Long-COVID Application Guide

Clinical Context

Clotting problems have long been identified as a mechanism generating morbidity in COVID-19 (Merrill, Nat Rev Rheumatol, 2020). New research suggests that clotting from an ongoing active thrombo-inflammatory disorder also appears to play a role in persistent Long-COVID (Cervia-Hasler, Science, 2024). **The question of whether there is an active thrombo-inflammatory disorder or just remnants of tissue damage from the acute phase of the disease becomes an important point of discernment.**

Does the patient have a fixed amount of microvascular damage that occurred during acute COVID illness? Or is an active thrombo-inflammatory disorder adding ongoing microvascular damage? **Patients with an active disorder would be expected to have a much harder time keeping up with neovascularization of hypoxic tissue, so they'll have trouble getting to a point of resolution.** Long-COVID that resolves is likely to involve a fixed amount of damage at the time of acute illness, without ongoing thrombo-inflammation, since the patient is able to accomplish sufficient tissue repair to resolve their symptoms and restore function.

Cervia-Hasler, et al. describe several biomarkers of persistent Long-COVID, including **increased complement activity and higher levels of von Willebrand Factor (vWF).** Interestingly, IgG antibody titers for CMV and EBV were also significantly elevated in patients with six-month duration of Long-COVID.

Whether the patient's microvascular damage is from a bout of COVID that has passed, without persistent thrombo-inflammation, or if thrombo-inflammation is driving persistently developing microvascular damage, **in both cases you'll be dealing with some amount of hypoxia, ROS induced by the hypoxia, and NFkB induced by the HIF1α from the hypoxia.** In both cases, a stable amount of damage or ongoing damage, you'll want to help the body move toward resolution. If the patient hasn't yet reached the six-month post-acute point on their timeline at the time of presentation, you won't know for sure which situation you're in until the process unfolds further.

Low tissue oxygen (hypoxia) signals the body that new vessels are needed, to bring in more oxygen. Hypoxia triggers hypoxia inducible factor 1 alpha (HIF1α). HIF1α induces production of vascular endothelial growth factor (VEGF). VEGF causes the development of new vessels. New vessels bring oxygen to the previously hypoxic tissue.

Hypoxia > HIF1α > VEGF > Vessel Formation > Tissue Oxygenation > Negative Feedback to lower HIF1α > Resolution

It is sometimes suggested that VEGF elevation is a problem in Long-COVID. **However, VEGF is a signal that the body is making new vessels.** When the patient is no longer hypoxic, you can expect the VEGF level to go back down. That's different from other situations, like cancer for example, in which angiogenesis is certainly a problem. So in this case, the goal should not be to inhibit VEGF.

Assessment & Biological Considerations

1. It will be useful to develop an impression of whether the patient's Long-COVID might fall into the **"persistent" or "likely to resolve"** category, based on the duration of the patient's Long-COVID course of illness, the presence of comorbidities associated with inflammatory process, and whether there is a trend toward improvement. Also consider any pre-existing comorbidities like POTS, MCAS, gout, RA, or others that give you a picture of what their biology was like on the way into having COVID.

2. **Test for elevated vWF, or elevated IgG antibodies for CMV or EBV, at least twice**. The latter are not particularly specific but remember that we know from work done on the earlier SARS-CoV virus (Channappanavar, Cell Host Microbe, 2016) that the virus can destroy macrophage populations, so the initial illness can involve a race between the handoff from the innate to adaptive immune system versus the virus's attempt to damage the innate immune response on the other. **To the extent that the virus succeeds in damaging the immune system, background levels of other pathogens would be expected to expand.**

3. In your evaluation of a possible thrombo-inflammatory presentation, consider the following:
   a. Evaluate **clotting characteristics** carefully and within your scope of practice.
   b. Evaluate **vascular integrity.** Consider perfusion index, nail beds, extremity temperature, opthalmological exam, etc. Consider that microvascular damage may have occurred in tissue that is not readily accessible through these measures.
   c. Evaluate **inflammatory status**, recognizing that markers of inflammation are not particularly sensitive. Consider cardiac CRP, GlycA, ferritin, uric acid, omegacheck or other omega 3 status marker, etc.
   d. Evaluate the **oxidative stress / fibrosis activation system**: oxLDL, F2-isoprostane, glutathione, TGFβ.

Treatment

Rather than applying every one of these treatment options to every patient, work to understand what's most important in each case. This is best done through a series of treatment cycles, observing patient responses to components of treatment you introduce, rather than by declaring what's true at the start of the process. Keep in mind that you may need to escalate doses to see a response. Also keep in mind that some responses may take several weeks or longer to develop. This may be especially true for neovascularization. And of course, treatment components typically need to be combined into a working whole, like assembling an engine, before you see a change.

Thrombo-inflammatory processes: 1. Clotting

If the patient's vWF level is high, it may be important to bring it down into the normal range. This can be done with medication, or with substances like lumbrokinase or nattokinase. **NSK-SD** from Pure is a potentially useful nattokinase supplement. Dose is determined by blood levels of vWF. As usual, doing this piece of work presupposes that it's within your licensed area of practice.

Thrombo-inflammatory processes: 2. Hypoxia / HIF1α / VEGF / NFkB

Hypoxia will drive up HIF1α, which will promote VEGF, as discussed. This will drive up NFkB. In this case, you want to let the HIF1α run forward, so that VEGF can push neovascularization of tissue, for restoration of perfusion. But the HIF1α will also promote NFkB, so you'll need to keep inhibiting NFkB, while you let the HIF1α run forward. In this case, you won't want to use berberine, since that would inhibit HIF1α.

1. **Balanced Immune** (Pure Encapsulations) – 2 or 3 BID, to downregulate NFkB. Note that NFkB activation is also an essential step in the replication of Herpes family viruses, including CMV (aka HHV5) and EBV.
2. **Vitamin D** – Dose to get blood levels into the top quintile of the normal range. Vitamin D reduces inflammation and is also required for macrophages to form their lysosomal enzymes, so without vitamin D, innate immune response efficiency is diminished.
3. **Uric Acid Formula** (Pure) – 2 BID, to downregulate uric acid if it's elevated. Similarly, address other requirements related to inflammatory activation.
4. Identify sources of inflammatory activation (food, overtraining, insomnia, etc.) and inhibit them.
5. Attend to excessive sympathetic nervous system activation. The patient will likely have substantial body and CNS inflammation. The CNS inflammation will have activated the CNS inflammation > sympathetic nervous system activation > body inflammation > CNS inflammation loop. You'll need to downregulate this in order to move the ball.

Thrombo-inflammatory processes: 3. Hypoxia / ROS / TGFβ / Fibroblasts / Capillary Fibrosis

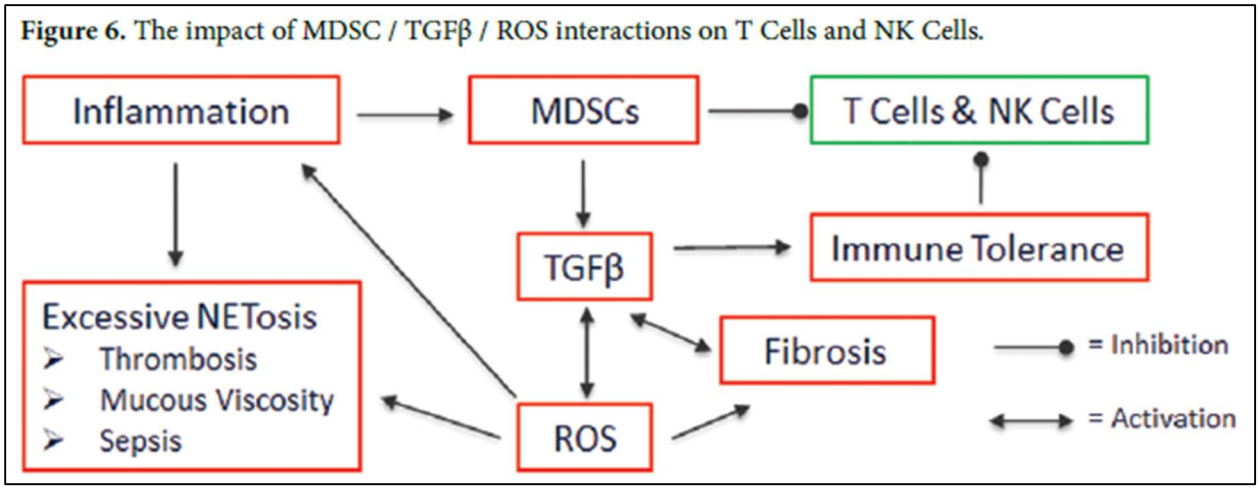
Inhibit the ROS driven by hypoxia. Remember also that hypoxia-mediated ROS activation is greater when the glutamine level is low.

Inhibit TGFβ. This is important for two reasons. First, the ROS elevation will push TGFβ levels up, in the TGFβ-ROS activation loop. **The TGFβ will drive fibroblast activation, driving capillary fibrosis, worsening microvascular damage.** TGFβ and ROS are also drivers of neutrophil extracellular trap (NET) formation. **Increased NET formation will increase clotting and drive more microvascular damage (see diagram below) (Yanuck, Integr Med, 2020).** Second, ROS-mediated depletion of glutathione will diminish Th1 cell activation, worsening viral burdens.

TGFβ-ROS loop > TGFβ-fibroblast loop activation > capillary fibrosis > microvascular destruction > hypoxia > ROS > TGFβ-ROS loop

ROS > glutathione depletion > Loss of Th1 > Viral Burdens Expand

1. **Liposomal Glutathione** – 500mg BID. Purpose is to downregulate the ROS that drives the above mechanisms. These come in soy and sunflower liposome forms. Choose according to whether the patient has IgG antibodies to soy or not. Start with 500mg BID if glutathione level is below 240 for Labcorp, or below the top 2/3 of the normal range for Quest. Dose to get the levels up above these thresholds. Or, dose to get TGFβ down below 12,000 (Labcorp) or into the normal range (Quest), and to get oxLDL or other oxidative markers to be normal.
2. **Alpha Lipoic Acid** – 400mg BID. ALA can be used instead of or in addition to glutathione if the patient has POTS or other indications for needing ALA.
3. **Epi-Integrity** (Pure) – 1 scoop BID. To replete glutamine, so that hypoxia doesn't drive up ROS as much. Epi-Integrity also contains arabinogalactan, which increases NK cell activity, as well as perilla and astragalus, which downregulate Th2 dominance that interferes with autophagy. Reducing Th2 dominance will improve Th1-mediated anti-viral responses and also allow autophagy to go forward.
4. **Innate Immune Support** (Pure) – 2 caps BID. To promote NK cell activity, for production of IFNγ, to drive the Th1 system. This offsets the loss of Th1 and maintains anti-viral surveillance, to inhibit expansion of CMV and EBV viral burdens.
5. **Perilla Extract** (Pure) – 2 caps BID. To inhibit the IL-4 that drives the shift to Th2 dominance.



From: *Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery.* Integr Med (Encinitas). 2020;19(Suppl 1):8-35. Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN.

Support development of new microcirculation

1. **Vinpocetine** (Pure) – 40mg BID to support CNS circulatory integrity.
2. **Arterosil** – 2 caps BID. To support endothelial repair.
3. **Ginkgo 50** (Pure) – 2 caps BID. To support CNS circulatory integrity.

Support restoration of cognitive function and reduce loss of neurons

Patients with Long-COVID almost always have a need for restoration of cognitive function. This can be accomplished by first and foremost inhibiting further loss of neurons, then by supporting the repair of CNS neurons, reduction of CNS histamine, and support of autophagy, the mechanism by which neuronal repair takes place.

Inhibition of neuronal loss involves reducing microglial phagocytosis of live neurons.

1. **Brain Reset** (Pure) – 2 BID or TID. Brain Reset contains a special ginkgo phosphatidylserine phytosome that provides bioavailable ginkgo and also phosphatidylserine. It also contains Butcher's Broom and Feverfew that add to ginkgo's circulation-enhancing properties. Brain Reset also contains Bacopa, which enhances neurotransmitter activation. More neurotransmitter production by neurons serves as an OFF signal that inhibits microglia from phagocytizing (eating) the neurons. Brain Reset also contains Lion's Mane mushroom, which promotes the production of nerve growth factor, to promote neuronal growth and synaptic connections between neurons.

2. **His Reset** (Pure) – 2 caps BID or TID. Histamine generated by mast cells throughout the body can increase CNS histamine levels. When this happens, histamine receptors on CNS mast cells are stimulated, leading to degranulation of CNS mast cells and stimulation of microglial cells to an inflammatory morphology in which they are more likely to phagocytize (eat) live but poorly functioning neurons. The goal is to reduce histamine by inhibiting production and increasing clearance. Hist Reset contains quercetin, luteolin, and rutin to inhibit mast cell degranulation, B2, B3, and molybdenum (cofactors for Aldehyde dehydrogenase) to improve histamine clearance, and bromelain to break down mast cell mitochondrial DNA fragments (mtDNA's) that promote GI mast cell degranulation. Iron (another ALDH cofactor) is left out, so that it can be managed independently.

CNS neuronal repair is essential for patients with Long-COVID. Neuronal repair is based on autophagy. The first step of autophagy is formation of the autophagosome, which requires interferon gamma (IFNɣ) and is inhibited by interleukin-4 (IL-4). Autophagy is also inhibited by both ROS and NFkB, so your efforts to address both of those factors will make a difference here.

1. **Innate Immune Support** (Pure) – 2 caps BID. To promote NK cell activity, for production of IFNɣ, to facilitate autophagy. The NK cell activation will also inhibit CMV and EBV viral burdens.
2. **Renual** (Pure) – 2 caps BID. Renual is a source of urolithin A that promotes mitophagy.
3. **Perilla Extract** (Pure) – 2 caps BID. To inhibit IL-4, so that autophagy can go forward.

Vagus Nerve rehab may be an important component of functional restoration. If the patient has cognitive impairment, the diminished frequency of firing of cerebral cortex neurons will yield diminished cortical output, upon which proper brainstem function depends. This will yield diminished vagal motor outflow. The vagus nerve inhibits production of inflammatory cytokines in the small intestine, spleen, and liver. Vagal motor outflow also promotes down-going peristalsis, so loss of vagal motor outflow tends to yield SIBO, which is inflammatory and which also promotes food sensitivity reactions, further driving inflammation. Vagus nerve rehab should be accompanied by support for acetylcholine, the neurotransmitter in vagal synapses. Be aware that acetylcholine is also the neurotransmitter in neuromuscular junctions, so if you give too much acetylcholine support, you may get cramping. This can be diminished with magnesium, but too much magnesium will loosen stools. So, ramp up acetylcholine support slowly and carefully, perhaps accompanied by a modest dose of magnesium.

Attend to Pathogen Burden Expansion / T Cell Polarization

Keep in mind that Merrill, et al (Nat Rev Rheumatol. 2020) found that patients with Long-COVID, and actually all of the patients they evaluated after acute COVID-19 infection, had substantial elevation of IgG antibodies for CMV and EBV. We've discussed in other topic areas the tendency for patients with chronic inflammation and chronic stress chemistry to drift into Th2 dominance. This would dampen the Th1 system (Th1 cells, NK cells, CD8+ CTL's, M1 macs). That would allow expansion of viral burdens, including CMV, EBV, and if the view that persistence of COVID viral lacunae is a real thing, Th1 failure would also be permissive there.

1. **Innate Immune Support** (Pure) – 3 caps BID. To promote NK cell activity, for production of IFNɣ, to spin up the numbers and activity of cells of the Th1 system.
2. **Perilla Extract** (Pure) – 2 caps BID or TID. To inhibit IL-4, to downregulate Th2.
3. **Epi-Integrity** (Pure) – 1 scoop BID. To inhibit Th2 promotion by GI dysregulation (perilla and astragalus), support NK activation (arabinogalactan), and reduce intestinal permeability and ROS (glutamine).

Neurogenic Inflammation

In patients for whom COVID-19 illness has affected epithelial systems in lungs, GI tract, sinuses, etc., there is likely to be upregulation of mast cell activity. This may also be true if other factors are moving the patient toward greater expression of Th2 dominance. In this case, neurogenic inflammation may become an issue. For more information on neurogenic inflammation, see Module 18 Video 13, Module 21 Videos 10 and 11.

1. **Hist Reset** (Pure) – 2 caps BID or TID. To inhibit mast cell degranulation, reducing histamine production, to improve histamine clearance, and to degrade inflammatory mast cell mitochondrial DNA fragments (mtDNA's) that re-trigger mast cell degranulation.
2. It may be necessary to focus on elimination of histamine-promoting foods in patients with neurogenic inflammation.

Autoimmunity

Vagus nerve motor outflow inhibits IL-6 production by Kupfer cells in the liver and inhibits TNFα production in the spleen and small intestine. The combination of IL-6 and TNFα drives naïve T cell polarization to Th22. Th22 cells make IL-22, which increases antibody glycation, increasing the antibody binding affinity. This increases autoimmune activity, without any change in the number of anti-self tissue antibodies. So, improvement of vagus nerve motor outflow can be essential.

As usual, the NFkB-STAT3 co-activation axis is important to consider. Anything that increases the NFkB of the inflammatory process will increase STAT3, driving Th17 polarization, driving autoimmune tissue injury. As mentioned above, in the discussion of NFkB, it can be essential to identify interventions that reduce inflammation. Different patients will have different inflammatory drivers (food reactions, sleep issues, stress, overtraining, environmental exposures, etc.). And different patients will respond to different treatment interventions (**Balanced Immune, Curcumasorb, Boswellia, Uric Acid Formula, D, C,** etc.).

Barrier System Damage

Several secondary consequences of Long-COVID can affect the GI tract.

a) With inflammation there will be an associated loss of glutamine. We've discussed elsewhere that glutamine status depends on inflammatory status in the GI tract, rather than on dietary consumption. Loss of glutamine will mean that hypoxia drives more ROS production.
b) With loss of vagal motor outflow, SIBO may be an issue that needs to be addressed. More dysbiosis yields more food sensitivity reactions. (see the Clinical Pearl "How Dysbiosis Drives Food Reactions").
c) Increased GI inflammation drives epithelial production of TSLP, IL-25, and IL-33, driving Th2 polarization. This impairs anti-viral responses, impairs autophagy, and worsens dysbiosis.

1. **Epi-Integrity** (Pure) – 1 scoop BID. To inhibit Th2 promotion by GI dysregulation (perilla and astragalus), support NK activation (arabinogalactan), and reduce intestinal permeability and ROS (glutamine).
2. **AC Formula II and/or Microdefense** (Pure) – 2 or 3 caps BID, away from food, to address dysbiosis. Needless to say, this is a large topic and there are lots of strategies here.
3. **Perilla Extract** (Pure) **–** 2 caps BID or TID. To inhibit IL-4, to downregulate Th2.
4. **Liposomal Glutathione** – 500mg BID. To downregulate ROS. See above for further comments about glutathione.

Attend to ROS / T3R resistance / Over-fueling / Mitochondrial damage

Attend to mitochondrial damage, if there is any. Consider that the ROS may have driven a downregulation of insulin receptors and T3 receptors (Wittman, Antioxidants, 2022), yielding hyperglycemia and mitochondrial over-fueling that may yield mitochondrial damage where there was none before. If this happens, the mitochondria will generate more superoxide and less ATP, worsening the Long-COVID picture.

ROS > T3R resistance & IR > over-fueling of mitochondria > superoxide production (loop)

Over-fueled mitochondria generate ROS that drive NFkB, driving insulin resistance. Reducing over-fueling can improving insulin resistance, reduce inflammation, and reduce ROS. So, **caloric modesty or a few monthly cycles of a Fasting Mimicking Diet (FMD) may be useful.**

1. Consider **Renual** (Pure) – 2 BID. Recycling/clearing damaged mitochondria via mitophagy makes way for a healthier population of mitochondria that make less ROS.
2. Consider other substances that play potentially important roles in mitochondrial function, like **coenzyme Q10** and **carnitine.**
3. For some patients, IR is driven by the insulin receptor being shut off too soon, by an intracellular enzyme called PTP1b. This is discussed in the Clinical Pearl called "Insulin Resistance" and also in the "Insulin Resistance" Application Guide (see the Application Guides tab). For patients for whom this is occurring, **Reishi mushroom, aka Ganoderma** is very suitable. The dose is determined by blood sugar numbers. Note that Ganoderma is a key ingredient in **Innate Immune Support** (Pure).
4. Consider substances that play a role in normal glycemic control, like chromium, vanadium, bitter melon, and other glycemic control substances. **Glucofunction** (Pure) is a good choice to consider.

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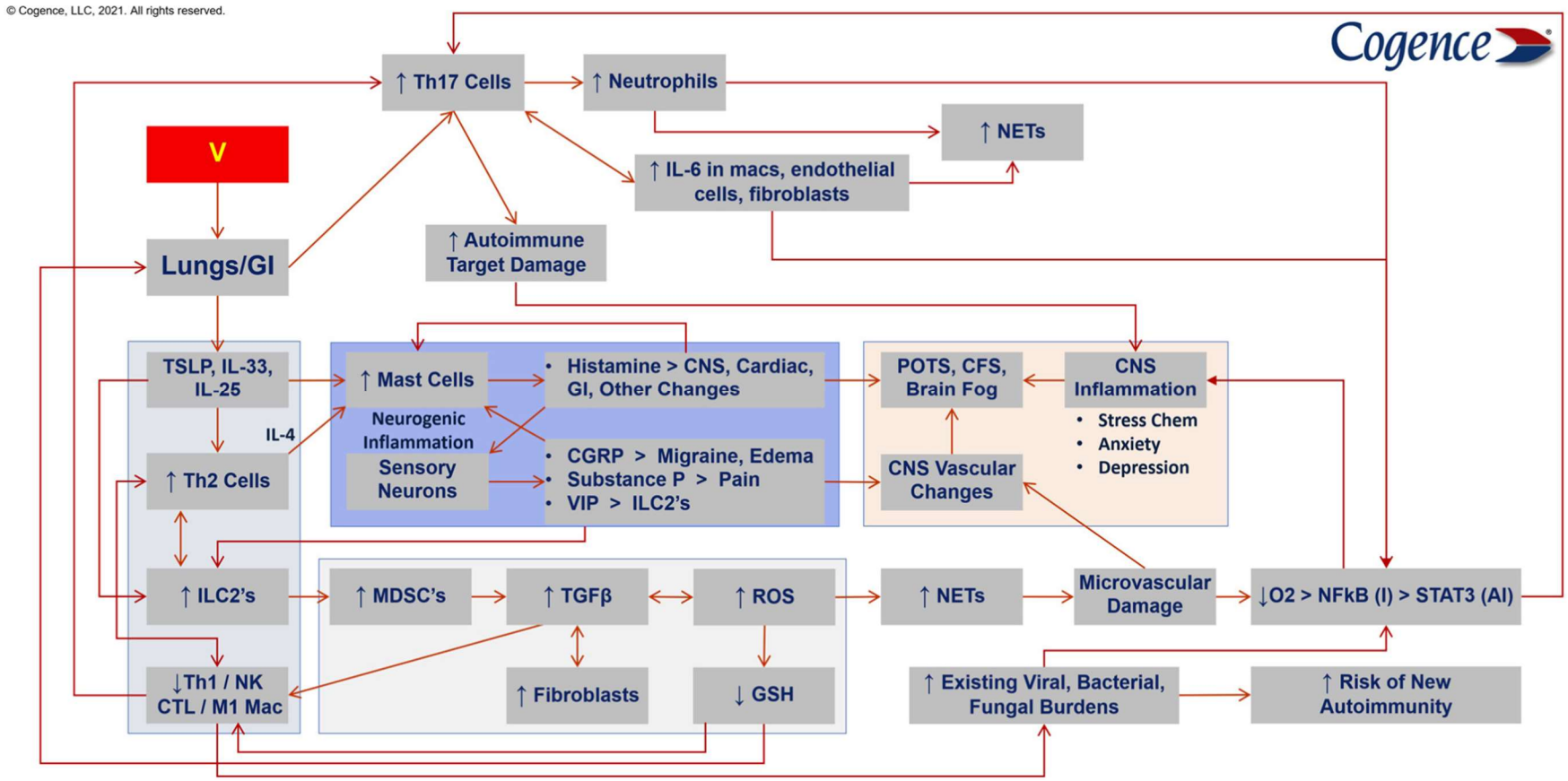

This diagram comes from Module 18 Video 11 – "Long COVID – The Big Picture." Module 18, Videos 11 to 14 are about Long-COVID.

The Research…

Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications.

Nat Rev Rheumatol. **2020** Oct;16(10):581-589. Merrill JT, et al.

Abstract

"Reports of widespread thromboses and disseminated intravascular coagulation (DIC) in patients with coronavirus disease 19 (COVID-19) have been rapidly increasing in number. Key features of this disorder include a lack of bleeding risk, only mildly low platelet counts, elevated plasma fibrinogen levels, and detection of both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and complement components in regions of thrombotic microangiopathy (TMA). This disorder is not typical DIC. Rather, it might be more similar to complement-mediated TMA syndromes, which are well known to rheumatologists who care for patients with severe systemic lupus erythematosus or catastrophic antiphospholipid syndrome. This perspective has critical implications for treatment. Anticoagulation and antiviral agents are standard treatments for DIC but are gravely insufficient for any of the TMA disorders that involve disorders of complement. Mediators of TMA syndromes overlap with those released in cytokine storm, suggesting close connections between ineffective immune responses to SARS-CoV-2, severe pneumonia and life-threatening microangiopathy."

Persistent complement dysregulation with signs of thromboinflammation in active Long Covid

Science. **2024** Jan 19;383(6680):eadg7942. Cervia-Hasler C, et al.

Abstract

"Long Covid is a debilitating condition of unknown etiology. We performed multimodal proteomics analyses of blood serum from COVID-19 patients followed up to 12 months after confirmed severe acute respiratory syndrome coronavirus 2 infection. Analysis of >6500 proteins in 268 longitudinal samples revealed dysregulated activation of the complement system, an innate immune protection and homeostasis mechanism, in individuals experiencing Long Covid. Thus, active Long Covid was characterized by terminal complement system dysregulation and ongoing activation of the alternative and classical complement pathways, the latter associated with increased antibody titers against several herpesviruses possibly stimulating this pathway. Moreover, **markers of hemolysis, tissue injury, platelet activation, and monocyte-platelet aggregates were increased in Long Covid. Machine learning confirmed complement and thromboinflammatory proteins as top biomarkers, warranting diagnostic and therapeutic interrogation of these systems."**

Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice.

Cell Host Microbe. **2016** Feb 10;19(2):181-93. Channappanavar R, et al.

Abstract

"Highly pathogenic human respiratory coronaviruses cause acute lethal disease characterized by exuberant inflammatory responses and lung damage. However, the factors leading to lung

pathology are not well understood. Using mice infected with SARS (severe acute respiratory syndrome)-CoV, we show that robust virus replication accompanied by delayed type I interferon (IFN-I) signaling orchestrates inflammatory responses and lung immunopathology with diminished survival. IFN-I remains detectable until after virus titers peak, but early IFN-I administration ameliorates immunopathology. This delayed IFN-I signaling promotes the accumulation of pathogenic inflammatory monocyte-macrophages (IMMs), resulting in elevated lung cytokine/chemokine levels, vascular leakage, and impaired virus-specific T cell responses. Genetic ablation of the IFN-αβ receptor (IFNAR) or IMM depletion protects mice from lethal infection, without affecting viral load. These results demonstrate that IFN-I and IMM promote lethal SARS-CoV infection and identify IFN-I and IMMs as potential therapeutic targets in patients infected with pathogenic coronavirus and perhaps other respiratory viruses."

And from the same paper…
"…robust virus replication and delayed IFN-I signaling promote severe disease."

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

Integr Med (Encinitas). **2020**;19(Suppl 1):8-35. Yanuck SF, Pizzorno J, Messier H, Fitzgerald KN.

Abstract

"This paper presents an evidence-based strategy for improving clinical outcomes in COVID-19. Recommendations are based on the phases of the disease, because optimal interventions for one phase may not be appropriate for a different phase. The four phases addressed are: Prevention, Infection, Inflammation and Recovery. Underlying this phased approach is recognition of emerging evidence for two different components of pathophysiology, early infection and late stage severe complications. These two aspects of the disease suggest two different patterns of clinical emphasis that seem on the surface to be not entirely concordant. We describe the application of therapeutic strategies and appropriate tactics that address four main stages of disease progression for COVID-19. Emerging evidence in COVID-19 suggests that the SARS-CoV-2 virus may both evade the innate immune response and kill macrophages. Delayed innate immune response and a depleted population of macrophages can theoretically result in a blunted antigen presentation, delaying and diminishing activation of the adaptive immune response. Thus, one clinical strategy involves supporting patient innate and adaptive immune responses early in the time course of illness, with the goal of improving the timeliness, readiness, and robustness of both the innate and adaptive immune responses. At the other end of the disease pathology spectrum, risk of fatality in COVID-19 is driven by excessive and persistent upregulation of inflammatory mechanisms associated with cytokine storm. Thus, the second clinical strategy is to prevent or mitigate excessive inflammatory response to prevent the cytokine storm associated with high mortality risk. Clinical support for immune system pathogen clearance mechanisms involves obligate activation of immune response components that are inherently inflammatory. This puts the goals of the first clinical strategy (immune activation) potentially at odds with the goals of the second strategy(mitigation of proinflammatory effects). This creates a need for discernment about the time course of the illness

and with that, understanding of which components of an overall strategy to apply at each phase of the time course of the illness. We review evidence from early observational studies and the existing literature on both outcomes and mechanisms of disease, to inform a phased approach to support the patient at risk for infection, with infection, with escalating inflammation during infection, and at risk of negative sequelae as they move into recovery."

The Common Single Cause of Chronic Multi-Hormonal Resistance in Oxidative Stress

Antioxidants (Basel). 2022 Dec 29;12(1):75. Wittmann I.

Abstract

"In diseases with concomitant oxidative stress, chronic multi-hormonal resistances could be detected. The most conspicuous component of these resistances is insulin resistance, but also leptin, erythropoietin, acetylcholine, triiodothyronine and glucagon-like peptide-1 resistances also occur. On the other hand, in oxidative stress, abnormal tyrosines, for instance, meta- and ortho-tyrosine are also produced and incorporated into the proteins through the translational process. In case these modified proteins are components of the intracellular signalling pathways, a hormonal resistance may develop. The above-mentioned hormones, owning overlapping signalling pathways at the insulin receptor substrate, develop an abnormal tyrosine phosphorylation dependent chronic multi-hormonal resistance. **A few weeks free of oxidative stress or the use of antioxidant therapy are required to provide a return from this resistance,** which return may be further supported by the supplementation of physiological para-tyrosine and by the add-on therapy of a pharmacological dose of glucagon-like peptide-1 receptor agonist, which is able to bypass the critical insulin receptor substrate signalling."