

Long COVID: A Primer for Primary Care



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Learning Objectives

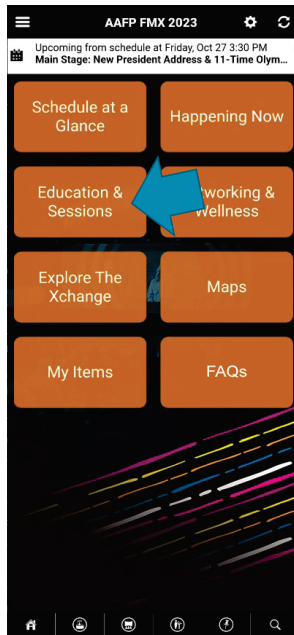
1. Define Long COVID.
2. Identify common signs and symptoms of Long COVID.
3. Discuss the proposed etiologies for Long COVID.
4. Provide management of Long COVID according to treatment recommendations for Long COVID.



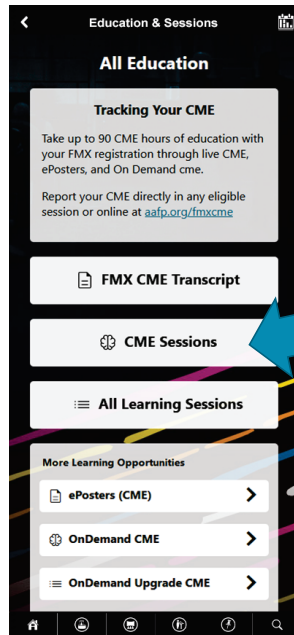
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Audience Engagement System

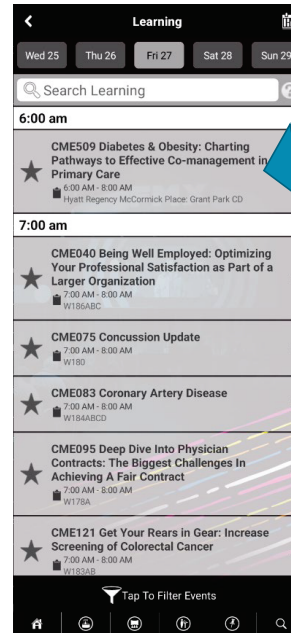
Step 1



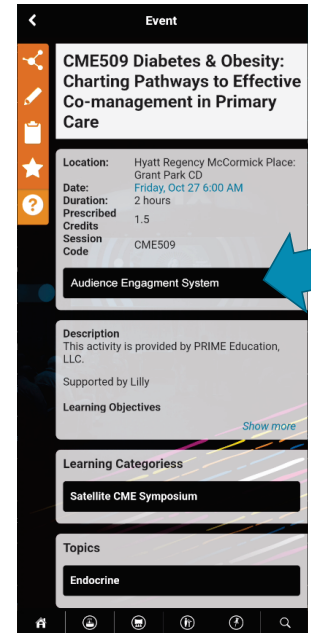
Step 2



Step 3



Step 4



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You may also be interested in the following AAFP activity(ies) related to this topic:

On Demand: Coronavirus (COVID-19) - www.aafp.org/cme/topic/covid-19.html

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Patient Story

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

Prior to getting COVID-19 in April 2020, she worked 50 hours a week and enjoyed travelling. Now she feels like she is wearing a lead weight on her body, after doing household chores she suffers profound exhaustion for days, and her heart races on occasion. 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, and is an enigma to the medical community. She doesn't understand what is wrong with her, wonders if she will get better, and contemplates if life is even worth living.

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Angela's Long COVID Footprint

HPI

- Wearing a lead weight on her body, after doing household chores she suffers profound exhaustion for days
- Heart races on occasion
- Difficulty finding words, staying focused, multi-tasking, and is mentally exhausted when going to the market
- She has unrestful sleep every night
- Scared she could die, and contemplates if life is worth living

Long COVID Manifestations

- Post-Exertional Malaise
- Dysautonomia - POTS
- Cognitive Impairment
- Sleep Disturbances
- Depression; PTSD

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Background

1. Post-COVID Conditions
2. Epidemiology
3. Vaccines & Risk Reduction

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What is Long COVID?

Post-COVID Conditions

- CDC: Range of new, returning, or ongoing health problems people can experience four or more weeks following initial SARS-CoV-2 infection
- Also known as:
 - **PASC** = Post Acute Sequela of SARS-CoV-2
 - Long COVID
 - COVID Long-Haulers

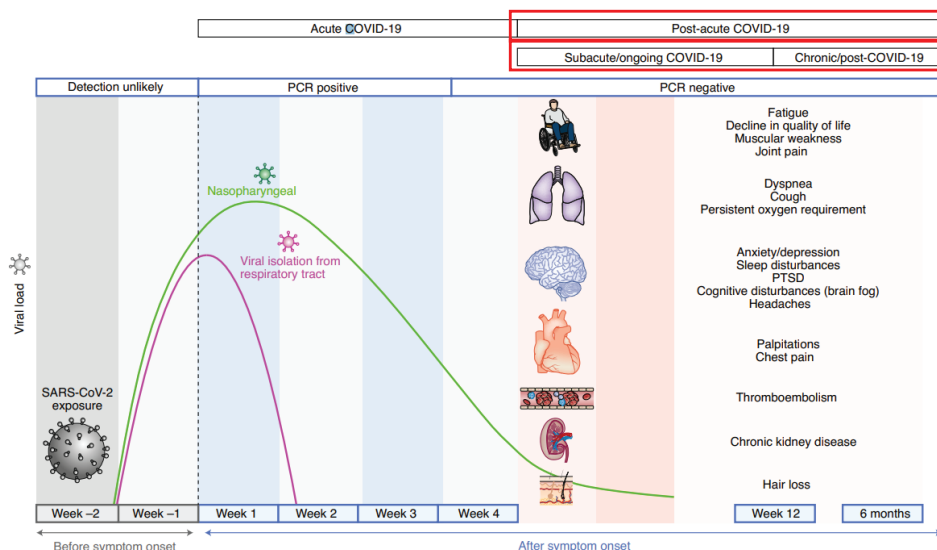
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Post-COVID Conditions

- Some conditions are more attributable to **SARS-CoV-2 infection**
 - e.g. anosmia, brain fog, POTS, post-exertional malaise...
- Some conditions are more attributable to **SARS-CoV-2 illness**
 - E.g. deconditioning, treatment side effects, bereavement, effects of isolation, Post-ICU syndrome, etc.
- All the above = **Post-COVID conditions**

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Disease Course



Post-acute ≥ 4 wk
Chronic ≥ 12 wk
Subacute 4 – 12 wk

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AES Question



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Question 1

How many patients with Long COVID have you managed? *(type in your answer)*

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Prevalence of COVID



	COVID	COVID Deaths	Long COVID (10 - 30%)
Global	770 million	7.0 million	77 – 231 million
US	100 million	1.1 million	10 – 30 million

- [CDC Interim Guidance:](#)
- WHO Dashboard: <https://covid19.who.int>

Prevalence Long COVID

Approximately
1 in 5 adults
ages 18+ have a
health condition
that might be related to
their previous COVID-19
illness, such as:

18–19% (nearly 1 in 5) of U.S. adults who reported ever having had COVID-19 currently have symptoms of long COVID, defined as symptoms lasting 3 or more months that were not present prior to having COVID-19.

- 10-30% of non-hospitalized
- 50-70% of hospitalized
- 10-12% of vaccinated (BTI)

- [CDC Interim Guidance:](#)
- Davis HE, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13;1–14

Who is Likely to Get Long COVID?

- **Most occur with mild acute illness**
- Affects all ages. Highest percentage 36 – 50 years.
- Higher prevalence
 - Females
 - Hispanic
 - Bisexual and transgender adults

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Other Risk Factors

- Pre-existing conditions
 - 1/3 have no pre-existing conditions
 - T2 DM, connective tissue disorders, ADD, chronic urticaria & allergic rhinitis
 - Obesity, lung disease, smoking, mood disorders, auto-immune, food allergies
- Lower income and inability to rest in the early weeks of acute infection
- Severity of acute infection
- SARS-CoV-2 RNAemia, EBV reactivation, autoantibodies against type-I IFN
- Reinfections - even if vaccinated

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Vaccinations & Risk Reduction

- Vaccination Prevention Against Long COVID
 - Earlier data: Equivocal
 - Recent EMR study favorable (Fatigue RR = 0.48)
- Long COVID patients after vaccination
 - Earlier data: Majority is unchanged, 17% improved, 21% worse
 - Recent data: UK cohort survey 28k patients – Decrease in Long COVID sx
 - Side effects tend to be more severe and last a few days longer*
- Paxlovid - 26% less risk of PASC at 90 days (Large VA study)
- **Reinfections often result in significant relapse in symptoms (highly demoralizing)***

* Anecdotal observations only

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Clinical Presentation

1. Symptoms
2. Important Conditions
3. Prognosis & Recovery

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What are the Characteristic Symptoms?

- **Fatigue / Post-Exertional Malaise**
- **Cognitive Impairment**
- Headache
- Breathing Pain
- Palpitations / tachycardia
- **Sleep disruption**
- GI problems
- **Depression / Anxiety / PTSD**
- Anosmia
- Nerve abnormalities
- Joint & muscle pain
- Many others - less frequent

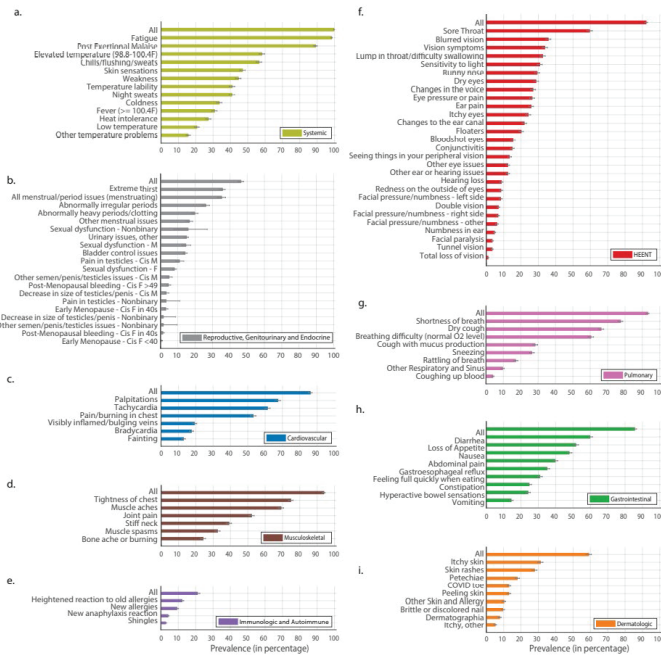
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Full Inventory of Symptoms

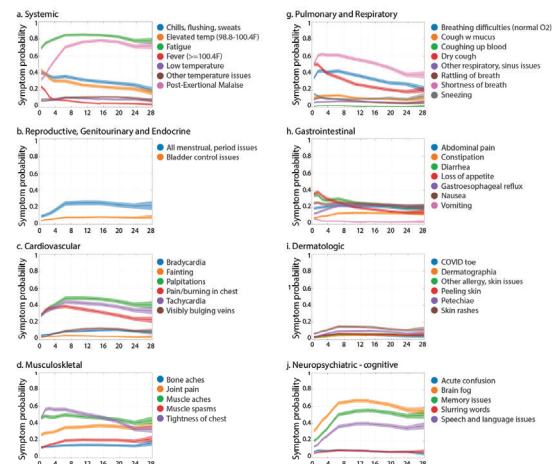
Patients Researchers Lead the Way

- A global network of citizen scientists
 - Founder of BodyPolitic started a patient support group
 - Lead to a world-wide patient-led research group
- Conducted unprecedented research on patient symptoms
 - 3,752 participants from 56 countries.
 - Questionnaire included 205 symptoms / 9 organ systems.

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- 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/ebcinn/article/PIIS2589-5370\(21\)00299-6/fulltext](https://www.thelancet.com/journals/ebcinn/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

Post-Exertional Malaise (PEM) A Hallmark Symptom

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

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Long COVID & ME/CFS

- 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

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AES Question



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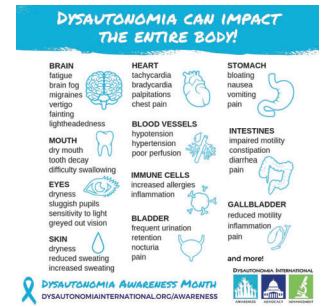
Question 2

Have you managed patients with POTS before?

- A. Yes
- B. No

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Dysautonomia



- Umbrella term for medical conditions that cause malfunction of the ANS
- POTS (Postural Orthostatic Tachycardia Syndrome) is most common in LC*
 - Tachycardic, lightheaded, chest tightness, dizziness, GI upset, HA, etc
 - Increase HR ≥ 30 bpm, or > 120 bpm, within first 10m of standing
- Patients often have clustering of complex sx suggestive of dysautonomia
- Observed in other post-viral conditions

* See appendix for POTS diagnosis and treatment considerations

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

- Word retrieval
- Processing
- Working memory
- Reasoning
- Problem solving
- Attention
- Executive functioning
- Spatial planning

Findings of Interest

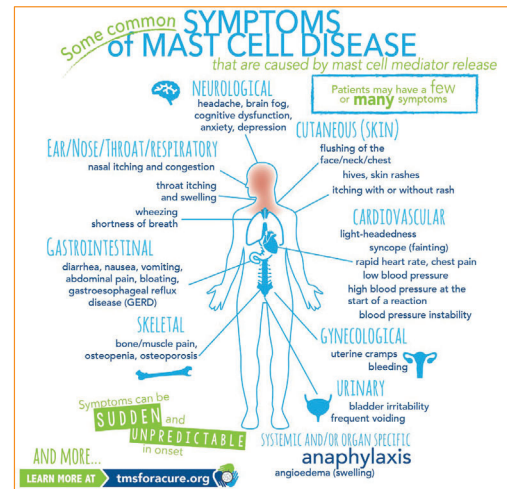
- 10 years of cognitive aging
- Characteristics of Chemo-brain
- Intoxication at UK driving limit
- Changes in brain structure on MRI
- Animal models demonstrating viral crossing of BBB and neuroinflammation
- Redox imbalance similar to ME/CFS
- Focal brain hypometabolism on FDG-PET

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Mast Cell Activation Syndrome

Irregular mast cell activation $\Rightarrow$ **Episodic** multisystem symptoms

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



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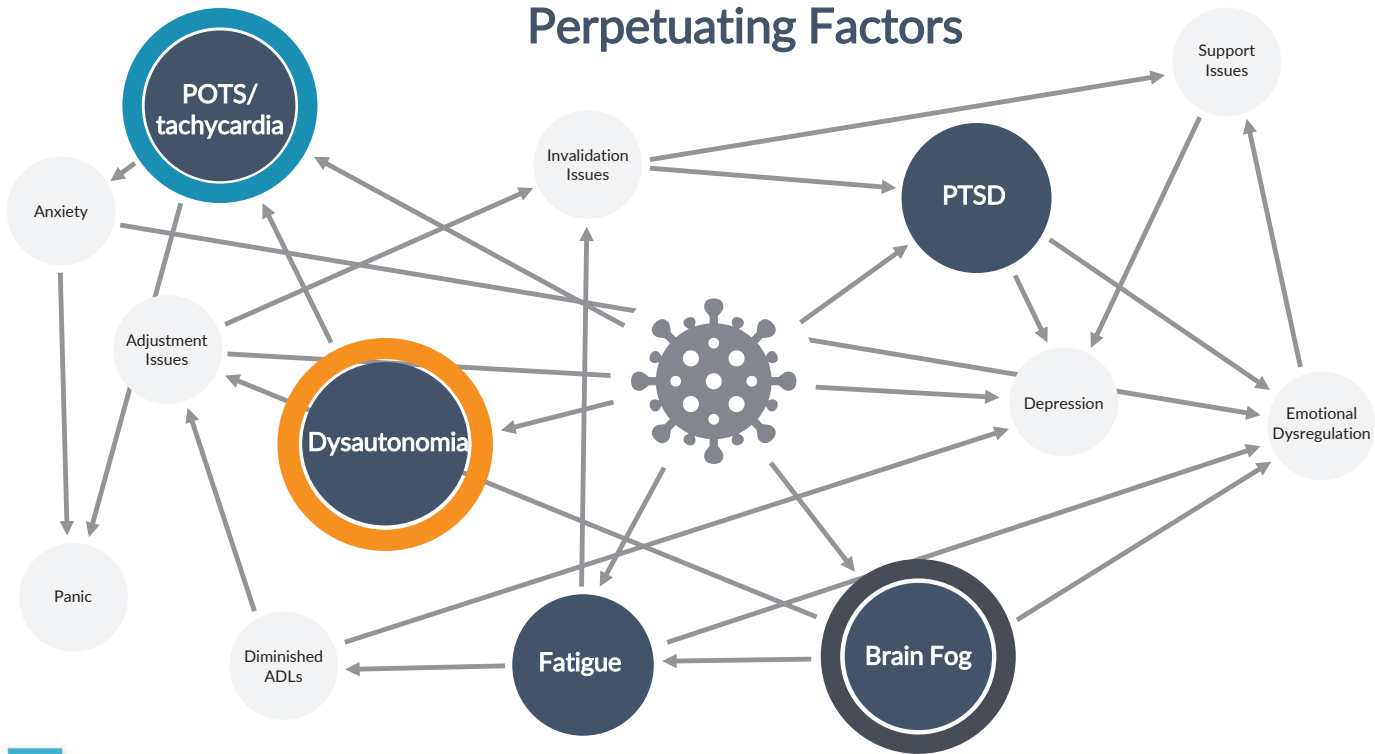
Small Fiber Neuropathy (SFN)

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 small fibers being burned (numb) without biopsy evidence

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Perpetuating Factors



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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

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Prognosis

- Long Term Prognosis Remains Uncertain
 - Long COVID Patients with symptoms at 2m
 - 85% reported persistent symptoms at 12m
 - Long COVID interfering with a return to daily activities
 - 35% @ 6 months
 - 22% @ 12 months
 - 13% @ 18 months

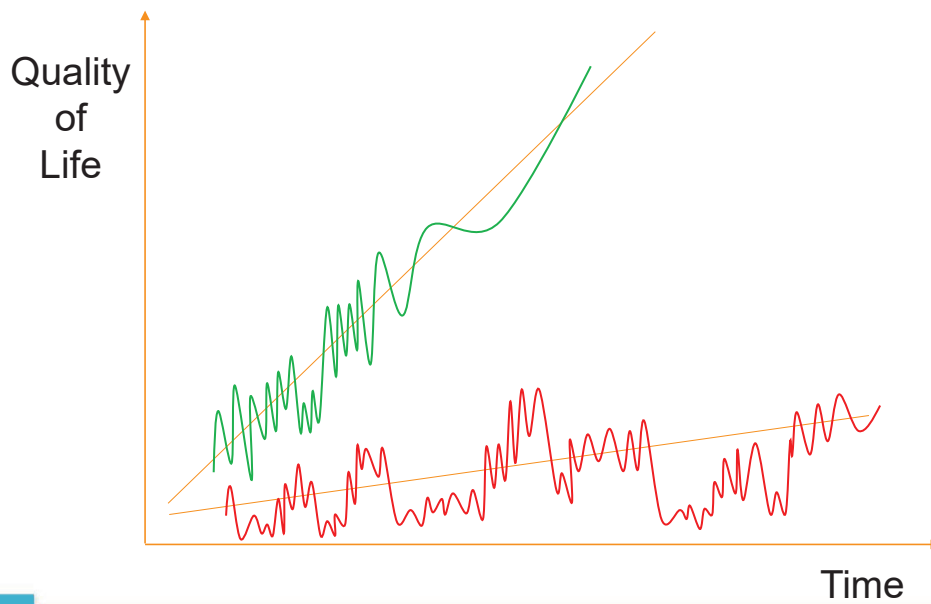
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Recovery

- Onset & time course varies – unable to predict
- Sx more likely to resolve: GI, respiratory, parosmia
- Sx more likely to persist 1 yr
 - Pain in joints, bones, ears, neck
 - Paresthesias, hair loss, blurry vision, swelling of legs, hand feet
- Neuro Sx
 - delayed onset
 - Some sx worsen over time and persist
- Recovery is worse: unvaccinated, older, women, blacks, disabilities, socially disparate, prior CV disease, mood disorders, acute severity, complex pre-existing comorbidities

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Goal For Recovery

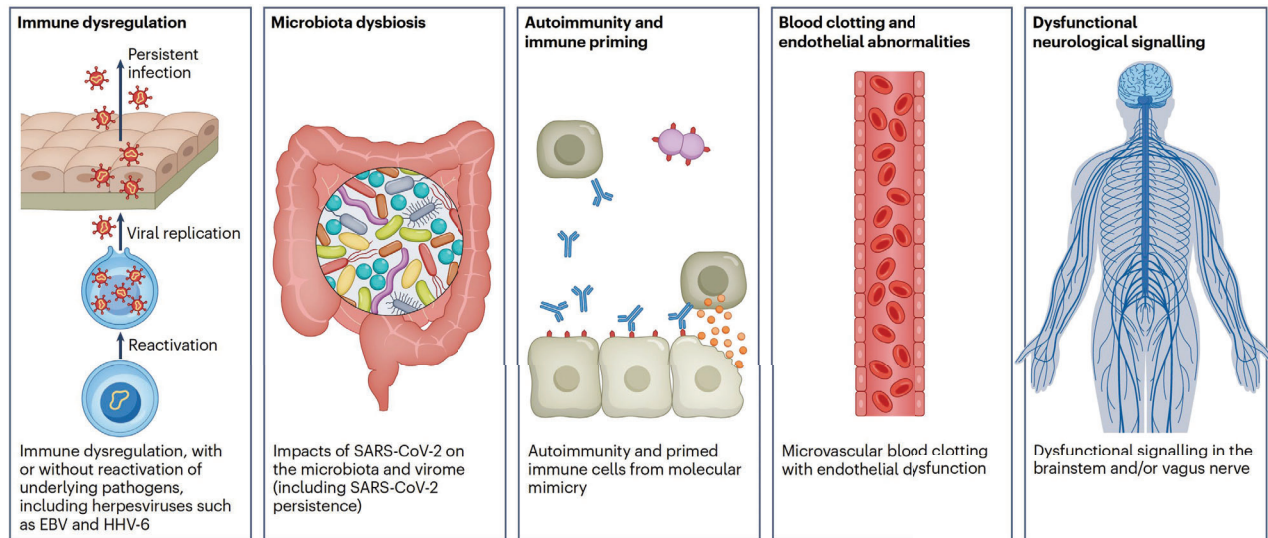


Goals:

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

Pathophysiology

Pathogenesis of Long Covid?



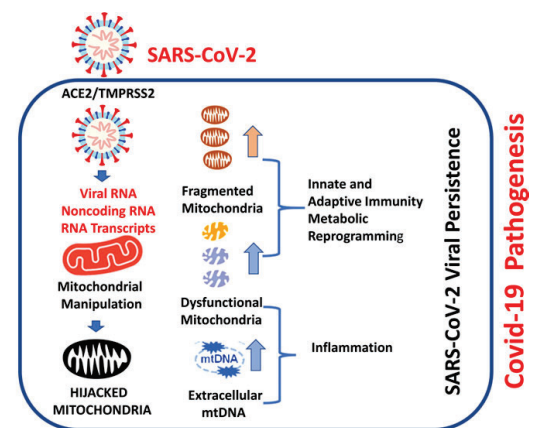
• Davis HE, et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023 Jan 13:1–14

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Mitochondrial Dysfunction

- Majority of SARS-CoV-2 genomic and structural RNA are targeted for mitochondrial matrix and disrupts normal function

- Decreases energy production
- Decreases anti-viral signaling and immune response
- Hijacked for viral replication and proliferation
- Increases inflammatory responses and reactive oxygen species
- Impairs ability to support immune response
- Loss of mitochondrial integrity and cell death



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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

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Evaluation and Management

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

-
1. Post-COVID Conditions
 2. Epidemiology
 3. Vaccines & Risk Reducdtion

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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 Interim Guidelines, AAPM&R PASC Collaborative Consensus Guidance Statements, AFP Rapid Evidence Review
- Transparent, well-coordinated, trauma-informed care is essential
- With a firm understanding of PEM, ME/CFS, POTS, MCAS, SFN, the majority of issues can be managed and supported
- Most states have a Long COVID clinic, but support is waning

- 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>

PASC Consensus Guidance

The Academy has undertaken comprehensive efforts to support our call for a national plan to address Post-Acute Sequelae of SARS-CoV-2 infection (PASC or Long COVID) and the 3 to 10 million Americans it is affecting.

The Academy understands the need for focused, meaningful, and ongoing clinical exchange between the medical community to assess and implement appropriate clinical practice for treating and following all long-term COVID issues, not just those issues requiring PASC intervention, is necessary. Therefore, AAPM&R has gathered a multidisciplinary collaborative with goals to foster engagement and share experiences to propel the health system towards defining standards of care for persons experiencing Long COVID-PASC.

The collaboration is working to publish guidance on a rolling basis. Writing groups are working within a consensus process with 3 months. All published guidance will be listed here as it becomes available.

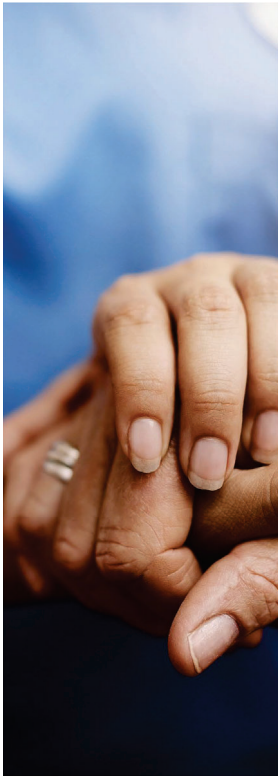
[Download Guidance Statement](#) [Download Guidance Statement](#)

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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
 - An appreciation that most routine studies are often normal
- Symptoms are often not explained or out of proportion to objective findings.
- Listen and validate even when diagnostic testing and exam is normal!

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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**

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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 overwhelming and unpredictable sx
 - Examples: Difficulty finding words, flushing, phantom smells, hair loss, paresthesias, sensory overload, orthostatic intolerance, dental findings

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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)
- Screen for known risk factors

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)
- Family-related COVID-19 illness or death, bereavement
- ***Finances, employment disability (FMLA)***

Medication Review

- Drugs that cause side effects similar to Long COVID symptoms (e.g.)
 - Anti-histamines, anticholinergic
 - Anti-depressant, anti-anxiety
 - Alpha receptor blockers, beta receptor blockers, calcium channel blockers, diuretics, ACE- Inhibitors, nitrates
 - Gabapentinoids, opiates
- Polypharmacy
- BEERS

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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

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Physical Exam – Orthostatics

Traditional POTS Protocol

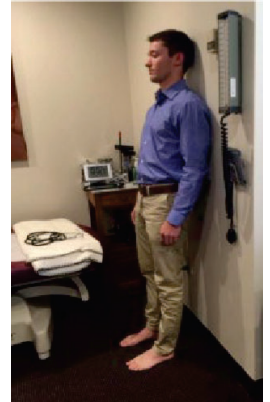
HR & BP

- Taken in supine & sitting position
- Taken in standing position at 3, 5, 7, 10m

NASA 10m Lean Test*

HR & BP

- Taken in supine & sitting position
- Taken in standing position every minute until to 10 m



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](#)

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AES Question



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Question 3

Do you think you could implement POTS screening in your practice?

- A. Yes
- B. No

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Physical Exam Focused Exam

- Neurologic: **SFN** (pinprick / temp), vestibular
- Pulmonary Interstitial lung disease, RAD
- Cardiovascular Dysautonomia (inappropriate sinus tachycardia)
- GI Dysautonomia, MCAS, 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

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Exercise Capacity Assessments

Can play important role in evaluating and monitoring

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

*Be mindful of post-exertional malaise, prepare home supports

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Diagnostic Studies

- Positive COVID test is not required to establish the diagnosis
- 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

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Basic Lab Testing

Screening for treatable conditions*

- CBC, CMP, UA
- CRP, ESR, Ferritin
- TSH and free T4
- Vit D, Vit B12
- Chest X-Ray, EKG

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

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Directed Laboratory Testing

- Further testing directed towards history, exam, ruling out specific etiologies:
 - CV: Echo, BNP
 - Dysautonomia: Autonomic reflex testing, heart rate monitor, morning cortisol
 - SFN: SFN Biopsy / QSART
 - Pulmonary: Spirometry
 - Neurologic: Vitamins B1, B6, B12, and D, magnesium and HgA1c
 - MCAS: Tryptase (baseline, episodic), 24h urine studies
 - Rheum: ESR/CRP, ANA, RF, anti-CCP, anti-cardiolipin, CPK
 - Coag: D-Dimer, PT/INR, CK, fibrinogen

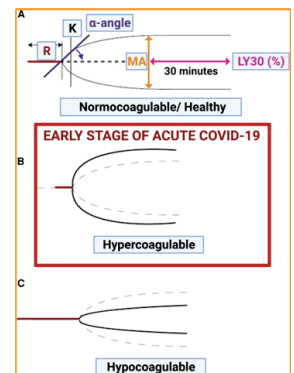
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Advanced Imaging

- Not routinely recommended unless:
 - MRI Brain (red flag headache symptoms, not brain fog)
 - CT Chest (abnormal CXR, PFTs, O2)
 - Cardiac MRI (abnormalities in echo, consider in consultation with specialty care)

Coagulopathies

- PT, aPTT, INR, D-Dimer = **little diagnostic value**
- Diagnostics for microclots are available only in select research locations



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:** {LCSleep: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 Screening: ***
- 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](#)

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Management & Treatment

- Fatigue / PEM
- Brain Fog
- Notable Sx & Conditions
- Most other Sx & Conditions

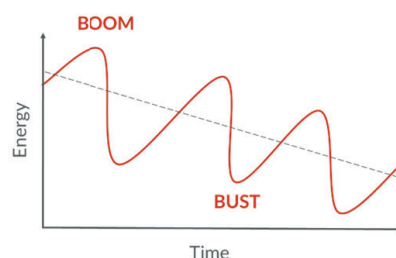
AMERICAN ACADEMY OF FAMILY PHYSICIANS

Fatigue and Post- Exertional Malaise

STOP, REST, PACE

- Key to a Stable Recovery Trajectory = The Four P's*

- Pacing
- Prioritization
- Posture
- Planning



* See appendix for more detail on the 4Ps

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Return to Activity Program

Carefully Implemented Physical Therapy*

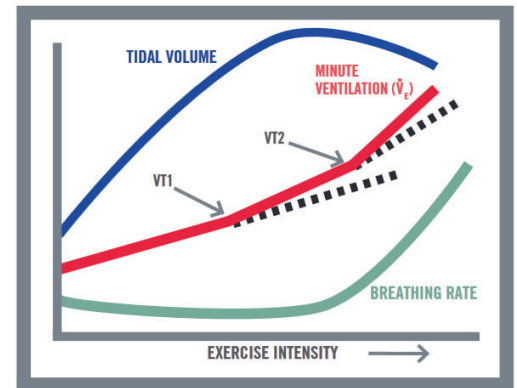
- Not an 'aerobic exercise' or graded exercise program!
 - Individualize the optimal level of activity and exertion
 - Systematically titer the progression of activity
- It is a function of
 - Breathing test: Awareness of understanding how breathing patterns link directly to maximal effort
 - Heart Rate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

* See appendix for detailed guidelines

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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

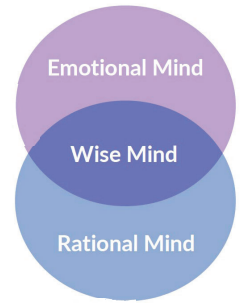
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Return to Activity Program (PT)

- Patients **learn** the breathing test as
 - The best gauge of appropriate level of activity
- Titrated physical activity < VT1 can help improve recovery
 - Avoid PEM
 - Improve physical stamina
 - Gradually titer their level of exertion as VT1 improves

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Somatic & Nervous System Regulation



- Long COVID Autonomic Nervous system is 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

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Cognitive Impairment (Brain Fog)

- Speech Language Pathologist*
 - Initially 1x / week then biweekly
- Evaluate: Language, attention, memory, energy, sleep, other
- Measure repeatable outcomes: Memory, attention, executive functioning, visuospatial processing (e.g. RBANS, MoCA)
- Monitor: Processing speed, word errors, metacognition
- Recommendations: sleep, diet, exercise, brain / body connection
- *Guanfacine (0.5 - 2 mg QHS)?*

* See appendix for details on SLP approach

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Other Important Conditions

- **POTS / Dysautonomia:**
 - Salt, compression garments, small frequent meals*
 - Rx: fludrocortisone, beta-blockers, pyridostigmine, midodrine
- **MCAS:** H1 and H2 blockers, cromolyn, mast-cell stabilizers
- **Small Fiber Neuropathy:** Anti-depressants, gabapentinoids
- **Anosmia:** Smell training with 4 essential oils, 15-20m BID. (unproven)
- **Insomnia:** CBT-Insomnia, Sleep hygiene, melatonin.
 - Caution with heavier sedatives (e.g. ambien) or antihistamines (brain fog)
- **Pain:** Low Dose Naltrexone (1.5 – 4.5 mg QD)

* See appendix for more details on POTS treatments

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Psychotropics

Consider unique side effect profile and benefit

- Some interfere with cognition or worsen fatigue
- SSRI, SNRIs better tolerated at low doses
- Considerations for First Line Agents
 - Pain: Duloxetine
 - Sleep Issues: Mirtazapine
 - Hypotension / syncope: Venlafaxine
 - Anxiety / Panic: Beta blockers
- Brain fog – Stimulants can worsen tachycardia & “feeling good” can risk PEM

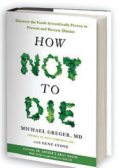
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Sleep Dysfunction

- CBT-Insomnia
 - Sleep hygiene
- Melatonin
- Caution with heavier sedatives (Ambien)
- Caution with antihistamines that can worsen brain fog (diphenhydramine or hydroxyzine)

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Nutrition!



- As of yet, no clear evidence yet for how nutrition focused therapies can improve outcomes for LC
- Anecdotally, at the national level, LC providers are starting to see the benefit of 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.

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Other Treatments in Practice / Research

More commonly in practice

- Low Dose Naltrexone (Pain, fatigue, neuroinflammation)
- Acupuncture
- Psychophysiologic symptom relief therapy (PSRT)
- Sleep Restriction Therapy
- NAC (brain fog)
- Coenzyme Q10, D-ribose (Fatigue)
- Probiotics (GI sx)
- Natokinase

Not standard practice / active research

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

AES Question



Question 4

Are there other treatments you have used for treatment of Long COVID?

- A. Yes
- B. No

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Impact on Well-Being

Understanding the Impact
of Long COVID at a Personal
Level

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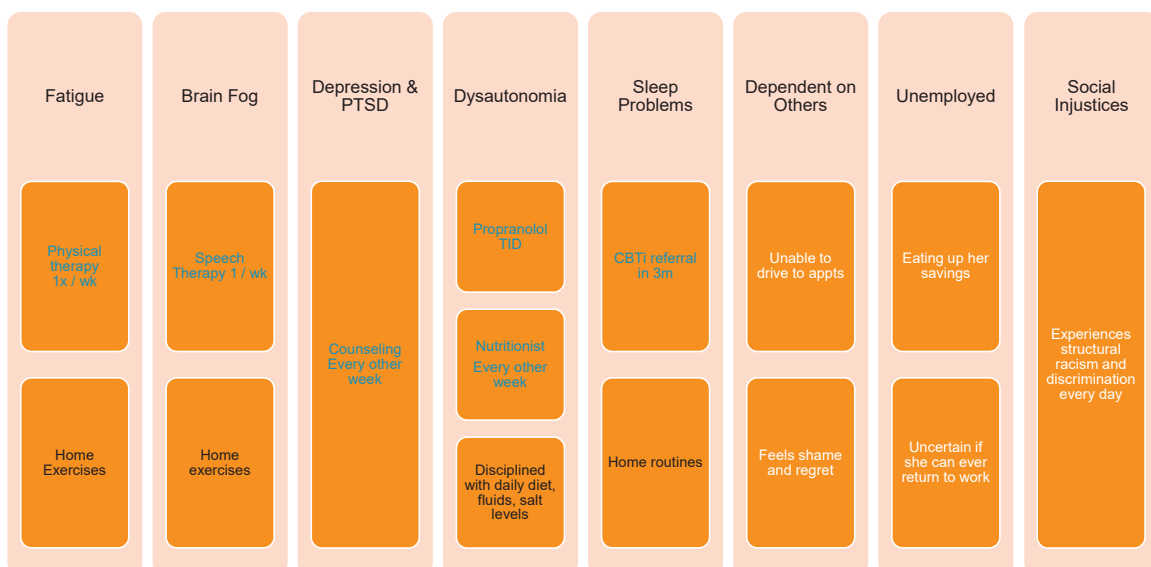
Angela's Well Being

- **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!

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Angela's Journey

She is unequivocally overwhelmed!!



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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

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Establishing Therapeutic Partnerships

- Validate! Be attuned!
- Holistic, trauma-informed care, with 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
- Patient support groups and social media*

* See appendix for more details on patient support groups

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Support For Disability & Work Accommodations

Likely the 2nd most important thing we can do!

- All patients need to time to recover
- Relapses are common
- 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

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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

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Final Considerations

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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 novel diagnostic and treatment options

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Investment in Long COVID Research

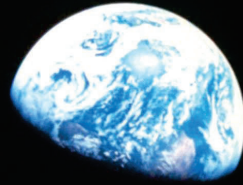
- *\$1.15 billion NIH funding over four years to support PASC research*
 - *RECOVER Initiative*
- White House Orders Federal Action Plan,
- AHRQ
 - Grants for 9 Long COVID clinics
 - Researching models of care

Managing PASC in Your Practice Top 10 Essential Components

1. Knowledge Toolkit – CDC Guidelines, AAPM&R Guidelines, AFP Rapid Evidence Review, Pacing, PT protocol
2. Empathetic clinicians with committed interest – Behavioral Health, Neuro, dysautonomia, sleep medicine
3. Rehabilitation team familiar with titrated, 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

HOPE

An MyChart (EMR) Message from Angela



This clinic and all the resources I now have access to, has improved my life, my outlook on life and my livelihood. I am grateful for you first and foremost believing me that I know my own body better than anyone, listening to all of my concerns and having a thorough knowledge of my post-Covid medical history. Every provider should be willing to listen and care for minorities and any person seeking help. After all, if a doctor will not help someone in need, what other options are there??"

Image Credit: NASA



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

Thank You

Answers

1. No Correct Answer
2. No Correct Answer
3. No Correct Answer
4. No Correct Answer

Appendix

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.

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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

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POTS Conservative Tx

Salt

- 10 grams of salt per day total, 2-3 grams added to hydration. 3L water per day.
 - 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 be 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.

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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?>

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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, unnecessary. 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. Accommodations: 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

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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.



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.



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.



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?

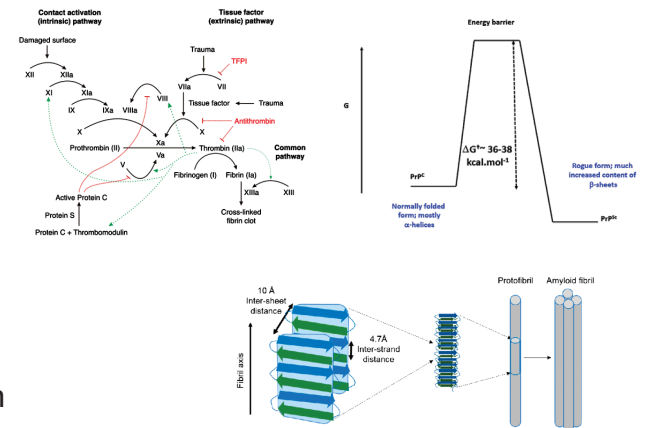
If yes, add **one point**.



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Microclots

Fibrin $\Rightarrow$ Amyloid Transformation



Inserts molecular crosslinks into the clot
Cross-links α 2AP to fibrin which inhibits plasmin

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)

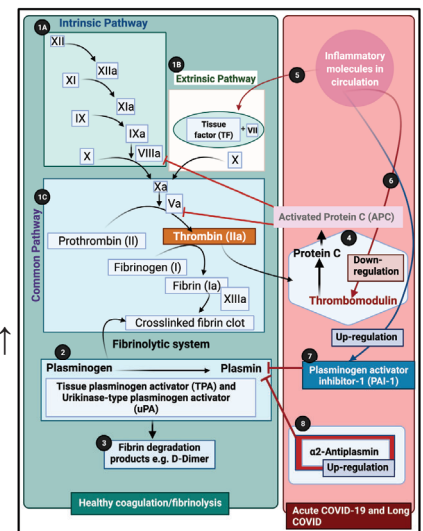
This version is highly resistant to proteolysis
Size of microclots varies from 1-200 microns (flow through most microcapillaries)
S1 spike protein can itself persist in CD16+ Monocytes for up to 15 months

- 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
 - $\uparrow$ Fibrinogen chains $\Rightarrow \uparrow$ clot production $\uparrow$
 - $\downarrow$ Thrombomodulin $\Rightarrow \uparrow$ clot production $\uparrow$
 - $\uparrow$ Plasminogen activator inhibitor-1 (PAI-1) $\Rightarrow \downarrow$ clot destruction $\downarrow$
 - $\uparrow$ VWF $\Rightarrow$ platelet activation and adhesion $\Rightarrow \uparrow$ clot production $\uparrow$
- Increased levels of α (2)-antiplasmin (α 2AP)
 - Crosslinked to fibrin thrombus by Factor XIIIa $\Rightarrow \downarrow$ clot destruction $\downarrow$
 - Increased α 2AP $\rightarrow$ ischemic stroke and failure of tPA therapy
- Plasmin - Protease responsible for fibrinolysis
 - Used to process viral S protein for cellular entry $\Rightarrow \downarrow$ clot destruction $\downarrow$



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.

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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 extracellular 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

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Patient Support Groups

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

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STRONG MEDICINE FOR AMERICA