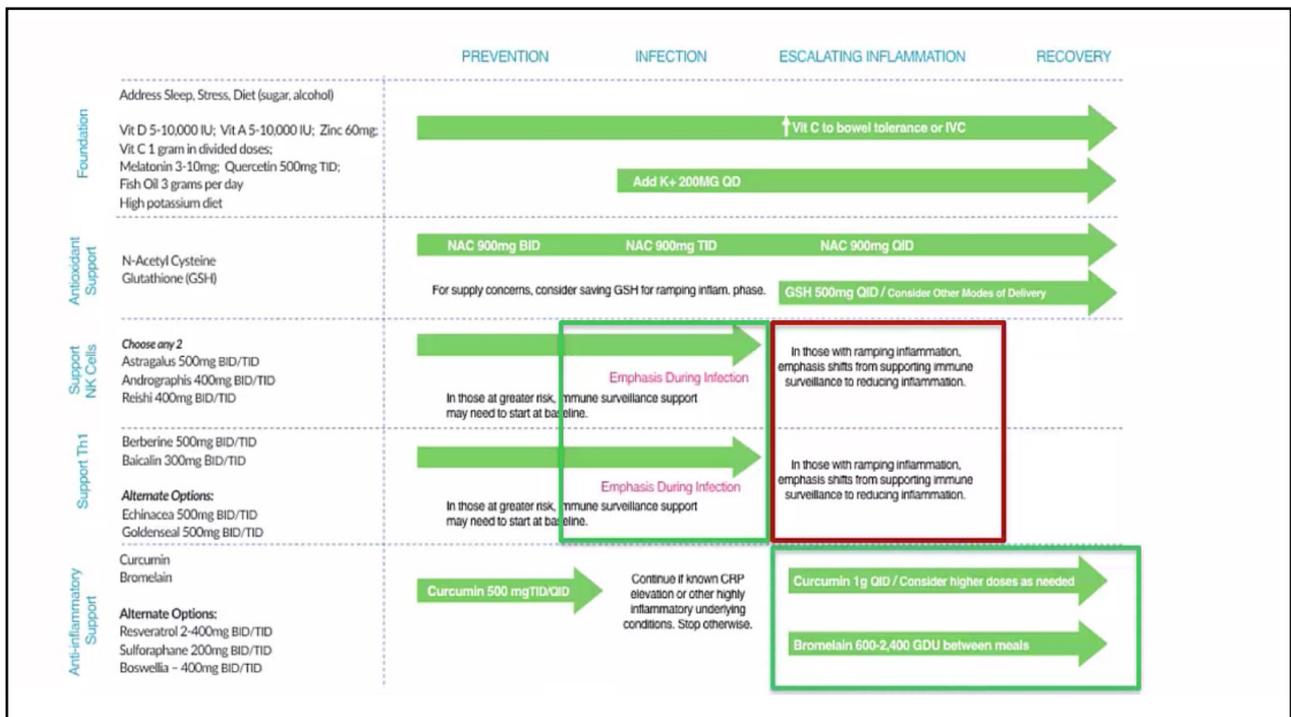
- Vitamin D – 3,000 iu
- Vitamin C - 1000mg x 3 (natural anti-histamine)
- Niacin (nicotinic acid) – 100mg-250mg +
- Zinc - 15-30 mg
- Quercetin – x 3 per day
- Selenium - 100mcg per day
- Magnesium – 100mg 2-3 X per day
- Help with methylation: MTHF, active B12, active B6

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STEP BY STEP APPROACH

PREVENTION
INFECTION
INFLAMMATION
RECOVERY

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Baseline support

- Vitamin D
- Vitamin A
- Zinc
- Vitamin C
- Fish Oil
- High potassium diet
- Antioxidant support NAC and glutathione

You want to make sure you have enough vitamins D, A, C, and E, and enough zinc.

You want to reduce any baseline inflammation.

If you are higher risk you may wish to add in extra so you get a head start on immune activation.

The main risk factors are CVD, diabetes, obesity, CKD, asthma or other respiratory disorders

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Infection

Support TH1 and NK cells

- Astragalus
- Andrographis
- Reishi
- Vitamin C
- Berberine
- Skullcap
- Echinacea
- Elderberry

Modulate TH2 / histamine

- Quercetin
- Melatonin
- Niacin
- Vitamin C

In this stage, you have symptoms that you're presuming to be related to the SARS-Cov2 virus that causes Covid-19 disease. You may have tested positive for the virus.

Aim is to supporting your ability to fight the infection.

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Lowering inflammation

Aim to prevent damage to organs

- Curcumin
- Bromelain (away from meals)
- Resveratrol
- Sulphoraphane
- Boswellia
- Green tea extract
- Melatonin
- Perilla
- Resolvins / Omega 3 fats

The inflammation is believed to be driven by activation of the NLRP3 inflammasome. So lots of potassium rich foods is also important

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Recovery

Down-regulation of chronic inflammation (curcumin, resveratrol, quercetin, sulforaphane, vitamins D, A, E, C, other factors) and inhibition of the self-reinforcing loop activation between TGF beta and fibroblasts that can drive persistent fibrotic processes (glutathione, NAC, E, etc.) **are a priority here.**

For overall immune health consider products such as Wholly Immune (ARG), Neonatal Multi Gland (BRC) or Immuno Gland Plex (BRC)

For mitochondrial health consider PQQ, NADH (e.g. Vitanadh Double express), COQ10, Resveratrol

Consider adrenal support if needed in addition.

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Importance of Glutathione

- Glutathione is an important antioxidant in lung epithelial cells
- When you have inflammation and damage it depletes glutathione
- As you are trying to kill pathogens macrophages take up glutathione and in turn reduces inflammation
- Low glutathione – worse lung disease response
- It will also shift you from TH1 to TH2 if low and therefore your anti-viral response
- Therefore critical you have enough glutathione

<https://pubmed.ncbi.nlm.nih.gov/16598818/>

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Supporting Glutathione

- N-acetyl-cysteine (NAC) (derived from cysteine-rich foods such as oats, broccoli, chicken, cottage cheese, eggs, fish and shellfish, onion, red pepper, ricotta cheese, soy beans, turkey and yogurt)
- Alpha lipoic acid (ALA) (found in beetroot/beet, broccoli, Brussels sprouts, carrot, lean red meat, liver, peas, spinach, tomato)
- L-glutamine (found in beans and legumes, cabbage, eggs, lean meat, liver, nuts, poultry, seafood)
- Selenium (selenium-rich foods include Brazil nuts, chicken, eggs, halibut, liver, sardines, spinach, turkey)
- Cordyceps (a medicinal mushroom)
- Milk thistle (active ingredient is silymarin) available as a supplement
- Acetyl glutathione (available as a supplement and can be boosted by whey protein powder)

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Clinical Application...

1. Patients who are recovering from severe COVID-19 are more likely to have developed new autoimmunity.
2. Screening for ANA and rheumatoid factor may be an effective way to identify these patients.
3. A high CRP during the course of severe disease increases the likelihood that new autoimmunity has arisen.
4. Consider Cyrex array 5

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Summary

Long-Covid can manifest in a wide array of symptoms but particularly:

- Fatigue / heart related: palpitations, low blood pressure, chest pains / respiratory: shortness of breath / digestive: IBS Symptoms / cognitive / neurological: fatigue, headaches, insomnia, anxiety and depression / not being able to think straight or focus ('brain fog') / rhinitis / poor exercise tolerance / joint or muscle pain.

These symptoms overlap with MCAS symptoms.

Consider a step by step approach as needed

- A low histamine diet, key supplements incl quercetin but especially niacin, and anti-histamines may be useful for Long-Covid sufferers.
- Key antioxidants may help the post-viral fatigue syndrome / CFS symptoms.

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Questions?



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