Long COVID: A Primer For Primary Care

- Eric D. Herman, MD
- Chief Primary Care and Population Health Officer
- Oregon Health & Science University

Feb 14, 2024

Learning Objectives

1. Definition
2. Signs and symptoms
3. Etiologies
4. Evaluation and management

Disclosures

- AAPM&R PASC Multidisciplinary Collaborative (Co-Chair)
- Secretary’s Advisory Committee on Long COVID (Chair)*

* Presentation is not affiliated nor endorsed by Secretary’s ACLC.

Patient Story

Angela is 55-year-old black female, works in tech-industry, divorced, lives with her adult daughter.

Prior to COVID, she worked 50 hours a week and enjoyed travelling. After COVID, she feels like there is a lead weight on her body with constant aches and pains. After doing household chores she suffers profound **exhaustion for days** and her **heart races** inexplicably. She has **difficulty finding words**, staying focused, multi-tasking, and is mentally exhausted from going to the market. She has **unrestful sleep** every night. Her past medical history is otherwise unremarkable.

Angela has had extensive medical studies without significant findings. She is unable to work, feels like a burden on her family, an enigma to the medical community. She doesn't understand what happened, contemplates if she will get better, and **if life is worth living?**

Angela's Long COVID Footprint

HPI		Manifestations of LC
▪ Exhaustion for days	→	Post-Exertional Malaise
▪ Heart races	→	Dysautonomia
▪ Difficulty finding words	→	Cognitive Impairment
▪ Unrestful sleep	→	Sleep Disturbances
▪ Is life worth living	→	Depression / PTSD

Background

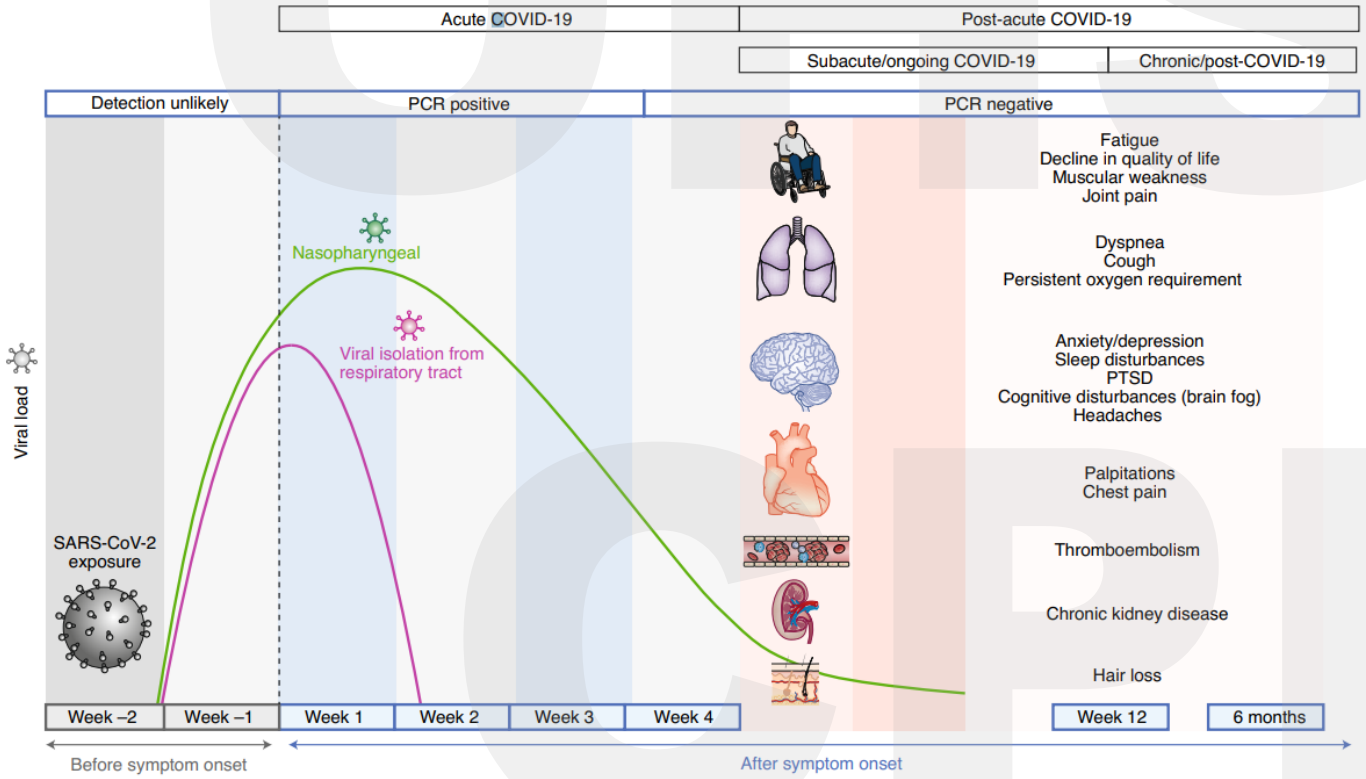
What is Long COVID?

- An **infection-associated chronic condition** that occurs after SARS-CoV-2 infection and is present for at least **3 months** as a continuous, **relapsing and remitting**, or progressive disease state that affects one or more organ systems.

- Also known as
  - **PASC** = Post Acute Sequela of SARS-CoV-2

- National Academies of Sciences, Engineering, and Medicine. 2024. A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences. Washington, DC: The National Academies Press. https://doi.org/10.17226/27768.

Disease Course



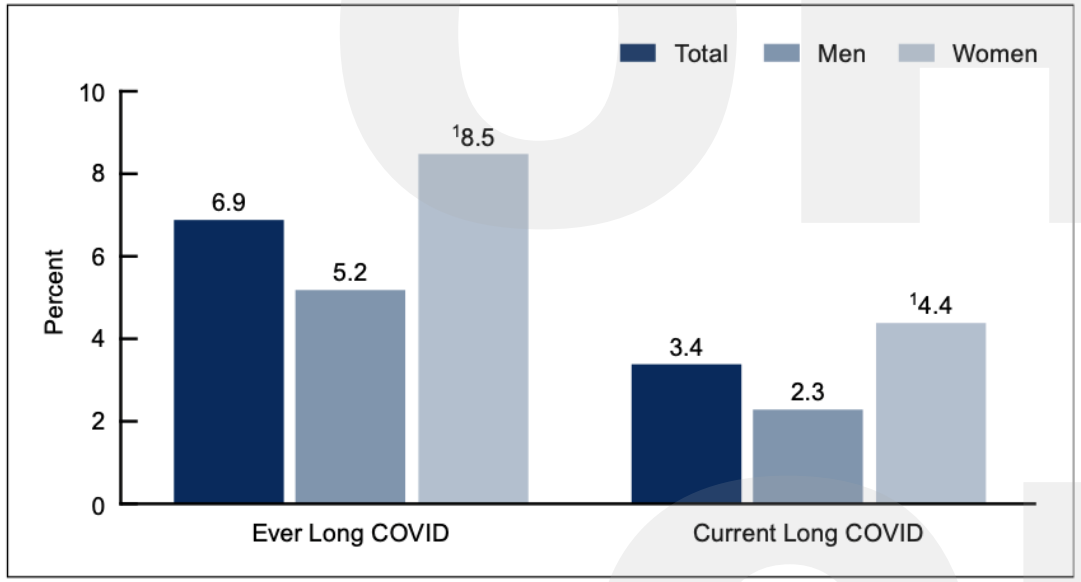
Acute	≤ 4 wk
Subacute	5 – 11 wk
Chronic	≥ 12 wk

The chronic period can be quite different than acute.

Fatigue is throughout.

- Nalbandian A, Sehgal, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615.

Incidence & Prevalence



- Among those with a Positive test or Dr Dx
  - **6.9% Ever;** 3.4% Current
  - 200-300% below poverty level > 400%
- Earlier Data
  - 10-30% of non-hospitalized
  - 50-70% of **hospitalized**
  - 10-12% of vaccinated (**Breakthrough infx**.)

The incidence of new Long COVID cases has decreased over time with newer variants

- Data from the 2022 National Health Interview Survey Sample Adult interview (*n* = 27,651) https://www.cdc.gov/nchs/data/databriefs/db480.pdf
- 6.2% with symptomatic infection
- Davis HE, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13:1–14
- Prevalence (proportion over a given time period); Incidence (# new cases per time period)
- Atchison, Antonelli, Cai, Pfrommer. (Incidence decreasing over time)

Global Perspective

	COVID	COVID Deaths	Long COVID **(7%)**
Global	775 million	7.0 million	53 million
US	100 million	1.2 million	7 million
Oregon	900,000	9000	62,000

- WHO Dashboard: https://covid19.who.int/
- https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/state/oregon/
- Prevalence estimates based off of Data from the 2022 National Health Interview Survey Sample Adult interview (*n* = 27,651)

Incidence in Vaccinated Patients

- Large retrospective cohort study of vaccinated pts who contracted COVID
- Incidence decreased from **10.4%** during the pre-delta pre-vaccination era to **3.5%** in the omicron era
  - 72% of the declining incidence was attributable to vaccination
    Possibly due to reducing severity of acute infection and/or viral persistence
  - 28% attributable to changes in the virus's characteristics.

Xie Y, Choi T, Al-Aly Z. Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras. N Engl J Med. 2024 Aug 8;391(6):515-525. doi: 10.1056/NEJMoa2403211. Epub 2024 Jul 17. PMID: 39018527.

Incidence of Sx with Newer Variants

- The incidence of most Long COVID symptoms has decreased
  - including cardiopulmonary and neurologic symptoms
- But among unvaccinated individuals
  - Incidence of gastrointestinal, metabolic, and musculoskeletal symptoms increased in the omicron era compared to the pre-omicron era.

Xie Y, Choi T, Al-Aly Z. Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras. N Engl J Med. 2024 Aug 8;391(6):515-525. doi: 10.1056/NEJMoa2403211. Epub 2024 Jul 17. PMID: 39018527.

Who is Likely to Get Long COVID?

- **Most had mild acute illness**
- **All ages**
  - Highest percentage 36 – 50 years
- **Unvaccinated**
- **Hispanic**

Figure 2. Percentage of adults who ever had Long COVID or currently have Long COVID, by age group: United States, 2022

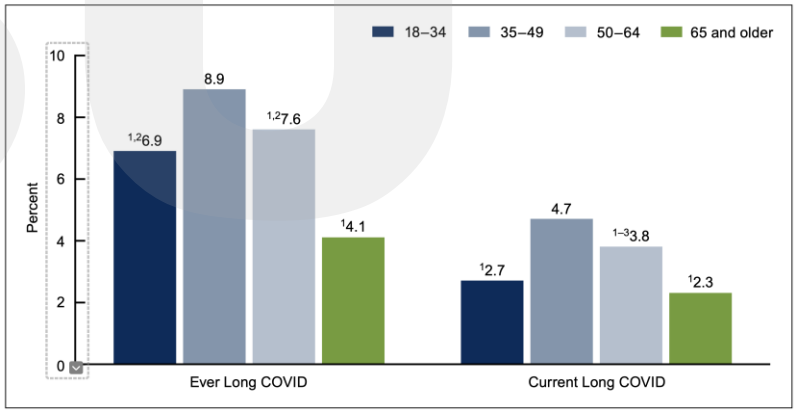
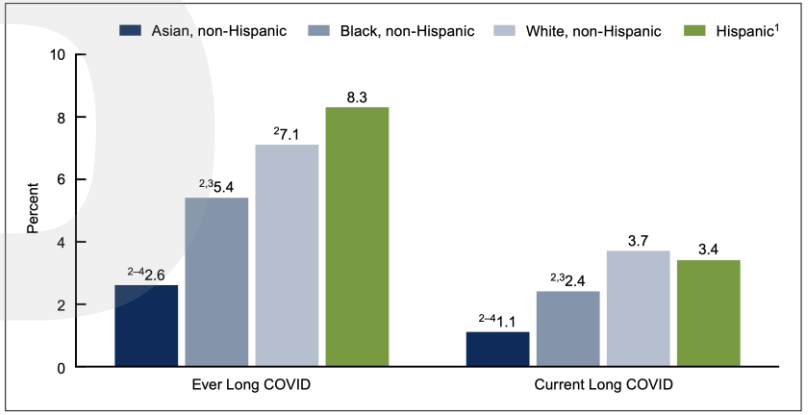


Figure 3. Percentage of adults who ever had Long COVID or currently have Long COVID, by race and Hispanic origin: United States, 2022



- **NCHS Data Brief, No. 480, September 2023, Long COVID in Adults: United States, 2022,** Dzifa Adjaye-Gbewonyo, Ph.D. https://www.cdc.gov/nchs/data/databriefs/db480.pdf
- https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

Other Risk Factors

- **1/3 have no pre-existing conditions**
- **Reinfections**
- **Severity of acute infection**
- Inability to rest in the early weeks of acute infection
- Lower income
- SARS-CoV-2 RNAemia, EBV reactivation, autoantibodies against type-I IFN

Higher prevalence

- Female sex
- Transgender / bisexual
- Minoritized racial and ethnic group status
- Disability
- Low socioeconomic status
- High BMI
- Tobacco use
- Unvaccinated status.

- https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html (severity, underlying conditions, vaccines)

Vaccinations & Other Risk Reduction

- **Vaccine Prevention Against Long COVID**
  - EMR study with lower rates of Long COVID (Fatigue RR = 0.48)
- **Post-Vaccination Symptom Improvement**
  - UK cohort survey 28k patients – Decrease in Long COVID sx
- **Paxlovid** – Large VA Study
  - 26% less risk of PASC at 90 days
  - Another study of the same records was inconclusive
- **Ivermectin and Fluvoxamine**
  - NIH-supported study concluded neither had impact on rate of Long COVID.
- **Reinfections may result in demoralizing relapses***

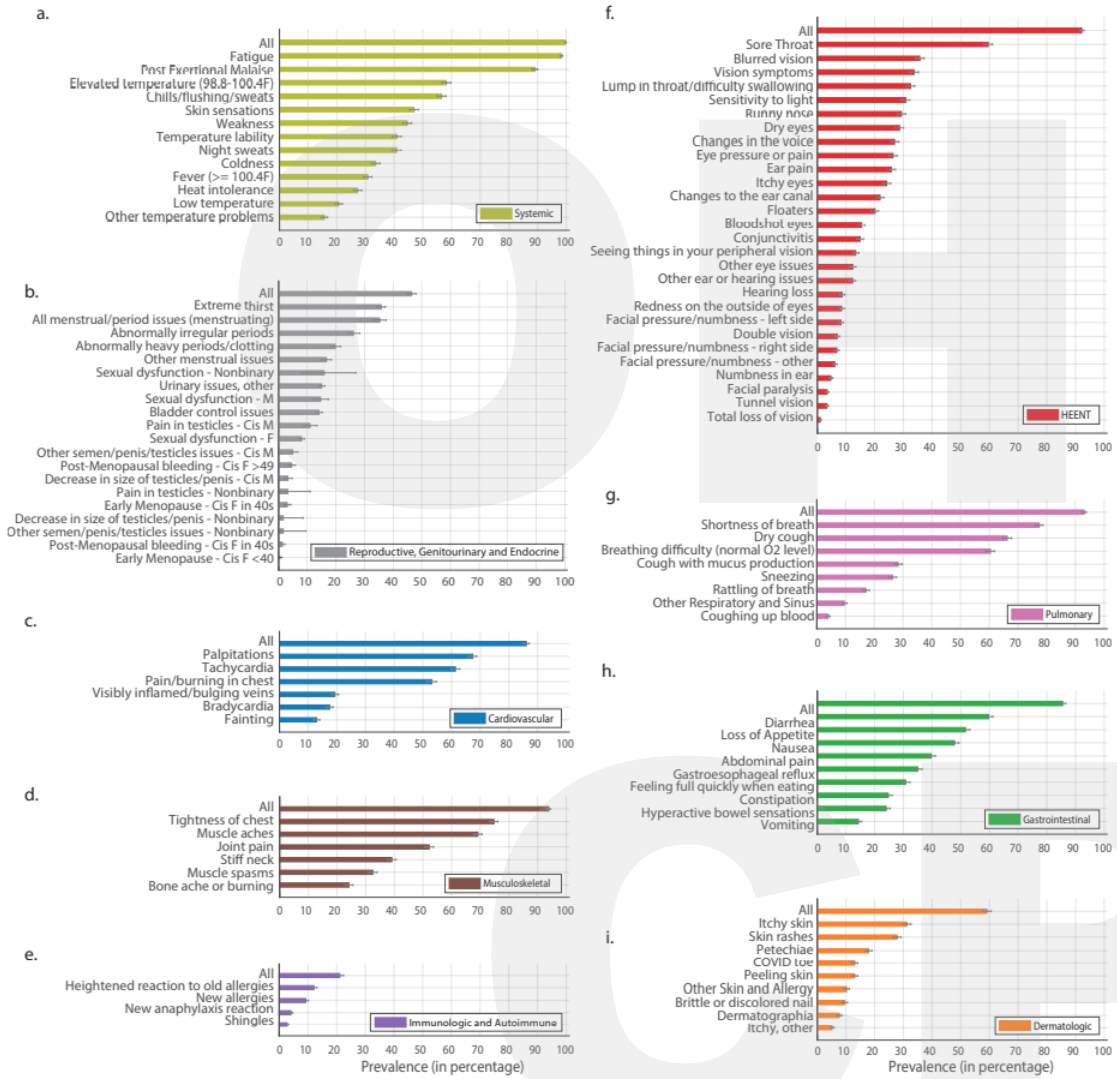
- Brannock MD, et al. RECOVER Consortia. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program. Nat Commun. 2023 May 22;14(1):2914.
- Xie Y, Choi T, Al-Aly Z. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition. *JAMA Intern Med.* 2023;183(6):554–564. doi:10.1001/jamainternmed.2023.0743
- Bramante CT, et al. Outpatient treatment of Covid-19 with metformin, ivermectin, and fluvoxamine and the development of Long Covid over 10-month follow-up. medRxiv [Preprint]. 2022 Dec 23:2022.12.21

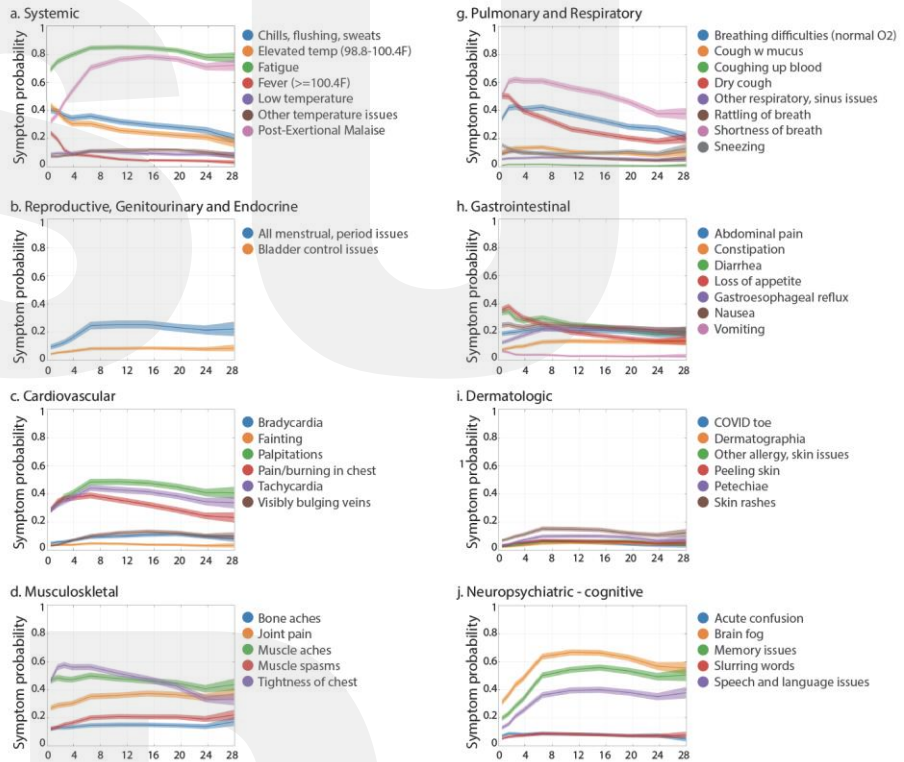
Clinical Presentation

What are the Characteristic Symptoms?

- **Fatigue / Post-Exertional Malaise**
- **Cognitive Impairment**
- **Palpitations / tachycardia**
- **Sleep disruption**
- **Depression / Anxiety**

- Headache
- Breathing Pain
- GI problems
- Anosmia
- Nerve abnormalities
- Joint & muscle pain
- Many others - less frequent





- Davis H et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. July 15, 2021:
- https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00299-6/fulltext

Important Conditions*

1. Post-Exertional Malaise & ME/CFS
2. Dysautonomia
3. Cognitive Impairment (Brain Fog)
4. Mast Cell Activation Syndrome
5. Small Fiber Neuropathy
6. Hypermobility syndromes*

* Out of scope for today's presentation

Post-Exertional Malaise (PEM)
A Hallmark Symptom

- Increased physical or mental exertion on a ‘good day’
  - Followed by **severe exhaustion & worsening of sx**
  - **Onset is delayed 12 to 72 hours**
  - Requiring **several days / weeks of recovery**
- Disabling exhaustion disproportionate to the effort exerted
- Triggered by physical activities (e.g. bathing), cognitive activities, stress.
- Different from fatigue = feeling of weariness, tiredness, or lack of energy
  - Not as delayed
  - Not associated with recurring cluster of symptoms

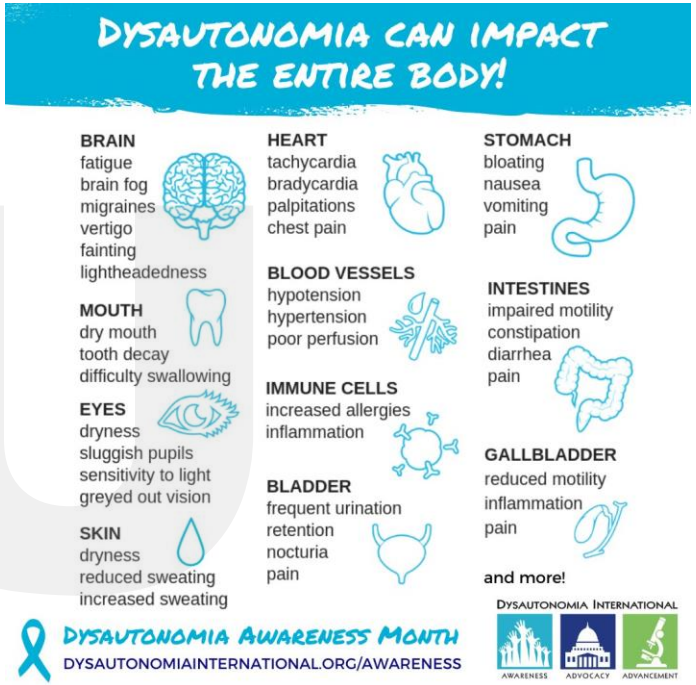
Long COVID & ME/Chronic Fatigue

- ME/CFS is a multisystem neuroimmune illness often following a viral infection*
  - > **6m** of profound fatigue, **PEM**, unrefreshing sleep, cognitive impairment, orthostatic intolerance, reduced activity levels
- PASC shares mechanistic & phenotypical characteristics of ME/CFS
  - **Half the individuals with LC meet criteria for ME/CFS**
- Understanding ME / CFS ⇔ Understanding Long COVID

* See appendix for formal dx criteria

PEM, POTS, Brain Fog, MCAS, SFN

Dysautonomia



- Umbrella term for medical conditions that cause malfunction of the ANS

- **POTS** (Postural Orthostatic Tachycardia Syndrome)
  - Most common dysautonomia in LC*
  - **Increase HR ≥ 30 bpm, or > 120 bpm, within first 10m of standing**
  - Tachycardic, lightheaded, chest tightness, dizziness, GI upset, HA, <u>etc</u>

- Patients often have clustering of complex sx suggestive of dysautonomia
- Observed in other post-viral conditions

* See appendix for POTS diagnosis and treatment considerations

Cognitive Impairment (Brain Fog) Similar to Post-Concussion Syndrome

- **Word retrieval**
- **Processing**
- **Working memory**
- **Reasoning**

- Problem solving
- Attention
- Executive functioning
- Spatial planning

Objective Research Findings:

- 10 years of cognitive aging
- Characteristics of Chemo-brain
- Intoxication at UK driving limit
- Changes in brain structure on MRI
- Animal models demonstrating viral crossing of BBB and neuroinflammation
- Redox imbalance similar to ME/CFS
- Focal brain hypometabolism on FDG-PET

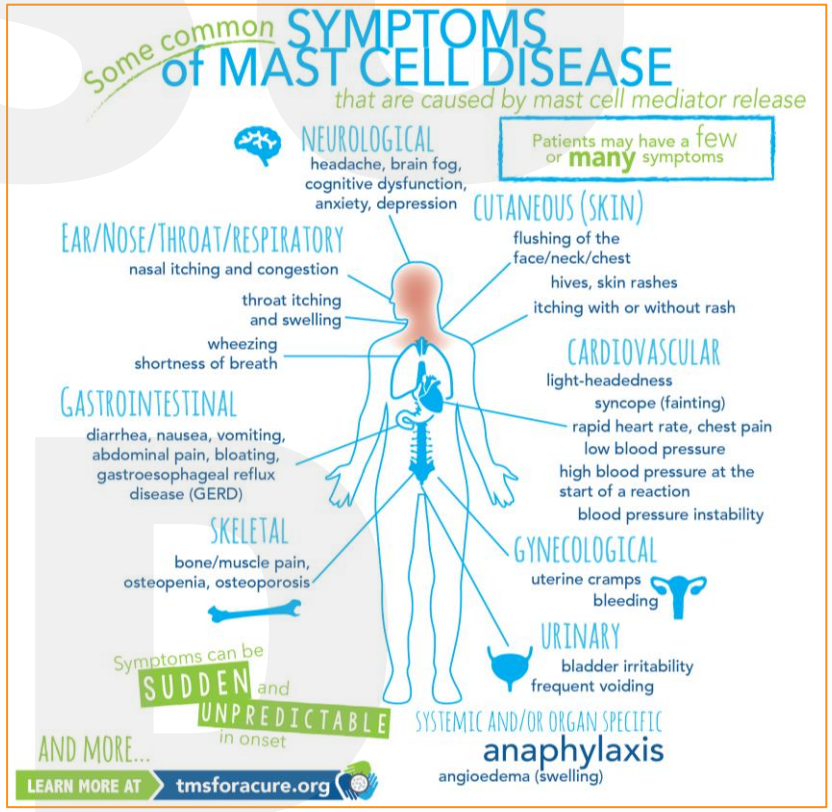
- more severe global cognitive impairment a/w associated **fewer than two COVID-19 vaccinations** prior to acute COVID-19 infection. (25)
- Decrease in cognitive ability when participating in tasks requiring **sustained attention and executive function**

PEM, POTS, Brain Fog, MCAS, SFN

Mast Cell Activation Syndrome

Irregular mast cell activation ⇌ Episodic multisystem symptoms

- **Flushing: face / neck / chest**
- **Derm: Itching, rashes, hives**
- **Palpitations and anxiety**
- **Rhinitis, conjunctivitis, sore throat**
- **GI: Bloating, nausea, diarrhea, pain**
- Light-headedness, BP instability
- Non-pitting and angioedema
- Wheezing
- Headache
- Brain fog



PEM, POTS, Brain Fog, MCAS, SFN

Small Fiber Neuropathy (SFN)

Damage to small unmyelinated C-fibers and thinly myelinated and A-delta fibers

- Mediate pain, thermal sensation, and autonomic function
  - Pain: Burning, prickling, shooting, and/or aching
  - Autonomic: Palpitations, abnormal sweating, light-headed, GI & GU dysfunction, dry mouth / eyes or skin, sexual dysfunction

- Different Variations
  - SFN without dysautonomia
  - Dysautonomia without neuropathy
  - Late SFN with without biopsy evidence

All Symptoms Flow with the Tide

- Symptoms tend to cluster together during cycles of improvement or worsening
- Worsening of all symptoms characteristically follows patterns of post-exertional malaise & stress
- Challenging to discern the complex of overlapping symptoms and conditions

Prognosis

- Long Term Prognosis Remains **Uncertain**
- Patients with symptoms at 2m
  - 85% reported persistent symptoms at 12m
- Patients at 18 months
  - **13% Unable to return to daily activities**
- **1/4 report significant activity limitations**

Zoe O Demko, et. Al. Two-year Longitudinal Study Reveals That Long COVID Symptoms Peak and Quality of Life Nadirs at 6–12 Months Postinfection, *Open Forum Infectious Diseases*, Volume 11, Issue 3, March 2024

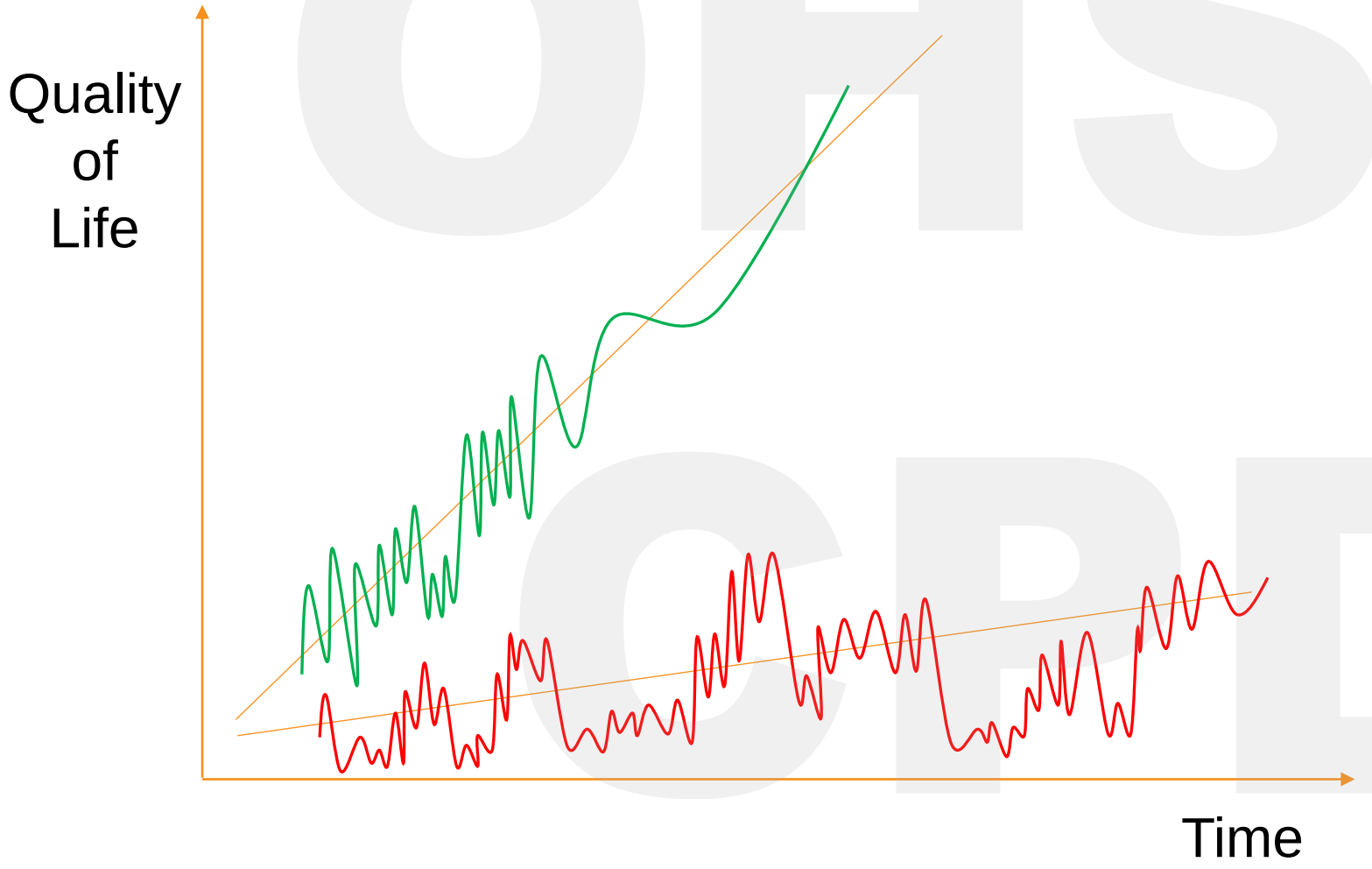
Ford ND, Slaughter D, Edwards D, et al. Long COVID and Significant Activity Limitation Among Adults, by Age - United States, June 1-13, 2022, to June 7-19, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(32):866-870. 2023 Aug 11

Recovery

- **Timeline is variable and unable to predict**
- Sx more likely to resolve: GI, respiratory, parosmia
- Sx more likely to persist:
  - **Arthralgias**, paresthesias, hair loss, blurry **vision**, swelling
  - **Neuro sx have delayed onset**, may worsen over time and persist
- More Challenging Recovery:
  - **Unvaccinated**, older, socially disparate, blacks, women, disabilities, mood disorders, acute severity, prior CV disease, mood disorders, complex pre-existing comorbidities

- Davis HE, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13:1–14

Goal For Recovery

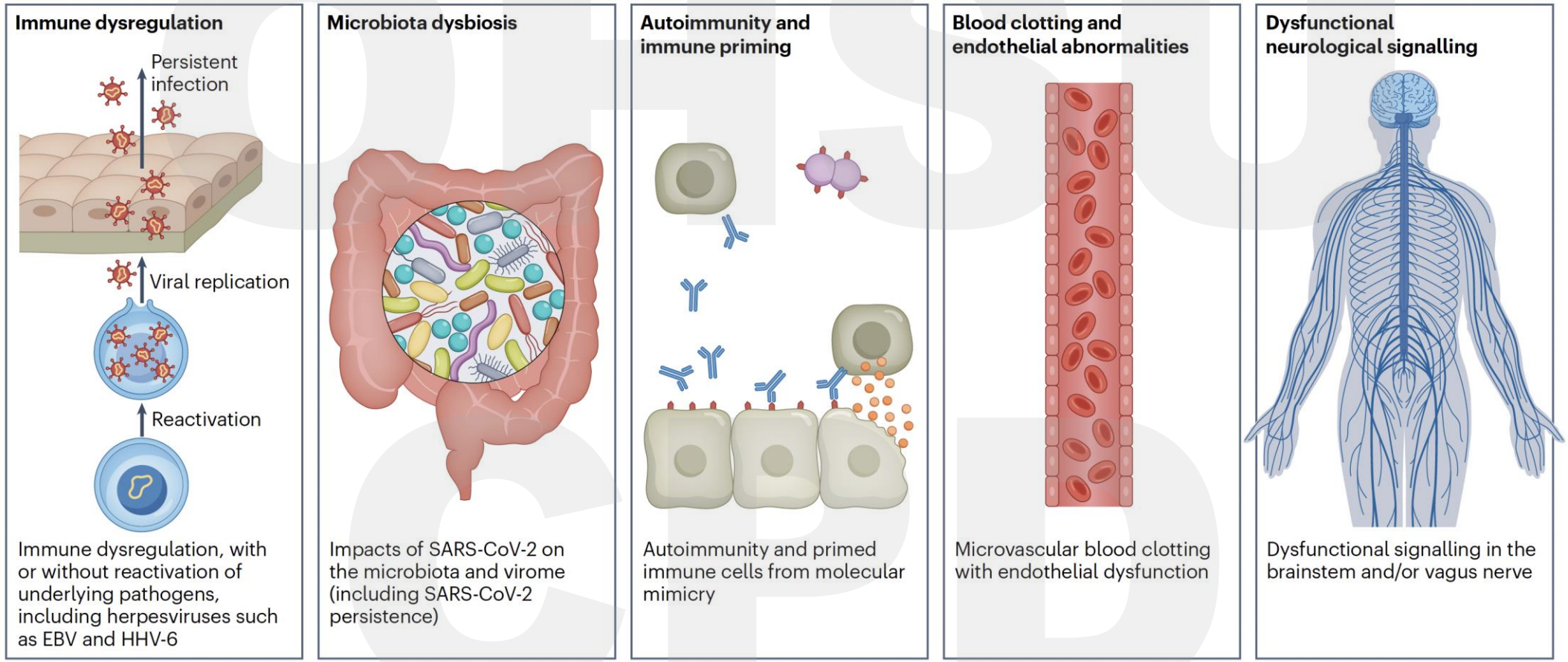


Goals:

- Accelerate and smoothen improvement trajectory
- Decrease number of relapses
- Empower patients with a vision of recovery

Pathophysiology

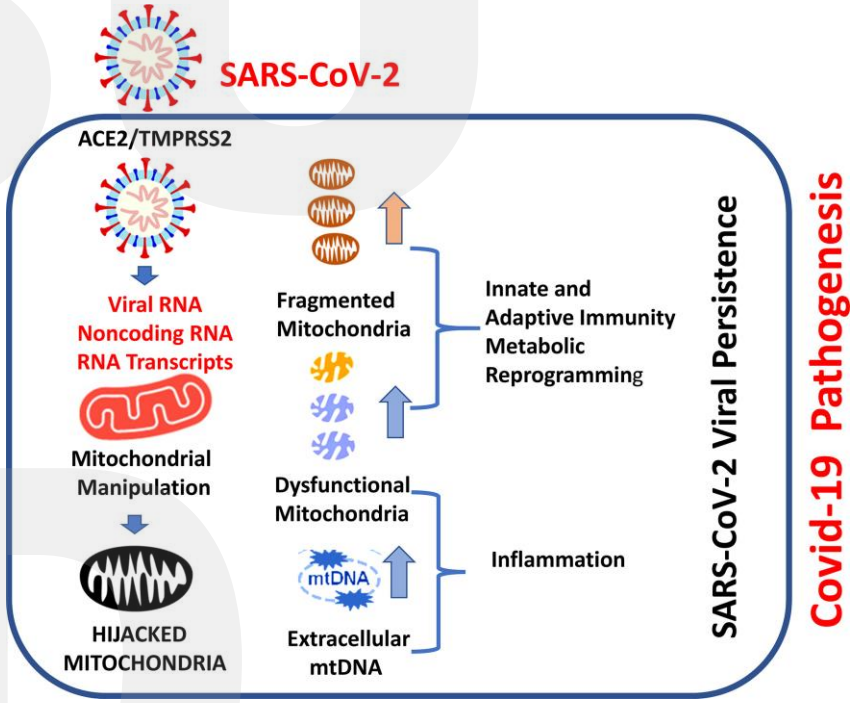
Pathogenesis of Long Covid?



- Davis HE, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13:1–14

Mitochondrial Dysfunction

- SARS-CoV-2 genomic and structural RNA are targeted for mitochondrial matrix
  - Decreases energy production
  - Decreases anti-viral signaling and immune response
  - Hijacked for viral replication
  - Increases inflammatory responses and reactive oxygen species



Role of Serotonin (5-HT)

- Many patients demonstrate decreased peripheral serotonin
- Mechanism
  - Viral persistence (e.g. gut reservoir)→ Chronic inflammation → ↑ IFN I → Reduction of 5HT and microclots*
- 5-HT affects Vagus nerve, influences hippocampal responses and memory
  - **Decreased 5-HT → BRAIN FOG**

- Wong AC, Serotonin reduction in post-acute sequelae of viral infection. Cell. 2023 Oct 26;186(22):4851-4867.e20.

PEM & Muscle Fiber Biopsies

- Lower skeletal muscle capacity for oxidative phosphorylation
- Shift to fast-fatigable muscle fibers (more glycolytic)
- **Severe exercise induced myopathy** and regeneration
  - Leading to muscle pain, fatigue, weakness
- Intramuscular accumulation of amyloid containing deposits

- Wong AC, Serotonin reduction in post-acute sequelae of viral infection. Cell. 2023 Oct 26;186(22):4851-4867.e20.

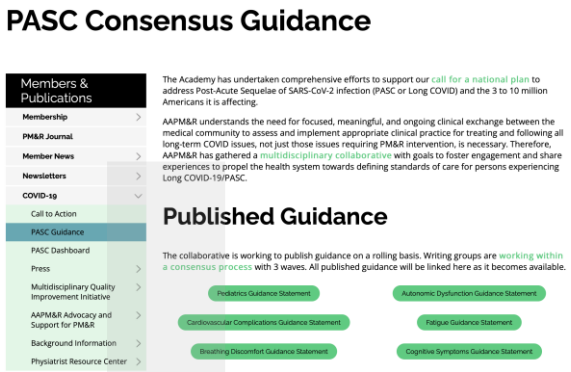
Evaluation and Management

Knowledgeable clinicians, earning trust, providing thoughtful, high-quality care

---

Best Practices

This is not the first or last post-viral syndrome

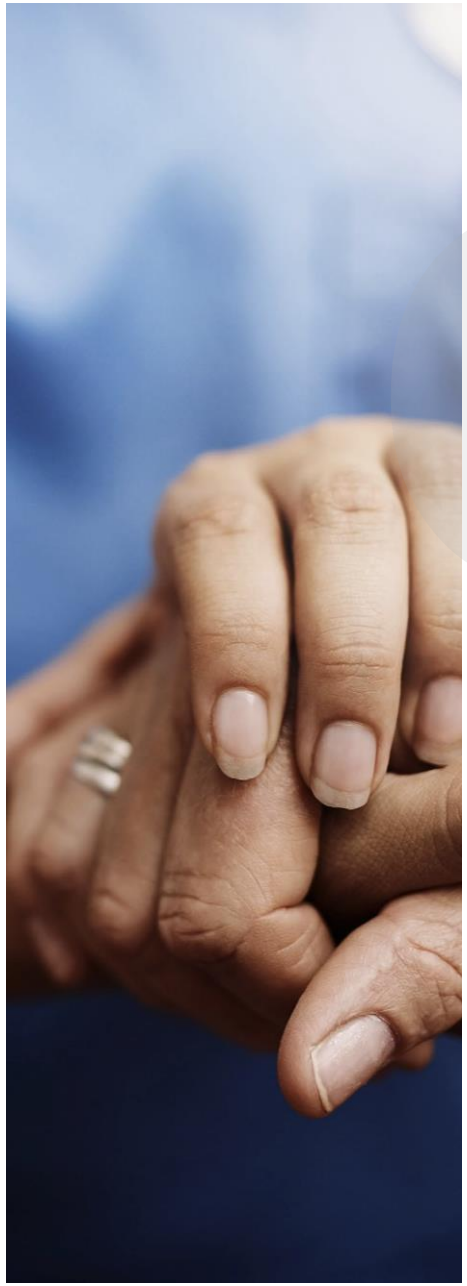


- At present, no comprehensive gold-standard guidelines or widely proven treatment protocol
- CDC Guidelines, AAPM&R PASC Collaborative Consensus Guidance Statements, VA, AFP Rapid Evidence Review
- Transparent, well-coordinated, trauma-informed care is essential
- With a firm understanding of PEM, POTS, Brain Fog, MCAS, SFN, the majority of issues can be managed and supported

- CDC Interim Guidance:
- AAPM&R Consensus Guidance Statements: https://www.aapmr.org/members-publications/covid-19/pasc-guidance
- AFP Rapid Evidence Review: https://www.aafp.org/pubs/afp/issues/2022/1100/long-covid.html

Basic Principles for Evaluation

- Most conditions can be diagnosed by history and exam
- Ordering of laboratory tests and imaging is guided by
  - Presenting symptoms or conditions
  - Duration and severity of complaints
  - Screening for treatable conditions
  - Appreciation that most routine studies are normal
- Symptoms are often not explained or out of proportion to objective findings.
- Listen and validate even when diagnostic testing and exam is normal!



History of Present Illness

- Baseline functioning & activity level prior to COVID
- Symptoms that impact quality of life the most
- Symptoms triggers – physical exertion, cognitive exertion, and stress
- **Attunement to the patient and calm the locked-in nervous system**

Review of Systems

- Requires comprehensive review of all symptoms
- Screen for the less common symptoms seen in POTS and MCAS
- Patient's can easily forget the many non-specific sx
  - Earn trust by exploring most impactful or less common sx
  - Examples: Word finding, flushing, hair loss, phantom smells, paresthesias, sensory overload, visual changes

Past Medical History

- Pre-existing conditions
  - Carefully review of onset & severity
  - Conditions often amplified: HA, sleep dysfunction, mood disorders, fibromyalgia, chronic pain, trauma
  - Subtle or latent conditions can be unmasked (e.g. Sjogren's, thyroid)

Social History Considerations

(Pre / Post COVID)

- Baseline daily activities (ADLs, iADLS)
- Social support, empathic partners, caretaker responsibilities
- **Unavoidable life stressors** (e.g. work, family, SDoH)
- **Finances, employment disability (FMLA)**

Medication Review

- Drugs that cause side effects similar to Long COVID sx
  - Anti-histamines, anticholinergic
  - Anti-depressant, anti-anxiety
  - Alpha receptor blockers, beta receptor blockers, calcium channel blockers, diuretics, ACE- Inhibitors, nitrates
  - Gabapentinoids, opiates

- **Polypharmacy**

Surveys

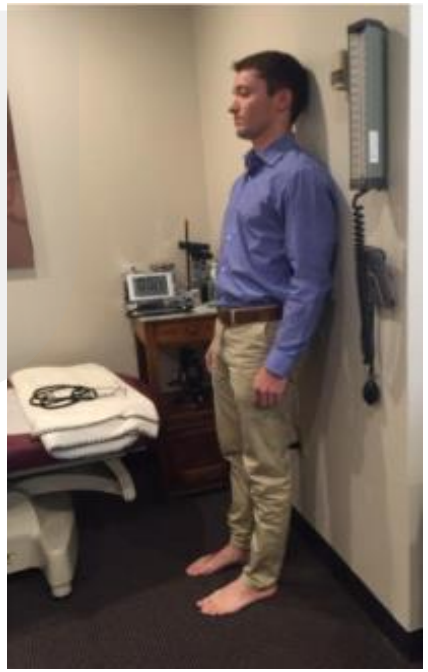
- Overall: DePaul Symptom Questionnaire – Short Form
- Respiratory: mMRC
- Neuro: MoCA, MMSE, Compass 31, Neurobehavioral Sx Survey
- Psych: GAD-7, PHQ-9, PTSD Screen
- Fatigue: Modified Fatigue Impact Scale, Fatigue Severity Scale
- Insomnia - Insomnia Severity Index (ISI)
- Quality of Life: PROMIS, PCFS, EQ-5D

- CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

Physical Exam – Orthostatics

NASA 10m Lean Test*

- HR & BP readings
- First taken in supine position after 5m supine
- Then taken once in sitting position
- Then standing position every minute until to 10 m
  - Position shown in the graphic
  - If needed, can do 3, 5, 7,10m instead.



Position reduces muscular influences on venous return, a major cause of variability in orthostatic testing

* For full instructions: Bateman Home Center – NASA 10m Lean Test - Instructions for Providers

Physical Exam
Focused Exam with Long COVID Lens

- Neurologic: SFN (pinprick / temp), vestibular
- Pulmonary Interstitial lung disease, RAD
- Cardiovascular Inappropriate sinus tachycardia
- GI IBS (bloating, pain)
- MSK Hypermobility (Beighton scoring system*), Rheumatologic
- Skin Telogen effluvium, vascular issues, dysautonomia, MCAS
- Psych Cognitive Impairment (word recall, memory), mood, ADHD

* See appendix for diagnostic graphic on Beighton scoring system

The Ehlers Danlos Society

THE BEIGHTON SCORING SYSTEM

Measuring joint hypermobility

A. 5th FINGER / 'PINKIES'

Test **both sides**: Rest palm of the hand and forearm a **flat surface** with palm side down and fingers out straight.

Can the **fifth finger** be bent/lifted upwards at the knuckle to go back **beyond 90 degrees?**

If yes, add **one point** for each hand.

1 POINT FOR EACH HAND

B. THUMBS

Test **both sides**: With the arm out straight, the palm facing down, and the wrist then fully bent downward, can the thumb be pushed back to touch the forearm?

If yes, add **one point** for each thumb.

1 POINT FOR EACH THUMB

1 POINT FOR EACH LEG

D. KNEES

Test **both sides**: While standing, with knees locked (bent backwards as far as possible), does the lower part of either leg extend **more than 10 degrees forward?**

If yes, add **one point** for each side.

C. ELBOWS

Test **both sides**: With arms outstretched and palms facing upwards, does the elbow extend (bend too far) upwards **more than an extra 10 degrees** beyond a normal outstretched position?

If yes, add **one point** for each side.

1 POINT FOR EACH ARM

E. SPINE

Bend forward, can you place the palms of your hands **flat on the floor in front of your feet without bending your knees?**

If yes, **add one point.**

1 POINT

Exercise Capacity Assessments

Can play important role in evaluating and monitoring

Usually done as part of PT Program

- 1 minute sit to stand
- 2 minute step test
- 10 meter walk test

- 6 minute walk test can cause PEM

Diagnostic Studies

- Positive COVID test is not required to establish dx
- Review all prior records in advance
- Establish clear goals as most studies are normal
  - Diagnostic testing may be of limited value and harmful (e.g. anxiety, costs)
  - Absence of findings does not mean symptoms have no functional impact

Basic Lab Testing

Screening for treatable conditions*

- CBC, CMP, UA
- hs-CRP, ESR, Ferritin
- TSH and free T4
- Vit B1 / B12 (Vit D?!)
- Chest X-Ray, EKG

* Will likely change after more results are found from clinical studies

Biomarkers

- No gold standard serologic test
- Non-specific with better evidence
  - Cortisol (low), Serotonin (low), IL-6 (high)
- EBV Antibodies & PCR
  - Controversial
  - May indicate reactivation
  - LC patients may have titers beyond detectible limits

Directed Laboratory Testing

Based on history, exam, ruling out specific etiologies

- **Dysautonomia**: Autonom. reflex testing, HR monitor, AM cortisol
- **SFN**: SFN Biopsy / QSART
- **MCAS:** Baseline & Episodic Tryptase (120% baseline +2)
  24h urine studies (N-methylhistamine and Urinary PGF2-alpha)

- CV: Echo, BNP
- Pulmonary: Spirometry
- Neurologic**:** Vitamins B1, B6, B12, Mg, & HgA1c
- Rheum: ESR/CRP, ANA, RF, anti-CCP, anti-cardiolipin, CPK

Advanced Imaging

- **Not routinely recommended unless**:
  - MRI Brain (red flag headache symptoms, not brain fog)
  - CT Chest (abnormal CXR, PFTs, O2)
  - Cardiac MRI (abnormalities in echo, hs-CRP)

Coagulopathies

- PT, aPTT, INR, D-Dimer = **little diagnostic value**
- Diagnostics for microclots are available only in select research locations and private firm (not standard)

- Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J. 2022 Feb 17;479(4):537-559. doi: 10.1042/BCJ20220016. PMID: 35195253; PMCID: PMC8883497.

Management & Treatment

- Fatigue / PEM
- Brain Fog
- POTS
- MCAS
- SFN
- Notable Conditions

Fatigue and Post- Exertional Malaise

STOP, REST, PACE

- The Four P's*
  - **Pacing**
  - Prioritization
  - Posture
  - Planning
- The Three D's
  - Delete
  - Defer
  - Delegate

* See appendix for more detail on the 4Ps

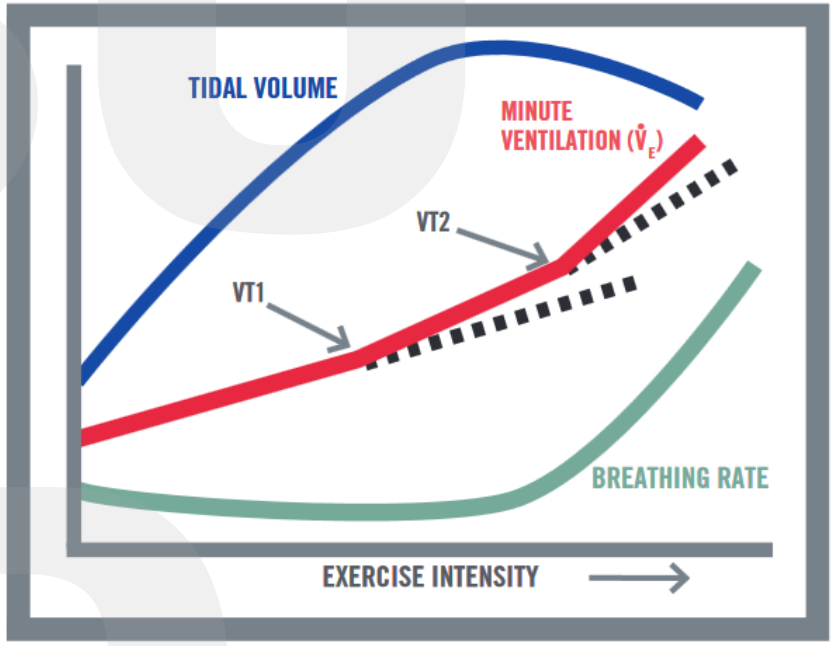
Return to Activity Program
Carefully Implemented Physical Therapy*

- **Not an 'aerobic exercise' or graded exercise program!**
  - Individualize the optimal level of activity and exertion
  - Systematically titer the progression of activity
- It is a function of
  - Breathing test: Awareness of understanding how breathing patters link directly to maximal effort
  - Heart Rate targets are often identified, but HR can vary widely
  - Most patients have dramatically reduced capabilities

* See appendix for detailed guidelines

Ventilatory Threshold

- During incremental exercise, there are two distinct changes in breathing patterns:
  - VT1 - first ventilatory threshold
  - VT2 - second ventilatory threshold
- **VT1** represents the breathing correlate of the body beginning to engage anaerobic fermentation in addition to oxidative metabolism
  - Can be identified using the "**talk test**." (Point at which it becomes difficult to speak in complete sentences."
  - Pushing past VT1 can lead to **PEM**
  - Above VT1 Blood lactate levels begin to rise from baseline but if work levels are held steady a lactate **plateau** may be held for a time as the body has some ability to clear lactate."
- VT2 occurs at the point the body must rely almost entirely upon anaerobic fermentation to deal with further increases in workload



Note: VT1 = First ventilatory threshold; VT2 = Second ventilatory threshold

Return to Activity Program (PT)

- Patients **learn** the breathing test as
  - The best gauge of appropriate level of activity

- Tittered physical activity < VT1 improves recovery
  - 1st Avoid PEM
  - 2nd Focus on building stamina
  - Gradually titer their level of exertion as VT1 improves

FIGURE 1: RETURN TO PHYSICAL ACTIVITY IN LONG COVID

APPROACH

DECREASE INTENSITY LEVEL:

- If current activity level triggers PEM/PESE

OR

- If recommended HR is exceeded during activity: slow/stop activity, monitor for PEM/PESE before resuming intensity level

INCREASE INTENSITY LEVEL:

- If current activity level is tolerated for 7-10 days without triggering PEM/PESE
- By 10% intensity every 7-10 days

DURATION / FREQUENCY:

- Increase *number* of daily/weekly activity bouts before increasing *duration* of a single activity bout
  - » (E.g., tolerate three 10-minute walks daily before trying a 30-minute walk)

Long-term Weekly Goals:

- 150-300 minutes of moderate-intensity activity

OR

75-150 minutes of vigorous-intensity activity

- Resistance training at least 2 times weekly

ACTIVITY INTENSITY LEVELS

1 DAILY ACTIVITIES:
START HERE, WORK UP AS TOLERATED

Minimal/no perceived exertion (1/10 RPE)

- Sedentary hobbies (e.g., knitting, sewing)
- Isometric exercises, breath work, meditation

2 LOW INTENSITY
♡ (<65% max HR):

Light perceived exertion (2-3/10 RPE)
(Able to talk or sing)

- ADLs (e.g., showering)
- IADLS (e.g., cooking)
- Gentle walking, recumbent cycling, aquatic activities at low intensity

3 MODERATE INTENSITY
♡ (65-75% max HR):

Somewhat hard perceived exertion (4-6/10 RPE)
(Able to talk but not sing)

- IADLs (e.g., vacuuming)
- Walking or jogging, cycling, swimming
- Resistance/strength training

4 VIGOROUS INTENSITY
♡ (>75% max HR):

Hard (heavy) perceived exertion (7+/10 RPE)
(Not able to talk or sing)

- Participation in competitive sport/recreation
- Sprinting
- Heavy resistance/strength training

CONTRAINDICATIONS

RELATIVE:

- Activity triggers PEM/PESE

ABSOLUTE:
(Until cardiology clearance)

- ACS, MI, arrhythmia, myocarditis, pericarditis
- If myocarditis or pericarditis:
  - » If LVEF normal and no arrhythmias, may start low-intensity activity 3 months after diagnosis under PCP supervision
  - » If LVEF reduced and arrhythmias documented, re-evaluate 6 months after diagnosis before continuing return to activity

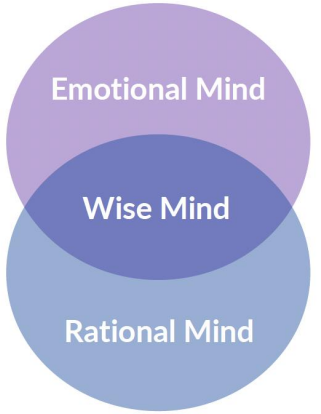
♡ Max HR =

If PEM/PESE:	Resting HR + 15
If CHD &/or on BB:	164 – (0.7*Age in years)
If ≥ 40 years old:	208 – (0.7*Age in years)
If < 40 years old:	220 – Age in years

Somatic & Nervous System Regulation

- **Long COVID Autonomic Nervous system is in a locked-in a defensive state**
  - Vagal nerve dysfunction proposed as a central feature
  - Vagus nerve influences immune system and inflammation

- Breathing exercises – Many approaches*



* See appendix for more details on breathing exercises

Cognitive Impairment (Brain Fog)

- **Speech Language Pathologist***
  - Evaluate, Measure, Monitor, Recommendations

- ***Neuro-stimulants***
  - if conservative measures fail
  - Caution PEM d/t tachycardia and/or false recovery

- ***Guanfacine (0.5 - 2 mg QHS)***

* See appendix for details on SLP approach

POTS*

- **POTS**:
  - Conservative Measures
    - **Salt** 4-6 grams / day (max 10g)
    - compression garments, small frequent meals and drink
    - Recumbent activity program with counterpressure exercise
  - Medical Management
    - **First Line**: Beta-blockers, midodrine, fludrocortisone, pyridostigmine
    - Start low low low, go slow
    - Often do better with multiple Rx at small doses
    - Many side effects that can be confusing with LC sx
    - May need to monitor electrolytes, BP
    - Second Line: clonidine, ivabradine, Methylphenidate, modafinil, droxidopa, SSRI/SNRI, buproprion

* See appendix for more details on POTS treatments;
Pathophysiology of POTS and use of tVNS

Other Important Conditions

- **MCAS**: H1 and H2 blockers, cromolyn, mast-cell stabilizers
- **Small Fiber Neuropathy**: Anti-depressants, gabapentionoids
- **Pain / Fatigue / HA**: Low Dose Naltrexone (1.5 – 4.5 mg QD)
- **Depression:** Differentiate between anhedonia vs. fatigue
- **Insomnia:** CBT-Insomnia, Sleep hygiene, melatonin.
  - Caution with heavier sedatives (e.g ambien) or antihistamines
- **Anosmia**: (limited evidence) Smell training with 4 essential oils, 15-20m BID. IN steroids, alpha-lipoic acid, Vit A drops

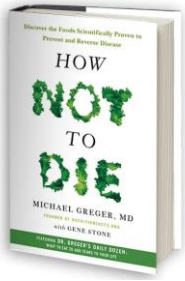
* See appendix for more details on POTS treatments

Psychotropics

Consider unique side effect profile and benefit

- Some interfere with cognition or worsen fatigue
- SSRI, SNRIs better tolerated at low doses
- First Line Agents
  - Anxiety / Panic: Beta blockers
  - Pain: Duloxetine
  - Hypotension / syncope: Venlafaxine
  - Sleep Issues: Mirtazapine

Nutrition!



- As of yet, no clear evidence yet for how nutrition focused therapies can improve outcomes for LC
- Healthy plant-based diets and avoidance of processed foods.
- However, healthy dietary choices may require more effort to shop and prepare. Consider working with nutrition expert.

RECOVER Initiative

https://recovercovid.org

- Paxlovid
- IV Ig for POTS
- Modafinil and solriamfetol (hypersomnia)
- Melatonin (complex sleep disturbances)

Other Treatments in Practice / Research

More commonly in practice

- Supplements for mitochondrial functioning
- Natokinase and variants
- SmartPhone apps (pacing)
- EECP (fatigue, CV impairment, Brain fog)
- Acupuncture
- Stellate Ganglion Blocks (smell/taste & autonomic)
- Non-invasive vegus nerve stimulation (POTS)
- Transcranial Direct Current Stimulation for neuropsychiatric sx
- Web-based Cognitive Retraining
- Resonant Frequency Breathing

Not standard practice / active research

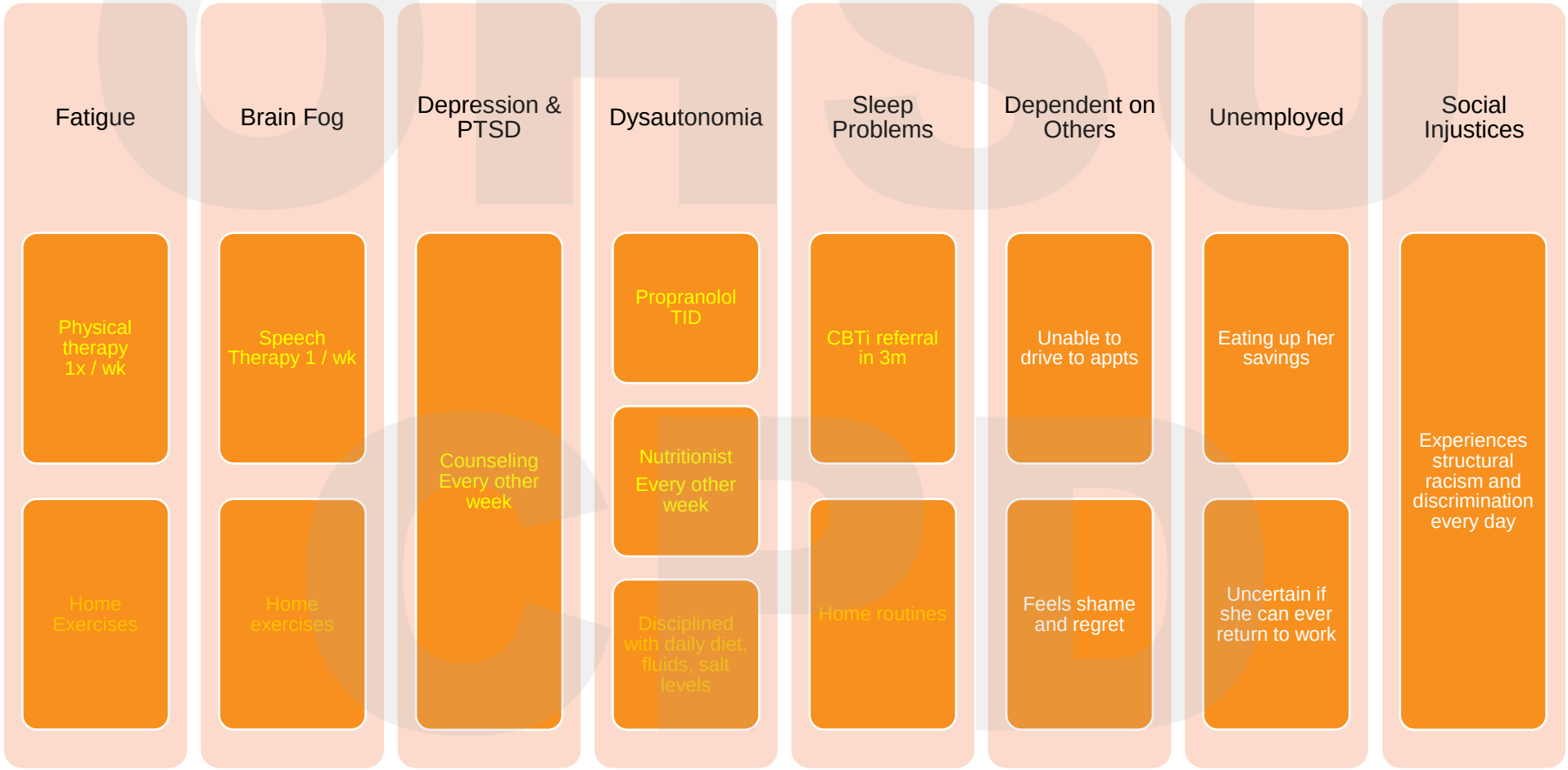
- Metformin for fatigue
- Fluvoxamine and Fisetin for brain fog
- Psychophysiologic symptom relief therapy (PSRT)
- Sleep Restriction Therapy

- Triple Therapy* (microclots)
- Transcutaneous Vagal Stimulation (Dysautonomia)
- Heart Rate Variability – Behavioral
- Paxlovid (Viral persistence)
- Apheresis
- Immunotherapies

Impact on Well-Being

Angela's Journey

She is unequivocally overwhelmed!!



Care Navigation is Critical for her Well-Being

- She has brain fog and is overwhelmed!
- Help is essential to put it all the plans together
- Best-practice programs have some nurse navigation, social work, and behavioral health support

Establishing Therapeutic Partnerships

- **Validate! Be attuned!**
- Holistic, trauma-informed care
- Goal to **improve QOL** and functioning
- Identifying achievable goals and setting expectations for recovery timeline
- Leverage **telemedicine** whenever possible
- Specialty partnerships should be recruited as needed

* See appendix for more details on patient support groups

Disability & Work Accommodations

One of the most important thing we can do!

- All patients need to time to recover
- Working, stress, pushing themselves too hard is the most common trigger for relapses and PEM
- Facilitating respite and / or reasonable reentry back to work is enormously beneficial for quality of life faster recovery

Accommodations & Disability for Fatigue & Brain Fog

Return to 100% work will fail 100% of the time!

Possible Disability Accommodations:

- Work from home
- Limited hours
- Alternating work days
- Frequent breaks
- Avoid standing
- Temporary disabled parking permits
- Limit tasks with divided attention
- Optimize range of movements
- Limit environments with multiple sensory inputs
- Graduated return to work activities

For Disability Applications, Document

- Activity levels pre/post infection
- Symptoms that are remitting and relapsing
- Specific work activities will result in physical and mental fatigue
- Environmental settings that result in sensory overload (markets, etc)
- Work-ups that rule out other associated causes including pre-existing conditions

Final Considerations

100,000 Ft View

- VT1 and Pacing is foundational to recovery
- Return to activity program is not exercise
- Remember PEM, POTS, Brain Fog (PCS), MCAS, SFN
- Directed workup with established goals
- Provide supportive routine care, expect relapses
- Validation, transparency, empathy, patience
- Stay tuned for
  - *Long COVID Compendium (AAPM&R)*
  - Novel diagnostic and treatment options

Investment in Long COVID Research

- *RECOVER Initiative*
- White House Orders Federal Action Plan
- AHRQ
  - Grants for 9 Long COVID clinics
  - Researching models of care
- Federal Advisory Committee

Managing PASC in Your Practice

Top 10 Essential Components

1. Knowledge Toolkit – CDC Guidelines, AAPM&R Guidelines, VA, AFP Rapid Evidence Review, Pacing, PT protocol
2. Empathetic clinicians with committed interest – Behavioral Health, Neuro, dysautonomia, sleep
3. Rehabilitation team familiar with tittered, individualized treatment coupled with breathing test (PT/SLT/PM&R)
4. Extended visit for a dedicated comprehensive assessment with records in advance
5. Screening instruments for your practice
6. Documentation template or clinical approach for initial assessment
7. Patient instructions for most common symptoms
8. Team members to support SDoH, care navigation, FMLA
9. Whenever possible, access to virtual visits
10. Patience and reassurance

Eric Herman, MD
Chief Primary Care & Population Health Officer
hermaner@ohsu.edu

Thank You

Appendix

What is Long COVID?

Post-COVID Conditions

- NASEM: Long COVID (LC) is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least **3 months** as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

- Also known as:
  - **PASC** = Post Acute Sequela of SARS-CoV-2
  - Long COVID
  - “Long Haulers”

Assessment and Plan:
- Longitudinal plan of care; Scope of PMR vs. PCP
- Gratitude for PCP for continued management of...

Care Navigation / Management
- Contact information, types of support (Care, Coordination, Education, SDoH)

Follow - Up
- Time for therapies, studies, referrals
- Patient can leverage nurse navigator and MyChart

Documentation Framework
For PMR, PCP, & Pt

History:

Onset
Symptoms began on: ***
Patient was hospitalized for COVID-19 infection: {Y/N:24016}
Persistent symptoms that impact quality of life: ***

Post Acute Sequelae of COVID-19 (PASC)
Fatigue & Exertional Malaise: {Fatigue:23787}. ***PEM***
Cardiopulmonary Impairment: {CP Impairment:23791} ***POTS***
Cognitive Impairment: {Cog Impairments:23784}. ***Brain Fog***
Dermatologic Impairment: {Derm:27760} ***MCAS***
GI Impairment: {GI:27759}
Neurologic Impairment: {Neuro:26652} ***SFN***
Neuropsychiatric Impairment: {NP Impairment:23786}.
Sleep Impairment: {LCSubSleep:23785}.
Other sequelae: {Sx:23770}.
Relapse Triggers: {Relapses:28415}

Other Health & Well-Being
Functional Impairment: {Fxl Impairments:23764}.
Social support: {Support:23766}.
Employment status: {Status:23803}
SDoH Screeing: ***
Nutrition & Hydration: ***

Past Medical History & Prior Studies:
Review before the visit; Avoid Long Auto-Filled Content

PMHx, PSHx, Fhx, Shx was reviewed and updated per discussion with patient.
Precovid Conditions of significance include: ***
Medications of significance include: ***
Prior labs: *** (significant for ***)
Prior Procedures: *** (significant for ***)
Specialty consultations: ***

Allergies:
@ALLERGY@

Vitals and Physical Exam:
@VSREF@
O2 Saturation: At rest ***; With Ambulation ***
Functional Capacity Testing: {Fxl:28416}

Standard Measures (Survey Instruments)
Fatigue (FSS, FIS, BFIS):
Breathing Discomfort (MMRC, MDP, MBDS, DASI):
Depression: PHQ 2/9: Anxiety: GAD-7:
Dysautonomia: COMPASS-31

Clinical Location and Coding Statement:
{PCG E/M Billing:24424:::1} typical disclaimer vetted by coding department
Provider: @ME@ Provide most appropriate yet direct contact information

National Academy of Medicine's Proposed Diagnostic Criteria for Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

Diagnosis requires that the patient has the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, education, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
2. **Postexertional malaise***
3. **Unrefreshing sleep***

At least one of the following:

1. **Cognitive impairment* or**
2. **Orthostatic intolerance**

*Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

POTS Dx

- Measure blood pressure and heart rate at regular intervals
  - Ideally at **3, 5, 7, and 10 minutes**, in standing position
  - After patients lies quietly in supine position for at least 10 minutes
- Criteria for POTS diagnosis includes
  - Increase in heart rate ≥ 30 beats/minute within 10 minutes of upright posture from supine position (increase in heart rate > 40 beats/minute required for patients < 20 years old)
  - Absence of orthostatic hypotension
  - Standing heart rate is often ≥ 120 beats/minute, typically higher in morning than evening
- Increases in orthostatic heart rate gradually decrease with age in patients with POTS
- **Sx often detected during PT program**
- Also consider tilt table testing, Quantitative Sudomotor Axon Reflex Test, Thermoregulatory Sweat Test (TST), skin biopsies looking at the small fiber nerves

POTS Conservative Tx

Salt

- 4-10 grams of salt per day total, 2-3 grams added to hydration. 3L water per day. (Typically 4-6 grams)
  - Drink mix options: LMNT™ electrolyte replacement, Re-Lyte™ electrolyte replacement, Nuun™ electrolyte replacement, Dr. Price's Electrolyte Mix™, Normalyte™. Drip Drop ORS™. Liquid IV™
  - Tablet/capsule Options: Salt Sticks Vitassium™ electrolyte capsules, Hi-Lyte™ , Thermotabs™ (1000mg sodium)
  - AVOID the following: Gatorade, Powerade, other sugary sports drinks

Hydration

- Finding the perfect amount of water can challenging. Drink 2-4 liters of water per day.
- Drinking water quickly rather than sipping helps expand blood volume more rapidly, mimicking the effects of IV saline.

Compression Garments

- Knee high compression socks come in variable strengths. The weakest strength is 15-20mmHg. Pick the most tolerable and helpful for you. Beware of socks too tight just below the knee.
- Waist high compression garments may work best for you
- Wear compression socks during all times with activity, especially standing for longer periods of time.
- Wear compression hose full time if it makes you feel better.
- Custom made garments are made for the “hard to fit” and are generally covered by insurance.
- Abdominal binders or Spanx may be helpful for abdominal compression.
- Abdomen to thigh compression is recommended for patients due to excessive splanchnic blood pooling.

“Zero Gravity reclining chairs”

- A reclined position can greatly improve energy and digestive symptoms.
- “Zero gravity” chairs range in price starting at about $45.
- Consider getting into zero gravity for 30 minutes prior to and during meals.

Digestive support

- Eat meals slowly and chew food thoroughly in a low stress environment.
- Drink at most, small amounts with meals.
- Over the counter digestive enzymes may be taken with meals to improve digestion and absorption of nutrients.
- Iberogast: This is an over the counter herb blend that can be found online and comes in both capsules and liquid. By improving digestive motility, nausea, bloating, and pain may be decreased. Take 20-30 drops by mouth 2-3 times daily, or as needed.

Heat Intolerance

- Ice packs to the face and neck
- Cold showers
- Koldtec ice towels
- Embr wave bracelet
- ChiliPAD for sleep support

Bed Risers

- Raising the head of the bed 4-6 inches with bed risers may lead to increased volume expansion and improve orthostatic intolerance.

Cognitive Impairment (Brain Fog) Similar to Post-Concussion Syndrome

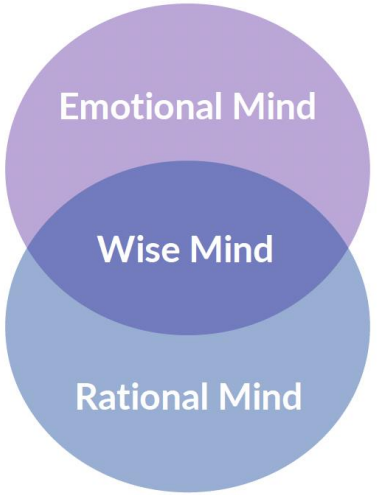
- **Word retrieval**
- **Processing**
- **Working memory**
- **Reasoning**

- Problem solving
- Attention
- Executive functioning
- Spatial planning

Objective Research Findings:

- 10 years of cognitive aging
- Characteristics of Chemo-brain
- Intoxication at UK driving limit
- Changes in brain structure on MRI
- Animal models demonstrating viral crossing of BBB and neuroinflammation
- Redox imbalance similar to ME/CFS
- Focal brain hypometabolism on FDG-PET

Somatic & Nervous System Regulatic



- **Long COVID Autonomic Nervous system is a locked-in a defensive state**
  - Vagal nerve dysfunction proposed as a central feature in Long COVID
  - Vagus nerve is involved in processes of the immune system and inflammation

- Breathing exercises – Many approaches
  - Diaphragmatic breathing, 10m BID, at least once before bedtime
  - Long COVID Breathing & Wellness Program - The Sadhguru center (BIDMC)
  - John Hopkin's Breathing Exercises
  - Stasis.life
  - For patients that have challenges focusing on breathing, recommend paying attention to any sensory experience

Angela's Well Being

- **Physical**: PEM, tachy, brain fog, insomnia
- **Economic**: No money, savings, dependents
- **Social**: Isolation, discrimination
- **Emotional**: Overwhelmed, scared
- **Psychological**: Depressed, traumatized
- **Life satisfaction**: Not worth living

- **It is not all in their head, but suicidal ideation might be!**

Survey Instruments For Long COVID

Post-COVID-19 functional status scale
https://gp-website-cdn-prod.s3.amazonaws.com/topic-downloads/1602682348-5fc74b64deceab6b45c679772acab0f4.pdf

Modified medical research council (mMRC) dyspnea scale
https://www.mdcalc.com/mmrc-modified-medical-research-council-dyspnea-scale#evidence

Montreal cognitive assessment (MoCA)
https://www.mdcalc.com/montreal-cognitive-assessment-moca#evidence

Patient health questionnaire (PHQ-9)
https://www.mdcalc.com/phq-9-patient-health-questionnaire-9#evidence

Generalized anxiety disorder scale (GAD-7)
https://www.mdcalc.com/gad-7-general-anxiety-disorder-7#evidence

Modified fatigue impact scale (MFIS)
https://www.mdcalc.com/modified-fatigue-impact-scale-mfis#evidence

Fatigue severity scale (FSS)
https://www.sralab.org/sites/default/files/2017-06/sleep-Fatigue-Severity-Scale.pdf

Insomnia severity index (ISI)
https://www.ons.org/sites/default/files/InsomniaSeverityIndex_ISI.pdf

Snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender (STOP-BANG) questionnaire:
https://www.mdcalc.com/stop-bang-score-obstructive-sleep-apnea

Geriatric Depression Scale (GDS)
https://web.stanford.edu/~yesavage/GDS.html

PTSD Checklist for DSM-5 (PCL-5)
https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp#obtain

10-item DePaul Symptoms Questionnaire – Post Exertional Malaise (DSQ-PEM)
https://csh.depaul.edu/about/centers-and-institutes/ccr/myalgic-encephalomyelitis-cfs/Pages/measures.aspx?

Energy Conservation – 4Ps

- **Pacing**: reasonable, short, more time, breaks, avoid push and crash
- **Prioritization**: What to do on specific days, left for time with more energy, uncessary. Avoid overexertion and crash
- **Positioning**: Modify activities to make easier. Sitting, workspace optimization, shower chairs,
- **Planning**: plan day / weeks / energy windows. Diary of good/bad/energy windows. Plan rest breaks, preparing tasks ahead of time, plan out completion of tasks. Plan out return to activities like work. Accomodations: limited hours, adjust work activities, breaks, parking. Voc rehab counselor
- https://www.hackneycitizen.co.uk/wp-content/uploads/Post-COVID-19-information-pack-5.pdf

General Attributes of Individually Titrated, Symptom-guided Program of Return to Activity Program

- Goal is to restore previous levels of activity and improve quality of life.
- Until goals are achieved, patients should not initiate high-intensity aerobic exercises or heavy weight training.
- If program is advanced too quickly, it can worsen symptoms and trigger PEM.
- Patients are directed to perform activities at sub-maximal levels.
- Activities are adjusted in response to symptoms that develop both during and after activity.
- Patients are educated on how to recognize perceived exertion and use other metrics such as heart rate or validated exertion scales.
- Activity recommendations depend on level of severity and progress according to symptom tolerance.
- An example of program progression could be bedside mobilization, range of motion exercises, tolerated household activities, stretching of extremities, limited community activities, submaximal exercise, and eventual higher intensity activities.
- Consider referral to a medical professional (physiatrist or physical therapist) who is knowledgeable with Long COVID care and can monitor the course of the program.

Example Strategies in SLP

Memory	•WRAP (write, repeat, associate, picture), associating word lists •Calendars, important items in the same place, follow directions
Attention	•Limit multitasking and distractions •Self-talk and self-cues and goal setting •Increase attention from sustained, selective, alternating
Communication	•Face speaker, ask for attention, talk the word •Pause / think / speak, •Tell others how they can help (‘give me a second or can you offer a guess’)
Sleep	•Avoid caffeine, alcohol, fatty meals, screentime •Bedtime rituals, sleep environment, sunlight
Language	•Extra time to think, describe what you’re thinking, scan alphabet for start letter •Draw, gestures, words with same meaning
Exec Function	•STOP (Stop, Think, Organize, Plan) •Self-talk, repetition, visualization, self-monitoring, puzzles, logic tasks

The Ehlers Danlos Society

THE BEIGHTON SCORING SYSTEM

Measuring joint hypermobility

A. 5th FINGER / 'PINKIES'

Test **both sides**: Rest palm of the hand and forearm a **flat surface** with palm side down and fingers out straight.

Can the **fifth finger** be bent/lifted upwards at the knuckle to go back **beyond 90 degrees?**

If yes, add **one point** for each hand.

1 POINT FOR EACH HAND

B. THUMBS

Test **both sides**: With the arm out straight, the palm facing down, and the wrist then fully bent downward, can the thumb be pushed back to touch the forearm?

If yes, add **one point** for each thumb.

1 POINT FOR EACH THUMB

1 POINT FOR EACH LEG

D. KNEES

Test **both sides**: While standing, with knees locked (bent backwards as far as possible), does the lower part of either leg extend **more than 10 degrees forward?**

If yes, add **one point** for each side.

C. ELBOWS

Test **both sides**: With arms outstretched and palms facing upwards, does the elbow extend (bend too far) upwards **more than an extra 10 degrees** beyond a normal outstretched position?

If yes, add **one point** for each side.

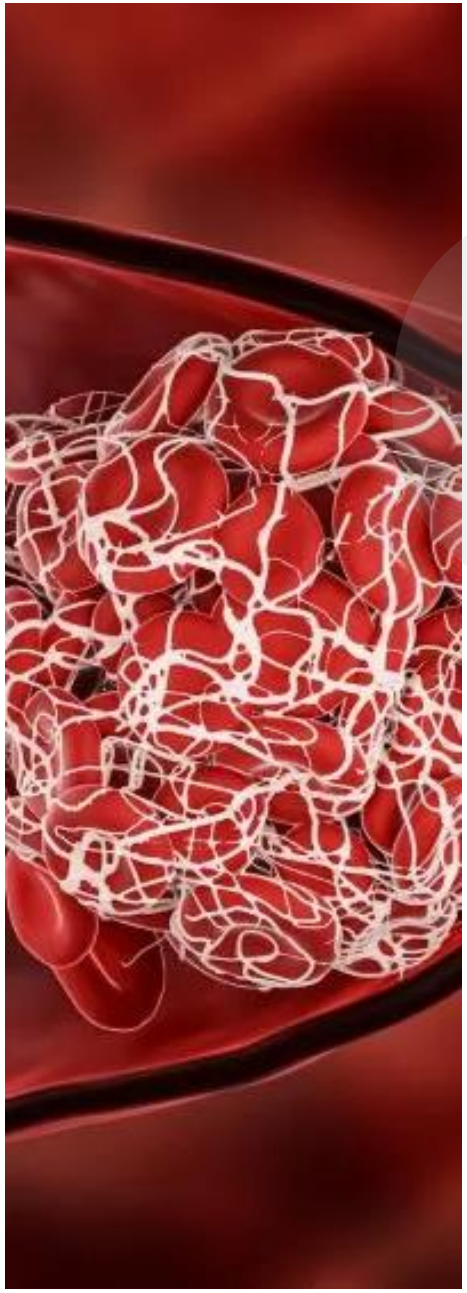
1 POINT FOR EACH ARM

E. SPINE

Bend forward, can you place the palms of your hands **flat on the floor in front of your feet without bending your knees?**

If yes, **add one point.**

1 POINT



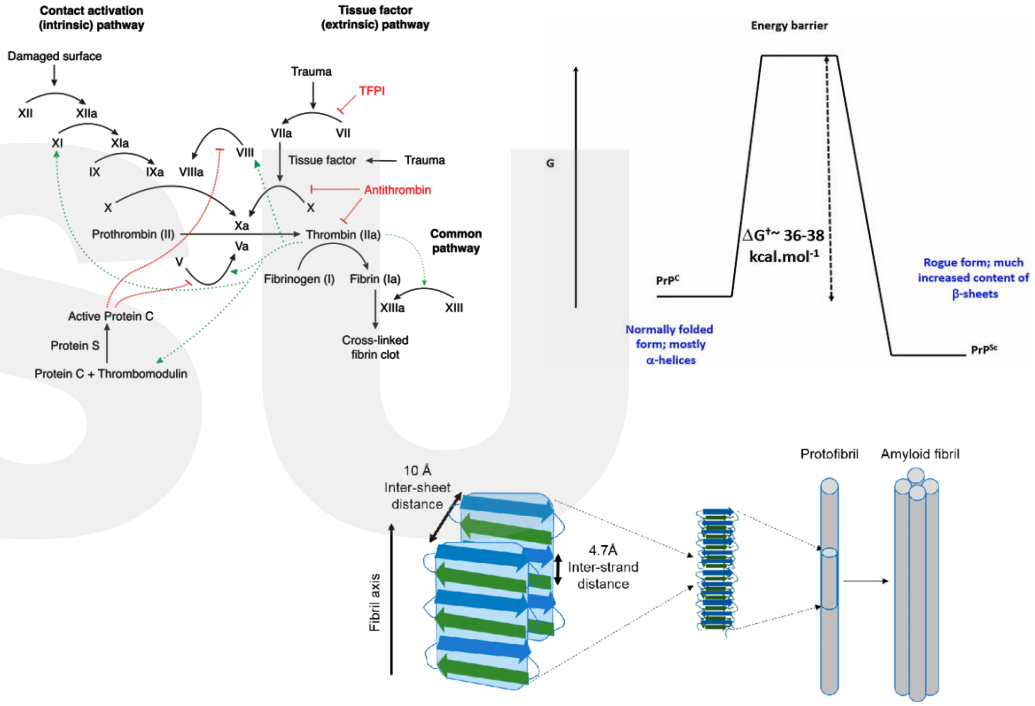
Microclots (Proposed Theory)

- Hypoxemia d/t microclots, platelet dysfunction, and endothelial injury
- Substantial volume of circulating microclots are found in the plasma
  - Surge of acute phase inflammatory molecules (e.g. SAA4)
  - Imbalance between hypercoagulation and hypofibrinolysis*
  - Anomalous fibrin amyloid microclots
    - Triggered by the SARS-CoV-2 spike protein
    - Resistant to fibrinolysis trapping proteins including the virus
    - Leads to production of autoantibodies & pro-inflammatory activity
- Ground glass opacities are largely formed of fibrin and persistent
- Amyloid structures can be cytotoxic itself, creating membrane disruption
- Evidence of similar pathogenesis in Alzheimer's with herpes viruses

* See appendix for details

Microclots

Fibrin ⇌ Amyloid Transformation



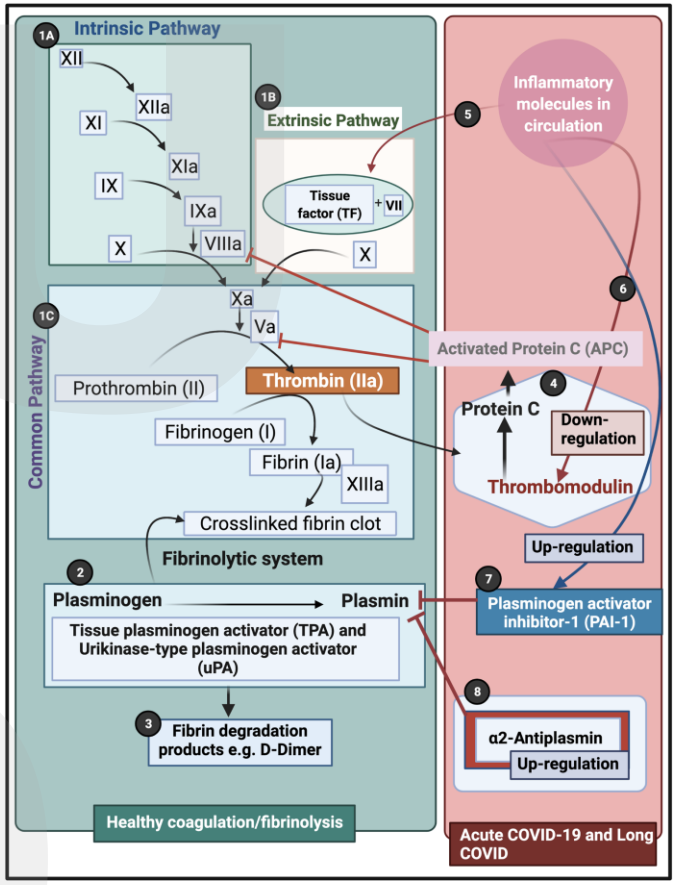
- Fibrinogen – Abundant protein in the plasma
- Thrombin acts on fibrinogen -> small protofibrils -> long fibrils
- Factor XIII
  - Inserts molecular crosslinks into the clot
  - Cross-links α2AP to fibrin which inhibits plasmin
- Prion Proteins
  - Proteins that can change their structure with the right catalyst (e.g. another prion)
  - New versions commonly take on amyloid forms (B-sheets) (e.g. Alzheimer's, Parkinson's, T2DM, RA)
- SARS-CoV-2 spike protein can trigger a prior protein conversion of fibrin into fibrin amyloid version
  - This version is highly resistant to proteolysis
  - Size of microclots varies from 1-200 microns (flow through most microcapillaries)
  - S1 spike protein can itself persist in CD16+ Monocytes for up to 15 months

- Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J. 2022 Feb 17;479(4):537-559. doi: 10.1042/BCJ20220016. PMID: 35195253; PMCID: PMC8883497.

Microclots

Hypercoagulation and Hypofibrinolysis

- Significant increases in inflammatory molecules leads to hypercoagulability
  - ↑ Fibrinogen chains ⇌ ↑ clot production↑
  - ↓ Thrombomodulin ⇌ ↑ clot production↑
  - ↑ Plasminogen activator inhibitor-1 (PAI-1) ⇌ ↓ clot destruction↓
  - ↑ VWF ⇌ platelet activation and adhesion ⇌ ↑ clot production↑
- Increased levels of α(2)-antiplasmin (α2AP)
  - Crosslinked to fibrin thrombus by Factor XIIIa ⇌ ↓ clot destruction↓
  - Increased α2AP -> ischemic stroke and failure of tPA therapy
- Plasmin - Protease responsible for fibrinolysis
  - Used to process viral S protein for cellular entry ⇌ ↓ clot destruction↓



Microclots (Unproven in RCT!)
Treatment – Triple Therapy x 1 Month

Below is the protocol implemented by researchers.
As of yet, there are no randomized clinical trials and this is not standard practice.

- Dual antiplatelet therapy (DPAT)
  - Clopidogrel 75 mg QD
  - Aspirin 75 mg QD
- Direct Oral AntiCoagulant (DOAC)
  - Apixaban 5 mg BID
- PPI Gastric Protection (e.g. pantaprazole 40 mg QD)
- Regular assessment of coagulation status before and during treatment

- Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J. 2022 Feb 17;479(4):537-559. doi: 10.1042/BCJ20220016. PMID: 35195253; PMCID: PMC8883497.

IFN I Mediated decrease in Serotonin

- Decreased transcription of genes in gut need for amino acid transport
  - ↓ Tryptophan reabsorption → ↓ 5HT
- Hyperactive platelets → thrombocytopenia → ↓ platelets with serotonin
- Increased MAO breakdown of serotonin

- Wong AC, Serotonin reduction in post-acute sequelae of viral infection. Cell. 2023 Oct 26;186(22):4851-4867.e20.

Future Diagnostic Tools

- Imaging to detect microclots
- Corneal microscopy to identify SFN
- Fragmentation of QRS complex suggestive of cardiac impairment
- Hyperpolarized MRI to detect pulmonary gas exchange abnormalities
- Biomarkers of Long COVID under investigation
  - Immune markers and levels of extracelluar vesicles
- Biomarker research in ME / CFS: Electrical impedance blood tests, saliva tests, erythrocyte deformation, lipid profiles, isocapnic buffering
- Dogs can identify individuals with Long COVID based on sweat samples 23 long COVID 51.1% sensitive, 100% specific

Patient Support Groups

- Body Politic
- Survivor Corps
- Long COVID Alliance
- Long COVID Kids