Recognizing Chronic Post-Viral Illness and Tools for Management

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BATEMAN HORNE CENTER (BHC)

BHC is a 501(c)3 non-profit organization with a mission to improve lives through direct **clinical care**, facilitation of **research** and dissemination of **educational** resources.

This specifically/exclusively includes the lives of people with:

- myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- fibromyalgia (FM)
- post-viral syndromes (including Long COVID)
- related comorbid conditions (small fiber neuropathy, mast cell activation syndrome, hypermobile EDS, postural orthostatic tachycardia syndrome/POTS)



SOME WELL-DESCRIBED POST-INFECTIOUS DISORDERS AND THEIR CAUSATIVE AGENTS (1988)

- Aplastic anemia: Non-A, Non-B hepatitis
- Arthritis: Shigella, salmonella, yersinia, campylobacter, meningococcus, rubella, mumps
- Encephalitis: Measles, varicella, influenza, rubella, vaccinia (smallpox vaccination), rabbit brain or duck embryo rabies vaccines
- Erythema(s): Tuberculosis, leprosy, yersinia, herpes simplex, hepatitis B
- Glomerulonephritis: Streptococcus pyogenes, hepatitis B, mumps
- Guillain-Barre Syndrome: Cytomegalovirus, Epstein-Barr virus, hepatitis A, hepatitis B
- Auto-immune: Syphilis, Mycoplasma pneumoniae
 - Hemolysis and cytopenia(s): Many common viral infections
- Hemolytic uremic syndrome: Escherichia coli
- Reiter's syndrome: Non-specific genital infection or bowel infections
- Rheumatic fever: Streptococcus pyogenes
- Serositis: Meningococcus

*vaccines *antimicrobials



Post-infectious disease syndrome. B A Bannister. Review Postgrad Med J. 1988 Jul;64(753):559-67. doi: 10.1136/pgmj.64.753.559. PMID: 3074289 PMCID: PMC2428896 DOI: 10.1136/pgmj.64.753.559 Free PMC article

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POST-VIRAL SYNDROMES (PVS)* HAVE BEEN RECOGNIZED FOR DECADES

Examples of viral infections associated with chronic lingering symptoms:

- Herpes family viruses: After primary infection remain latent. Chronic reactivating patterns are well known, particularly when immunocompromised, aged or stressed (EBV, CMV, VZV, HSV, HHV-6).
- Human parvovirus B19
- West Nile Virus and other viruses (dengue, Zika, others)
- Coronaviruses
 - SARS CoV-1 (Severe Acute Respiratory Syndrome Coronavirus)
 - 2002-03 China and 2003 outbreak in Toronto. 9% died, but mortality approached 50% in high-risk groups.
 - MERS CoV (Middle East Respiratory Syndrome)
 - A relatively small outbreak in 2012-2014. 35% died. A total of 2500 lab confirmed cases and 886 deaths recorded to date with very few cases in the last few years.
 - SARS CoV-2...



*ICD-10: G93.3 for PVS (and ME/CFS)

HERPES FAMILY VIRUSES

Herpes viruses establish latent infection within specific tissues, characteristic for each virus, and can reactivated. There are 100 known herpesviruses.

8 herpesviruses that routinely infect humans

- herpes simplex virus types 1 and 2 (HSV) *antivirals
- varicella-zoster virus (VZV) *vaccine
- cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- human herpesvirus 6 (HHV-6A and HHV-6B)
- human herpesvirus 7 (HHV-7)
- human herpesvirus 8 (Kaposi's sarcoma virus) (HHV-8)



THE ROLE OF STRESS

Lessons from NASA Space Program

47/89 (53%) astronauts from shuttle-flights and 14/23 (61%) astronauts from ISS (international space station) missions shed one or more herpes viruses in saliva/urine samples (detected by PCR).

Epstein–Barr virus (EBV), varicella-zoster virus (VZV), and herpes-simplex-1 (HSV-1) in saliva and cytomegalovirus (CMV) in urine.

The hypothalamus-pituitary-adrenal (HPA) axis along with the sympathetic-adrenal-medullary (SAM) axis partially mediate the stress response where glucocorticoids and catecholamines are secreted in proportionate concentrations relative to the stress stimulus.



Herpes Virus Reactivation in Astronauts During Spaceflight and Its Application on Earth. Bridgette V. Rooney1, Brian E. Crucian2, Duane L. Pierson2, Mark L. Laudenslager3 and Satish K. Mehta4*Frontiers in Microbiology. REVIEW. published: 07 February 2019. doi: 10.3389/fmicb.2019.00016

EX: WEST NILE VIRUS

- 40% of study participants (initial N=144) continued to experience symptoms related to their WNV infection <u>up to 8 years later</u>.
- The most commonly patient-reported sequelae were fatigue, weakness, depression, difficulty walking and/or feeling off balance, and memory loss. Paralysis was reported by 9% of study participants, followed by tremors (5%) and seizures (1%).
 - Two years following infection, 47% (44/94) were still reporting symptoms, with the most reported complaints being fatigue, weakness, difficulty walking, depression, and memory loss; 4% of study participants were still reporting paralysis.
 - After five years, 40% (29/73) were still reporting continued symptoms, with 26% of participants reporting depression.
 - By eight years post-infection, 40% (18/45) were still reporting WNV-related sequelae, with fatigue, depression, weakness, and neck/back pain most reported.



EX: CORONAVIRUS: SARS COV-1

A province-wide emergency was declared on March 26th, 2003 in Ontario. 3 months later **273 people had been identified as** confirmed SARS cases. 44 died.

Sleep physiology, somatic and mood symptoms of 22 Toronto subjects, 21 of whom were healthcare workers, (19 females, 3 males, mean age 46.29 yrs.+/- 11.02) who remained unable to return to their former occupation (mean 19.8 months, range: 13 to 36 months following SARS) were compared to 7 healthy female subjects, and 21 FM patients.

On most days Post-SARS subjects complained of tiredness, difficulty sleeping, myalgia and muscular weakness.

Compared to healthy controls, Post-SARS subjects had more:

- Mild to moderate depressive symptoms (BDI mean = 13.3 +/- 8 vs.0.86 +/- 1.5, p < .0001)</p>
- Sleep disturbances on the SAQc (mean total score = 30.9 +/- 5 vs. 10.9 +/- 3.4, p < .0001)</p>
- Fatigue post-sleep (p <.05)</p>
- Myalgia pre- and post-sleep (p < .01)</p>



What is Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? (ME/CFS)

- A chronic, debilitating, multisystem illness characterized by central and peripheral nervous system disease, immune manifestations, and impaired cellular metabolism.
- ME/CFS is thought to be a post-viral or post-infectious syndrome in the majority of cases. Now some Long COVID cases meet ME/CFS criteria.



Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. Bateman L, Bested AC, Bonilla HF, et al [the US ME/CFS Clinician Coalition] Mayo Clin Proc. 2021 Nov;96(11):2861-2878. doi: 10.1016/j.mayocp.2021.07.004. Epub 2021 Aug 25. PMID: 34454716

THE IOM (NAM) 2015 ME/CFS CLINICAL DIAGNOSTIC CRITERIA

The CORE criteria (all required for diagnosis) *Must be moderate-severe and present >50% of time

- 1) Impairment of normal function, accompanied by fatigue, persisting >6 months
- 2) PEM: post exertional malaise*
- 3) Unrefreshing sleep*
- 4) Plus at least one of the following:
 - Cognitive impairment*
 - > Orthostatic intolerance

Additional common but not CORE features of illness in the ME/CFS population:

- Chronic pain (headache, muscle and joint aches, hyperalgesia, central sensitivity)
- Immune/inflammatory manifestations (allergy, inflammation, chemical sensitivities)
- Infection manifestations (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers)
- Neuroendocrine manifestations



The IOM is now the National Academy of Medicine (NAM)

Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8

ME/CFS CAN BE TRIGGERED BY A VARIETY OF PATHOGENS

- Infections associated with onset of ME/CFS include Epstein-Barr Virus, other herpesviruses, Parvovirus B19, West Nile Virus, enteroviruses, Coronaviruses (including SARS CoV-2), and other non-viral pathogens as well
- People with ME/CFS share the same core symptoms but heterogeneity exists, likely due to the type of trigger, the systems affected, disease duration and the development of comorbid conditions. This heterogeneous illness is challenging to study.

By the time the diagnosis is made, there is generally

no definitive evidence left of the infectious trigger.

The COVID-19 pandemic has changed that due to worldwide scrutiny



ME/CFS is distinguished from other types of chronic fatigue by the degree of impairment/debilitation and the development of post-exertional malaise (PEM).

PEM is illness relapse or symptom worsening triggered by activity or stressors. These can be physical, cognitive, sensory, emotional or even being in upright posture.

PEM occurs in many patients with Long COVID.

Illness severity and functional capacity ranges from:



Mild impairment but difficulty maintaining a normal schedule of work, school or family, and low tolerance for exercise

Bedridden, barely able to speak or move





SARS COV-2 CREATED AN OVERWHELMING PANDEMIC

In 2020-21, focus was on saving the severely ill acute COVID-19 patients, preventing an overwhelming surge of **hospitalizations**, **vaccines**, and **variants**. *Now we are struggling with the aftermath of acute COVID-19*. The scientific focus has shifted to the Post-Acute Sequela of COVID-19 (PASC). >\$1 billion have been invested to create the RECOVER Initiative: <u>https://recovercovid.org/</u>



ACUTE COVID-19 IS KNOWN TO CAUSE WIDESPREAD ORGAN DAMAGE

Lung



- Cardiac and vascular
- Neurologic complications
- Gastrointestinal and liver
- Kidney damage, chronic kidney disease







COVID-19 POST-VIRAL SYNDROME

COVID-19: After the acute infection resolves, many people are still struggling with chronic multisystem illness manifestations.

Common post-COVID-19 chronic sequelae:

- Fatigue, sleepiness, and brain fog/cognitive complaints
- Musculoskeletal pain, headaches, fibromyalgia, reactive arthritis
- Respiratory tract inflammation, reactive airways, interstitial lung disease
- Heart inflammation: myocarditis, pericarditis, chest pains, palpitations, orthostatic intolerance
- Neurologic symptoms: TIA/stroke, dizziness, headache, confusion, memory impairment, neuropathy, loss of smell and taste, altered consciousness, sleep disturbances
- Hematologic: blood clots
- Others...hair loss, allergies, mast cell activation syndrome (MCAS), viral reactivation, anxiety, PTSD





THERE ARE MANY LINGERING CONSEQUENCES OF COVID-19

Roughly two main groups:

- People with severe infection, hospitalization, post-ICU syndrome and lingering organ damage identifiable with objective markers.
- People with mild to moderate infection but lack of recovery, or even increasingly worse symptoms and impairment, yet without apparent biological markers.

Right now, we call all lingering, unresolved, symptoms of acute COVID-19, "Long COVID," Long Haul COVID, Post-COVID or similar designations.

Hopefully, patients will eventually recover, and only a small portion of these people will have permanent organ damage or eventually meet ME/CFS criteria.





Long Covid symptoms and signs



Neurocognitive

Confusion

Memory impairment

Frontal release signs*

Concentration impairment

Other cognitive impairment*

People non-hospitalised during acute phase of Covid-19

People hospitalised during acute phase of Covid-19

Based on 26 studies with 7147 people*

Neurological and neuromuscular

Headache Tremors Slowness of movement* Lack of coordination* Muscle atrophy* Abnormal muscle tone* Walking/ gait abnormality Taste disturbance Smell disturbance Visual disturbance* Decreased sensation or sensibility Tingling Trigeminal neuralgia Abnormal reflex status* Other neurological diseases*

Musculoskeletal Muscle pain

Impaired mobility

Joint pain

Gastrointestinal Nausea or vomiting Diarrhoea Loss of appetite Stomach/abdominal pain Other stomach/abdominal discomfort Weight loss Bloody stools Neurocognitive Memory impairment Concentration impairment Confusion* Frontal release signs* Other cognitive impairment

Psychological and social

0

Anxiety Depression Sleep disorder Post-traumatic stress disorder Low mood Reduced quality of life Care dependency

Upper respiratory Sore throat Nasal congestion Voice change Other respiratory symptoms

Cardiopulmonary

Breathlessness Chest pain Cough Excessive sputum Palpitations Flushing Newly diagnosed hypertension Other cardiovascular symptoms*

Other Skin rash Hair loss ler Headache Tremors Seizures/ cramps Slowness of movement* Lack of coordination* Muscle atrophy* Abnormal muscle tone* Walking/ gait abnormality* Taste disturbance Smell disturbance Ear/ hearing conditions

Ear/ hearing conditions Visual disturbance Decreased sensation or sensibility* Tingling* Abnormal reflex status* Other neurological diseases*

Based on 4 studies with 1168 people*

Neurological and neuromuscular

Musculoskeletal Muscle pain Joint pain Impaired mobility*

Gastrointestinal Nausea or vomiting Diarrhoea Stomach/abdominal pain Weight loss

Systemic Fatigue Weakness* Fever Sweat or night sweats* Enlarged lymph nodes Dizziness



Psychological and social

- Anxiety* Depression* Sleep disorder* Post-traumatic stress disorder Low mood* Reduced quality of life* Care dependency*
- Upper respiratory
- Sore throat Nasal congestion Other respiratory symptoms
- Cardiopulmonary Breathlessness Chest pain Cough Excessive sputum Palpitations Other cardiovascular symptoms*

Other Skin rash Hair loss Conjunctivitis

* Identified only in studies including both hospitalised and non-hospitalised people (9 studies including 2636 people)

Systemic

Weakness

Dizziness

Sweat or night sweats

General malaise

Fatigue

Fever



Michelen M, Manoharan L, Elkheir N, et al. Characterising long COVID: a living systematic review BMJ Global Health 2021; 6:e005427 7/27/2022

Last updated 17 Mar 202

UK STUDY OF HEALTHCARE PROVIDERS

- Longitudinal surveillance of >2000 clinical and non-clinical healthcare workers in the UK was done using monthly blood sampling for SARS-CoV-2 antibodies starting in March 2020. Approx. 12% developed COVID-19 by lab testing, mainly in March/April 2020.
- Nov 2020 (8 months later): An online questionnaire assessed 72 current symptoms:
 - 140 (10.8%) were mild-to-moderate seropositive cases (none of the cases had been hospitalized for COVID-19).
 - 20 (14.3%) of the 140 COVID ab positive cases had ongoing (3.5%) or episodic (11.2%) symptoms.
 - 1160 (89.2%) were asymptomatic seronegative controls.



UK STUDY OF HEALTHCARE PROVIDERS

- Three clusters of symptoms associated with Long COVID were identified:
 - Sensory: lack of taste and smell, loss of appetite, and blurred vision
 - Neurocognitive: forgetfulness, short-term memory loss, and confusion/brain fog
 - Cardiorespiratory: chest tightness/pain, unusual fatigue, breathlessness after minimal exertion/at rest, palpitations
- Dermatological, gynaecological, gastrointestinal, or mental health symptoms were not significantly different between cases and controls.



MENTAL HEALTH SYMPTOMS WERE COMMON IN BOTH GROUPS

	Cases	Controls
Stress	76 (54.3%)	666 (57.4%)
Anxiety	72 (51.4%)	547 (47.2%)
Difficulty to sleep at night	69 (49.3%)	497 (42.8%)
Frustration	60 (42.9%)	51 (44.9%)
Sadness	59 (42.1%)	484 (41.7%)
Difficult to wake in morning	47 (33.6%)	389 (33.5%)
Mood swings	54 (38.6%)	382 (32.9%)
Depression	31 (22.1%)	246 (21.2%)
Loneliness	24 (17.1%)	278 (24.0%)



How Common is "Long COVID?" ...we don't know for sure

- An online survey of about 1,500 people with confirmed or suspected COVID-19 was conducted by a group of "long haulers" in late 2020 (patient.research.covid19@gmail.com).
- 80% of the people were between the ages of 30 and 60.
- The majority (54%) reported symptoms that had lasted at least 3 months since the start of the illness.
- Many had sought medical attention for these ongoing symptoms: 41% reported that the doctors had not listened to or believed them.



CDC GUIDANCE

Multiorgan system effects of COVID-19 have been documented in most, if not all, body systems including cardiovascular, pulmonary, renal, dermatologic, neurologic, and psychiatric.

Multisystem inflammatory syndrome (MIS) and **autoimmune conditions** can also occur after COVID-19.

A wide variety of health effects can persist after the acute illness has resolved (e.g., **pulmonary fibrosis, myocarditis**).

It is unknown how long multiorgan system effects might last and whether the effects could lead to chronic health conditions.



COMMON SYMPTOMS OF POST-COVID CONDITIONS (CDC GUIDANCE)

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise and/or poor endurance*
- "Brain fog," or cognitive impairment
- Cough
- Chest pain
- Headache
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia

- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Pain
- Rash (e.g., urticaria)
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities



LONG COVID CLINIC AT BHC

We recruited people from the private Utah COVID-19 Long Hauler Facebook group (3,500 members) who:

- Were never sick enough to be hospitalized with COVID-19
- Have an uncomplicated medical history prior to acute COVID
- Have an uncomplicated psychiatric history prior to acute COVID
- Are still sick at least 6 months after COVID-19

We have seen more than 75 patients in clinic now; 40 have been recruited for NIHfunded research participation



*60% met IOM criteria for ME/CFS based on screening questionnaires

MANY LONG COVID PATIENTS APPEAR TO MEET THE IOM/NAM ME/CFS CLINICAL DIAGNOSTIC CRITERIA

- Keep in mind our Long COVID cohort is relatively small and subject to selection bias (i.e. who joins the Facebook group, who seeks care at BHC and why?)
- The majority of our initial cohort had been sick 8-12 months since acute COVID-19.



LONG COVID SYMPTOMS PRIOR TO IN-PERSON ASSESSMENT

2015 IOM/NAM ME/CFS Criteria*	Percent with frequent (>50%) and moderate to very severe symptoms	Other symptoms common in ME/CFS	Percent with frequent (>50%) and moderate to very severe symptoms
Fatigue	76%	Chronic Widespread Pain	42%
Impairment of function	88%	Headache	26%
Post-Exertional Malaise (PEM)	92%	POTS	46%
Unrefreshing Sleep	80%	Allergies	34%
Cognitive Impairment	60%	Sensory sensitivities	46%
Orthostatic Intolerance	52%		



*60% met IOM criteria for ME/CFS based on screening questionnaires.

OTHER LONG COVID SYMPTOMS IN OUR APPLICANTS

Symptoms present in >50% of people								
Weakness	92%	Muscle pain	86%					
Sleepy	90%	Joint pain	78%					
Palpitations	90%	Stomachache	76%					
Dizzy	78%	Nausea	70%					
SOB	78%	Diarrhea	74%					
Vision	62%	Dry mouth/eyes	76%					
Fever	60%	Vertigo	64%					
Parasthesia	58%	Night sweats	62%					
Tinnitus	58%	Anxiety/depression	66%					
Hair loss	50%	Rashes	40%					
Symptoms present in <50% of people								
Sexual dysfunction	32%	Wheeze	20%					
Cough	26%	Cough mucus	16%					
Breath pain	44%	Taste/smell loss	28%					



WHAT CAUSES LONG COVID? ...MUCH IS STILL UNCLEAR

- Inflammation may persist for several weeks or months after acute infection in specific organs such as the respiratory or cardiovascular systems.
- Post-viral, immune-mediated disruption of the **autonomic nervous system** has been implicated.
- Autoreactive T cells and SARS-CoV-2 antibodies that persist after viral clearance may cross-react with host self-antigens, including those found in the central nervous system, which could manifest as neurological symptoms.
- Long-term neuropsychiatric consequences after viral infections are well-described in the literature, including in previous pandemics such as the 1918 Spanish influenza (encephalitis lethargica) or the 2003 SARS epidemic (chronic myalgia, fatigue and disordered sleep).



There is a growing body of literature suggesting that a combination of virus and host factors might contribute to PASC, including:

- Viral antigen persistence (preliminary)
- Herpesvirus reactivation
- Dysbiosis
- Residual inflammation
- Microvascular dysregulation
- Autoimmune phenomena

[endothelial dysfunction and thrombotic phenomenon?]



Proposed contributing mechanisms



Early clues regarding the pathogenesis of long-COVID. Peluso MJ, Deeks SG. Trends Immunol. 2022 Apr; 43(4): 268–270. doi: 10.1016/j.it.2022.02.008 PMID: 35272932

Trends in Immunology

CASE PRESENTATION: 70 YEAR OLD RETIRED HEALTHY FEMALE



Healthy and avid exerciser. On losartan 100 mg for high BP. Statin started in July for mild cholesterol elevation.

Early April 2020: Acquired SARS CoV-2 infection, possibly from grocery shopping. Low grade fever, extreme fatigue, rash.

Acute COVID-19 illness improved in 10 days, but she remained fatigued. Able to maintain light activity, but any increase in activity triggered feverishness and fatigue.

June 2020: labs, ECHO, CXR, chest CT were unremarkable.



LATE AUGUST 2020: 5 MONTHS AFTER COVID-19

- Physical therapist recommended a gentle reconditioning program:
 - Monday: 30 min recumbent bike. Tuesday rest.
 - Wednesday: 1 mile walk. Thursday rest.
 - Friday: 10 min on the elliptical trainer.
- After the elliptical exercise she became feverish (T 99.9), exhausted and ill.
- Then she was unable to do much. Mostly supine or sedentary. Marked fatigue, impaired function, exercise intolerance and PEM. Naps daily for an hour. Sleep is unrefreshing. Pain in arms and leg muscles after using them. Mild dizziness. Difficulty sleeping and mounting anxiety.



OCTOBER 2020 ...6 WEEKS AFTER ILLNESS RELAPSE FROM EXERCISING

- No significant improvement. No constructive advice from PCP, a neuro-COVID doc, or an ID specialist (who told her to exercise more).
- BP medication has been reduced 75% due to unusually low BPs. No marked cognitive impairment. No marked orthostatic symptoms. Sleep disrupted by anxiety. O2 sat normal.
- Mild low white blood cell count. Mild anemia. Elevated ferritin.



HOME 10-MIN STAND/LEAN TEST (ORTHOSTATIC TESTING)

Lying dow	n - <mark>129/7</mark> 1	<mark>l</mark> HR 7	4	PP 58(Pulse pressure)
Standing	74/53	HR 98	3 2 min		
	75/54	HR 100	4 min		
	84/62	HR 105	6 min		
	84/59	HR 106	8 min	PP 25	PP/SBP= 30% (not abnormally narrowed)
Lying dowr	n - <mark>124/6</mark> 8	<mark>3</mark> HR 7	5	PP 56	
Standing	103/61	HR 82	2 2 min		
	97/61	HR 94	4 min		
	88/63	HR 93	6 min		
	80/64	HR 94	8 min	PP 16	PP/SBP= 20% (abnormally narrowed should be >25%)

A SBP drop of >20 points = **systolic orthostatic hypotension**



HOME 10-MIN STAND/LEAN TEST (ORTHOSTATIC TESTING)





CASE PRESENTATION: <u>45 YEAR OLD</u> MALE TEACHER. NOW 7 MONTHS SINCE ACUTE COVID-19



- Fatigue, impaired function, post-exertional malaise (PEM) are very severe and present 75-100%.
- On GOOD days, 2-3/mo, he can manage 8 HUA.*
 - Can walk around or clean house, but not exercise or work.
- On BAD days, 26-28/mo, he manages only 2 HUA.*
 - Can only sit on the couch and make food, but can't stand for long, walk around outside.
- Gets PEM after low physical exertion and poor sleep.

*HUA= Hours of Upright Activity in 24 hours (seated with feet on floor, or standing, walking)



MALE TEACHER, AGE 45, WITH LONG COVID*

- Unrefreshing sleep, moderate, present 50% of the time. Daytime somnolence moderate, 25-50%.
- **Cognitive impairment**, severe, present 50-75% of the time. Brain fog and trouble thinking.
- Orthostatic intolerance, very severe, present 75-100%. Dizzy, palpitations, heat intolerance.

*He meets criteria for ME/CFS due to impaired function, fatigue, PEM, unrefreshing sleep, cognitive impairment and orthostatic intolerance >6 months. Mod-severe and present more than 50% of the time.



MALE TEACHER, AGE 45, WITH LONG COVID

His other symptoms that are less frequent and less severe:

- SOB, mild, present 25-50% of the time. No cough, wheezing, CP.
- Myalgia, mild, present 25-50% of the time. HA, mild, infrequent.
- Nausea, moderate, present 25-50% of the time. UGI sx, mild, infrequent.
- Loss of taste/smell, mild, present 25-50% of the time.
- Skin rashes, moderate, present 25-50% of the time.
- Tinnitus, mild, infrequent.
- Vision problems, mild, infrequent.
- Allergies, insignificant.



THE 10-MINUTE NASA LEAN TEST

A standardized form of stand/lean test

HR and BP after 10-15 minutes of quiet supine rest

HR and BP every 1-2 minutes for 10 minutes while standing/leaning in upright posture





MALE TEACHER, AGE 45, LONG COVID (POTS) POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME*

s	eated B	lood Pres	sure	0/20	∑ Hea	rt Rate	<u>82_oxygen_99</u> BP 120/80
c	Orthosta	tic Testin	g:	Star	t Time	12	: <u>30</u> : End time::
ſ		Blood SBP	Pressure DBP	HR	O2 Sat	Minute PP	Comments/Symptoms
Γ	Sup 1	115	75	67	98		Relaxo
	Sup 2	115	75	65	97		
┢	1 min		05				
	2 min	110	95	103			ticalize Bight hand mild mentilize both hand
	3 min	110	90	115			hands and feet feel cold, also to the torch. also
Ľ	4 min	105	90	110			hands number, legs and feet heavy
1	5 min	120	90	118	99	NPP-	Feels a rish in hards
Ľ	6 min	115	90	118			Severe matting in both hands tringling and numb.
	7 min	120	90	120			lightheoded, training in feet, pulse paradoxist
2	8 min (5.			138	98		Shortness of breath
[9 min						Test terminated due to symptoms
F	10 min					NPP-	HR 65 bpm → 138 bpm= +73 bpm



*A diagnosis of POTS requires an increase of HR >30 bpm for adults and 40 bpm up to age 18

TIPS FOR ASSESSING PATIENTS WITH POST VIRAL SYNDROMES

- Rank major symptoms by frequency and severity. Focus on cause and best supportive treatment.
- Assess ability to function and the consequences of activity. This includes physical, orthostatic and neurocognitive function. Advise "pacing" to prevent PEM and advise best supportive care.
- Group symptoms to identify treatable comorbid conditions if possible.
- Sensibly treat symptoms if it improves function and/or quality of life.



A SIMPLE TOOL TO COMMUNICATE FUNCTION IMPAIRED BY ORTHOSTATIC INTOLERANCE: HUA

HUA: Hours of "Upright" Activity:

The # of hours spent with <u>feet-on-floor</u> in 24 hours

(sitting, standing, walking)

Must ask the question clearly to be sure time spent sitting with feet on the floor is considered in the total.



Thanks, and credit to David Bell, MD

TYPICAL HUA* HOURS OF UPRIGHT ACTIVITY IN 24 HOURS

- Normal healthy folks: HUA 14-17
- Chronic illness/FM: HUA 10-12
- ME/CFS HUA 0-8

*Based on thousands of patient reported outcomes at Bateman Horne Center

It is imperative to rule out severe depression as a reason to stay in bed.



Clinically accessible tools for documenting the impact of orthostatic intolerance on symptoms and function in ME/CFS. Jihyun Lee, Pelle Wall, Chris Kimler, Lucinda Bateman and Suzanne D. Vernon* Work. 2020;66(2):257-263. doi: 10.3233/WOR-203169. PMID: 32568144

GOOD DAY/BAD DAY QUESTIONNAIRES*

- Average number of GOOD _____ BAD ____ days per MONTH:
- Average hours of UPRIGHT activity (HUA) on a GOOD _____ BAD _____ day:
 - <u>Sitting</u>, standing, walking --- activities with FEET ON FLOOR

(Hours of upright activity + Hours of non-upright activity = 24 hours)

- Give examples of activities/tasks you CAN do on a:
 - GOOD day_____
 - BAD day_____
- Give examples of activities/tasks you CAN <u>NOT</u> do on a:
 - GOOD day______
 - BAD day_____



*Designed for use at BHC by Lucinda Bateman, MD

Good Day/Bad Day Questionnaire Example

- On GOOD days, 4-5/mo, he can manage 8 HUA*
 - Can: read (<30 min), watch TV, listen to music, cook a meal, shower, walk one block, drive short distances
 - Cannot: walk more than 3 blocks, work, complete household chores exceeding 15 minutes, drive >30 minutes
- On BAD days, 25-26/mo, he manages only 2 HUA*
 - **Can:** recline on the couch, microwave prepared food, have a short conversation (<5 min)
 - Cannot: read, listen to music, work, do household chores, take a shower, exercise, drive

*HUA= Hours of Upright Activity (seated with feet on floor, standing, walking)



IMPORTANT CO-MORBID CONDITIONS TO CONSIDER IN LONG COVID PATIENTS <u>BEYOND</u> OBJECTIVE ORGAN DAMAGE

- Cognitive impairment. *Can be significant.*
- Orthostatic Intolerance (OI) and ANS dysregulation. Postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension or other forms of dysautonomia. *Common.*
- Mast Cell Activation Syndrome (MCAS): a ramped up allergic response system. *Common.*
- Small fiber neuropathy (can lead to widespread pain, sensory sensitivities, orthostatic intolerance syndromes). *Common**
- Sleep apnea syndromes and other sleep disturbances.
- GERD and IBS, dysbiosis

Dx ME/CFS: if symptoms persist > 6 months and meet established criteria



SELECTED COMMON CO-MORBID CONDITIONS OF INTEREST IN ME/CFS PATIENTS AND LONG COVID

- Fibromyalgia/pain amplification, central sensitivity
- Small fiber poly neuropathies (SFPN) and peripheral neuropathies
- Chronic sleep disorders ("primary" and otherwise)
- Celiac disease and gluten intolerance
- IBS, gastroparesis, SIBO (small intestine bacterial overgrowth)
- Postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, other dysautonomias
- Allergies, chemical sensitivities, mast-cell activation syndrome (MCAS), food intolerances
- Viral reactivation (VZV, HSV, HHV-6, EBV, CMV...)
- Autoimmune thyroid disease, subclinical hypothyroidism, euthyroid-sick syndrome
- Sjogren syndrome/sicca syndrome (dry eyes and dry mouth)



A TIME-TESTED TREATMENT APPROACH

- 1) Identify and treat all identifiable medical conditions (co-morbid or separate).
- 2) Learn to "pace" activity to prevent, and reduce severity/duration of "Post-Exertional Malaise" (PEM).
- 3) Address the major symptomatic aspects of illness:
 - Sleep: when corrupted and non-restorative.
 - Pain: especially when pain is a stressor.
 - Orthostatic Intolerance (OI) syndromes: —good literature available—
 - Mental health: reduce grief/despair/discouragement/anxiety. Seek insight.
 - Fitness: only as compatible with illness manifestations. PACING trumps FITNESS.



EVALUATING AND CARING FOR PATIENTS WITH POST-COVID CONDITIONS: INTERIM GUIDANCE FROM THE CDC (JUNE 14, 2021)

Key Points

- The term "Post-COVID Conditions" is an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.
- Based on current information, many post-COVID conditions can be managed by primary care providers, with the incorporation of patient-centered approaches to optimize the quality of life and function in affected patients.
- Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions.



EVALUATING AND CARING FOR PATIENTS WITH POST-COVID CONDITIONS: INTERIM GUIDANCE FROM THE CDC

Key Points continued...

- Healthcare professionals and patients are encouraged to set achievable goals through shared decision-making and to approach treatment by focusing on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia); a comprehensive management plan focusing on improving physical, mental, and social wellbeing may be helpful for some patients.
- Understanding of post-COVID conditions remains incomplete and guidance for healthcare professionals will likely change over time as the evidence evolves.



