

Post-Acute COVID Syndrome (PACS)
a.k.a.
Post-Acute Sequelae of COVID (PASC)
a.k.a.
Long COVID, Post-COVID, Long Haul

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Common Manifestations of PACS

- Neuropsychiatric
 - Fatigue
 - Cognitive deficits
 - Memory
 - Word finding
 - Multitasking
 - Depression
 - Anxiety
 - Insomnia
 - Headache
 - Dizziness
 - Neuropathy
- Tinnitus
- Anosmia/dysgeusia
- Respiratory
 - Cough
 - Dyspnea on exertion
- Cardiovascular
 - Palpitations
 - Tachycardia
 - Resting
 - Exertional
- Gastrointestinal
 - Diarrhea
- Dermatologic
 - Hair loss
- Musculoskeletal
 - Weakness
 - Myalgia/arthralgia
 - Chest pain

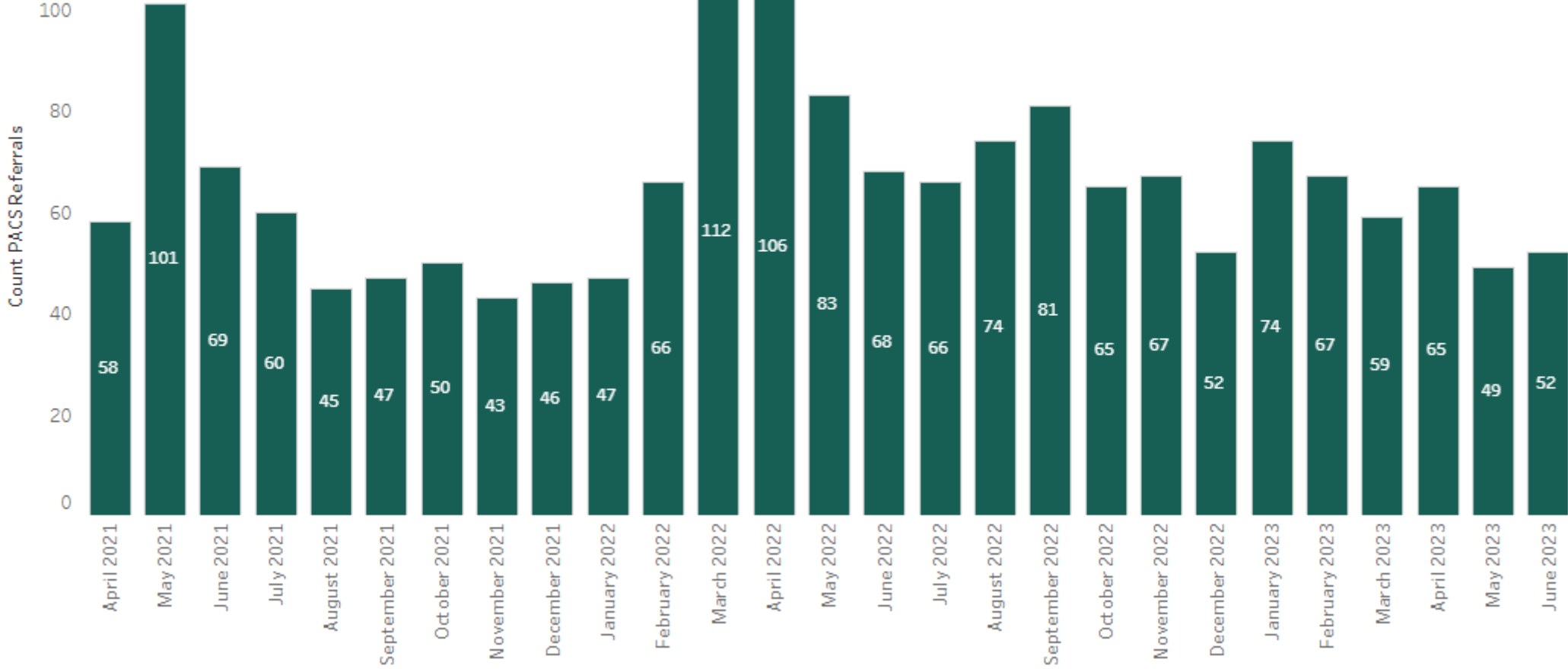
Dartmouth-Hitchcock PACS Clinic

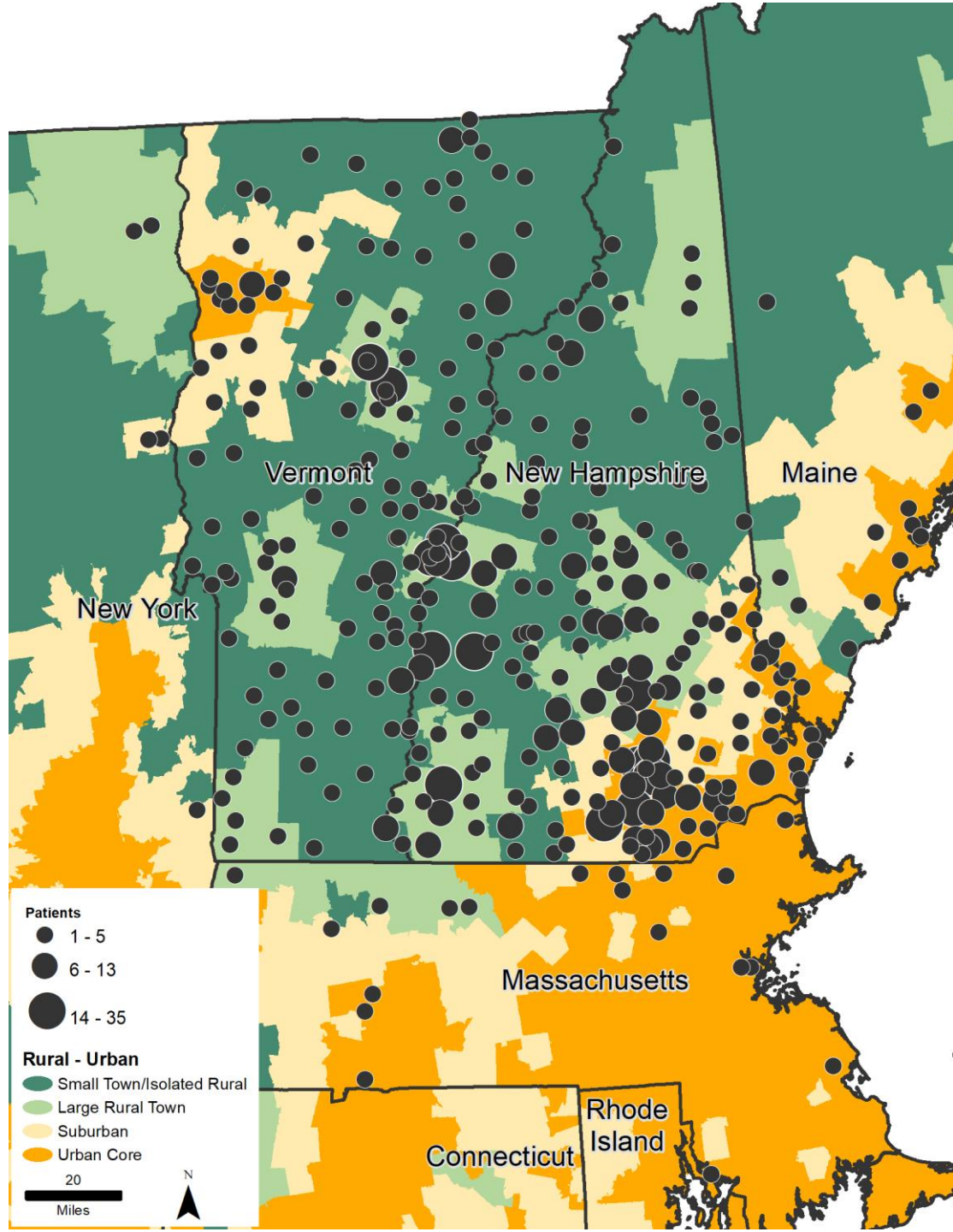
- Infectious Diseases
 - Three providers
- Pulmonary Medicine
 - One provider
- Neurology
 - Four providers
- Cardiology
 - One provider
- Psychiatry
 - Two providers
- Family Medicine
 - One provider
- Rehabilitation Medicine
 - Seven providers

D-H PACS Clinic: Criteria for Intake

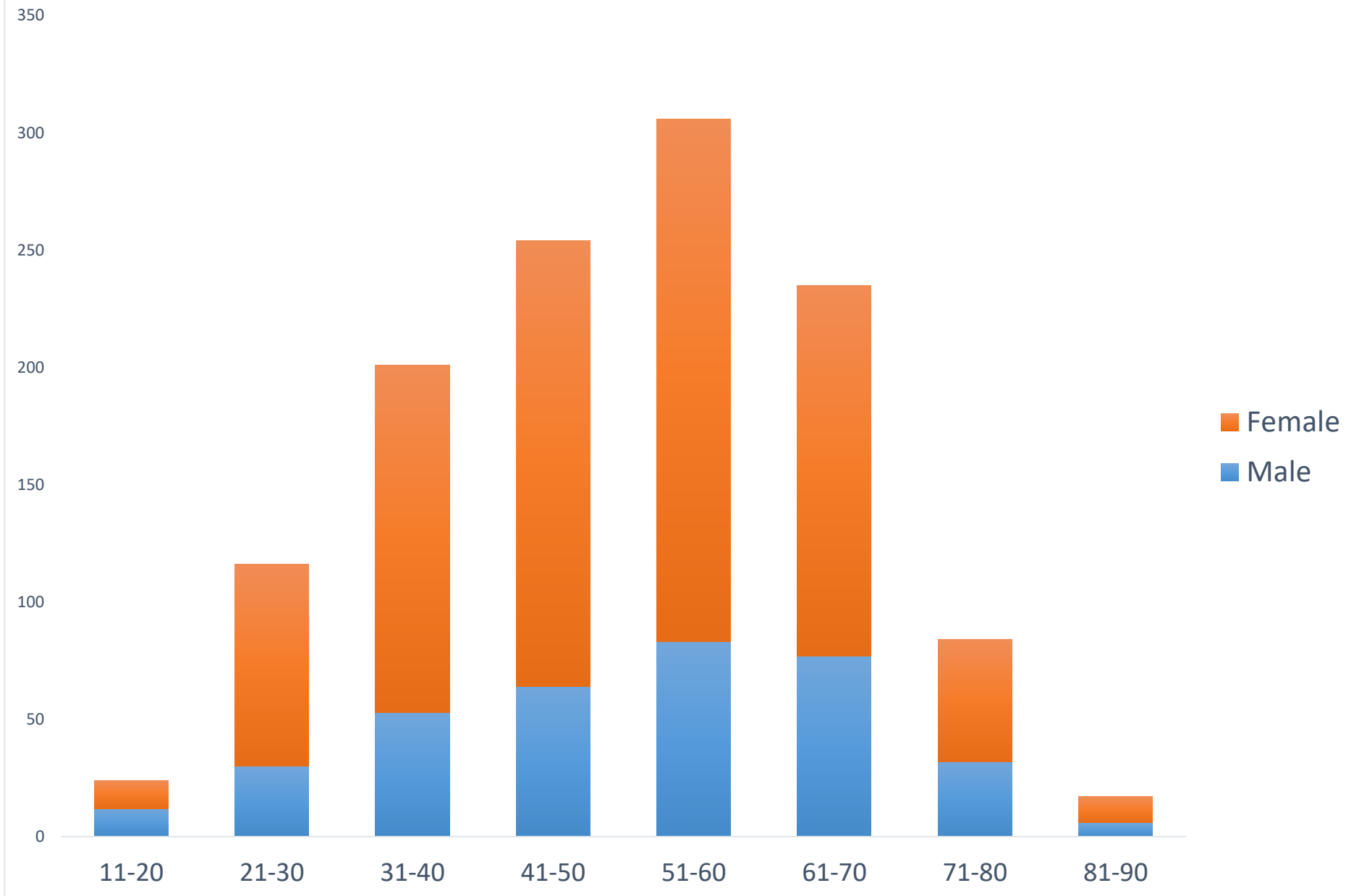
- Evidence of prior COVID-19 infection
 - Positive respiratory PCR or antigen test, or
 - Positive SARS-CoV-2 nucleocapsid antibody test, or
 - Convincing history (e.g., characteristic symptoms, epidemiology, absence of other likely causes of symptoms)
- Age ≥ 18
- Symptoms ≥ 12 weeks after acute COVID-19
- Referral by a primary care provider

DH PACS Clinic Referrals per Month





Age and Gender of PACS Referrals



Prevalence of PACS (“Long hauler symptoms”)

- Reported prevalence depends on definition, which includes severity of symptoms and timing (how far out from acute illness).
- Multiple sources report prevalence of 10-30%, but some estimates are much higher.
- We can conservatively expect more than 15 million cases of “long COVID” in the US resulting from the pandemic.
- Longer recovery time in patients requiring hospitalization, older patients, patients who experienced complications of acute COVID.
- Hospitalized patients:
 - Wuhan study: 76% of patients had at least one symptom at 6 months
 - Italian study: 87% still with symptoms at 60 days.

Predictors of Post-COVID Syndrome

- The majority of patients with PACS had *mild* acute illness, but those with severe illness may have worse organ-specific symptoms (e.g., persistent pulmonary).
 - DH PACS Clinic: only 17% of patients seen had been admitted for COVID-19
- Female: $\geq 60\%$ (71% of referrals so far at DHMC)
 - Probably both biological and sociocultural determinants
 - Female:male ratio of 2.3:1 is reminiscent of MS (2:1), RA (3:1), SLE (7:1)
 - Higher rate of positive ANA among PACS patients
- Age. Study: incidence 27% in patients age 18-39, 43% \geq age 65.

Predictors of Post-COVID Syndrome

- Premorbid medical conditions?
 - Depression/anxiety, other mental health issues
 - Wang S, et al. “Associations of depression, anxiety, worry, perceived stress, and loneliness prior to infection with risk of post-COVID-19 conditions.” JAMA Psychiatry 2022. Participants with two or more types of distress prior to infection were at 50% increased risk for post-COVID-19 conditions.
 - Asthma, COPD, other chronic lung diseases
 - Obesity?
 - Diabetes?
- Other purported predictors:
 - Respiratory symptoms at onset of illness
 - Belonging to an ethnic minority
 - Socioeconomic deprivation
 - Smoking

Predictors of Post-COVID Syndrome

- Su Y et al. Multiple early factors anticipate post-acute COVID-19 Sequelae. Cell 2022;185:881
- Identified four PASC-anticipating risk factors at the time of initial COVID-19 diagnosis, 309 patients
 - SARS-CoV-2 RNAemia during acute illness
 - Autoantibodies, especially those that neutralize type I interferons, often associated with SLE
 - Type 2 diabetes
 - Epstein-Barr virus viremia

Underlying Conditions: D-H Data, 577 patients

- 35% with prior diagnosis of obesity or BMI >30 (but background prevalence of 26% in VT, 30% in NH).
- Mental health diagnoses prior to PACS Clinic visit:
 - 34% with history of depression
 - 36% with history of anxiety
 - 6% with history of PTSD
- 19% with history of migraine headaches
- 17% with history of asthma, COPD, or other chronic lung disease
- 8% with history of diabetes

Effect of Vaccination on Risk for PACS

- Review of 8 studies on effect of vaccination before COVID-19.
 - 6 of 8 studies suggested that vaccinated patients who got COVID-19 were less likely to develop long COVID. (An underestimate of benefit, because vaccination also prevents COVID-19.)
 - Fully vaccinated patients were less likely to have fatigue, HA, muscle pain, dizziness, SOB, and anosmia.
- Review of 8 studies on effect of vaccination on symptoms of long COVID (among patients who have it).
 - Some studies showed that more patients improve after vaccination. But some patients feel worse, and most showed no change among symptoms.
- These were all uncontrolled studies with great heterogeneity of patients.

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Fatigue

- The most common persistent symptom following COVID-19.
- Can be physical, cognitive or emotional, mild or severe, intermittent or persistent.
- May appear similar to myalgic encephalomyelitis/chronic fatigue syndrome
- Can be severe enough to cause confinement to home, difficulty completing ADLs; disabling for many patients.
- Post-exertional fatigue: worsening fatigue following even minor physical or mental exertion; can last for days or weeks.

Treatment of PACS Fatigue

- Begin an individualized and structured, titrated return to activity program. Very gradual progression.
- Discuss energy conservation strategies – the four P’s
 - Planning: plan the day or week to avoid over-exertion, recognize “energy windows”
 - Pacing: avoid the “push and crash cycle” that is common in post-COVID recovery
 - Prioritizing: focus on which activities need to get done
 - Positioning: modify activities to make them easier to perform
- Healthy diet, hydration. Mediterranean diet?
- Address sleep disorders, pain, mood disorders

Treatment of PACS Fatigue

- No consensus on use of medications or supplements
- Some PACS clinics use stimulants, such as modafinil, or “activating anti-depressants,” such as bupropion, fluoxetine
 - Recent review touting modafinil; personal communication touting armodafinil.
- Many patients express an interest in herbal remedies/supplements, but there are no controlled data to support.
- Acupuncture has been reported to improve fatigue (preliminary, low-quality supportive evidence).
- Physical therapy, but not to the point of exhaustion. Recumbent or sitting favored over standing activities.

Referral Indications for Physical Therapy at DHMC

- Fatigue
- Dyspnea on exertion
- Chest pain
- Post-exertional malaise
- Desaturation
- Deconditioning
- Muscular weakness
- Neuropathy
- Exercise intolerance
- Decreased exercise capacity
- Dizziness
- Dysautonomia
- Postural orthostatic tachycardia syndrome(POTS)

“Brain Fog”

- Probably the second most common long COVID symptom.
- Difficulty with short-term memory, multitasking, word-finding, fluent speech, concentration.
- Symptoms often fluctuate – “good days and bad days.”
- No clear correlation with severity of acute COVID, age or comorbidities
- Often accompanied by depression, anxiety

Cognitive Deficits in People Who Have Recovered

- Hampshire et al., Lancet, 2021
- Analyzed data from 81,337 individuals who completed a questionnaire: The Great British Intelligence Test.
- “People who had recovered from COVID-19 exhibited significant cognitive deficits vs. controls when controlling for age, gender, education level, income, racial-ethnic group, preexisting conditions, fatigue, anxiety, depression.”
- Substantial deficits for both hospitalized and non-hospitalized patients; e.g., for hospitalized patients, greater than the average 10-year decline in global performance between ages 20 to 70, or the mean deficit of people who had previously suffered a stroke. (IQ test equivalent 7 points.)

Other Neurologic Symptoms

- Headaches
 - Often described as a constant pressure that fluctuates in severity
 - Often no prior history of headaches
 - Often exacerbation of prior migraine history
- Paresthesias
 - Tingling, numbness, burning sensation, often “stocking-glove” distribution
- Tinnitus

Pathology of PACS: Neuroradiology

- Douaud et al: “Brain imaging before and after COVID-19 in UK Biobank.” BMJ preprint
- UK Biobank had scans (“multimodal MRI”) on 40,000 people before pandemic, then re-scanned 785 adults – 401 after recovery from acute COVID-19, 384 matched controls
- Did “structural, diffusion and functional brain scans” (including ^{18}F -FDG PET) before and after COVID-19
- Findings among cases
 - Reduction in grey matter thickness and contrast in the lateral orbitofrontal cortex and parahippocampal gyrus

Pathology of PACS: Neuroradiology

- Increase in diffusion indices (a marker of tissue damage) in the regions of the brain functionally connected to the piriform cortex, anterior olfactory nucleus and olfactory tubercle
- Reduction in global measures of brain size and increase in CSF volume, suggesting diffuse atrophy in infected participants
- Imaging findings were associated with worse performance on cognitive screening test.
- “Our findings relate to longitudinal abnormalities in limbic cortical area with direct neuronal connectivity to the primary olfactory system.... These results may be the *in vivo* hallmarks of a degenerative spread of the virus via olfactory pathways or of neuroinflammatory events due to infection, or to the loss of sensory input due to anosmia.”
- “Uncertain” whether this deleterious impact can be reversed or will persist.

Post-COVID Postural Tachycardia Syndrome

- POTS: sustained heart rate increment of ≥ 30 beats/min upon standing or head-up tilt, without hypotension; enhanced resting sympathetic tone.
- Orthostatic intolerance: development of symptoms during standing that clears upon recumbence.
- Pathogenesis following COVID-19 is unknown (multiple hypotheses).
- Orthostatic symptoms and dysautonomia are common in PACS
 - Unexplained sinus tachycardia, dizziness on standing, palpitations
 - Fatigue, “brain fog,” GI symptoms, headache, sleep abnormalities

POTS Treatment

- Non-pharmacologic
 - High salt intake (4-10 grams!), at least 3 L of water/day
 - Compression stockings
 - Avoidance of heat, fatigue, hunger and dehydration
- Pharmacologic
 - Beta-blockers
 - Fludrocortisone
 - Midodrine
 - Ivabradine

Treatment of Cognitive Deficits in POTS

- Non-pharmacological
 - High fluid and salt intake
 - Acute water ingestion
 - Compression stockings, abdominal binder
- Pharmacological
 - Stimulants?: e.g., methylphenidate, amphetamines, modafinil
 - Serotonin-norepinephrine reuptake inhibitors?: e.g., duloxetine
- Cognitive therapies
 - Cognitive behavioral therapy (CBT)?
 - Mindfulness-based stress reduction (MBSR)?

Other Symptoms

- Altered taste and smell: often resolve by one month, but many patients have persistent hyposmia or parosmia.
 - Can be accompanied by weight loss, anorexia, or weight gain
 - Treatment: use of “olfactory training kit” (but no controlled data)
- Chest discomfort. Often described as “tightness” or heaviness. Not typical of angina.
 - Palpitations and tachycardia common, but Holter or Zio patch usually shows only sinus tachycardia.
 - More thorough evaluation for patients with myocarditis during acute illness.
 - Reassurance! “You’re not having a heart attack.”

Possible Cause(s) of PACS

- Persistent virus? Demonstrated in GI tract. Persistent viral remnants?
 - Anecdotal reports of response to Paxlovid.
- Robust immune response with inflammatory cytokine production?
“Immune dysregulation”?
 - Persistent activation of the immune system has been demonstrated.
 - Autoimmunity.
- Dysautonomia, including postural orthostatic tachycardia syndrome.
- Endothelial damage and microvascular injury?
- Coagulation activation, “fibrin amyloid microclots.”

Coagulation Abnormalities

- Pretorius E, et al. “Combined triple treatment of fibrin amyloid microclots and platelet pathology in individuals with long COVID/post-acute sequelae of COVID-19 can resolve their persistent symptoms.”
- One of a number of recent articles by this group about “fibrin(ogen) amyloid microclots.”
 - Fibrinogen can clot into an amyloid form that is resistant to fibrinolysis
 - Large, anomalous (amyloid) fibrin(ogen) deposits are present in plasma from acute COVID-19 patients. Plasma samples from long-COVID patients still contain large anomalous (amyloid) deposits, and these are resistant to fibrinolysis.

Coagulation Abnormalities

- Analyzed blood samples from 70 patients, all had significant fibrin amyloid microclots and platelet pathology.
- A subset of 24 patients were treated with clopidrogel (75 mg qd), ASA (75 mg qd) and apixiban (5 mg bid). And pantoprazole.
- “Each of the 24 treated cases reported that their main symptoms were resolved, including fatigue, and this was reflected in a decrease in both the fibrin amyloid microclots and platelet pathology scores.”
- “Fibrin amyloid microclots that block capillaries and inhibit the transport of O₂ to tissues, accompanied by platelet hyperactivation, provide a ready explanation for the symptoms of PASC.”

Approach to Evaluation and Treatment

- Listen. Validate. Educate. Reassure.
 - First visit with D-H PACS Clinic 60 minutes, after thorough chart review.
- The tests are (almost) always normal! MRIs, Echocardiograms, stress tests, PFTs, B12/folate, TSH ... etc.
 - 37% of patients seen in PACS Clinic have already had echocardiograms. All essentially normal.
 - 14% of patients have already had cardiac stress tests. All essentially normal.
 - 19% of patients have already had a Zio Patch or Holter monitor. Many with sinus tachycardia but no significant arrhythmias.
 - 18% of patients have had a brain MRI. All essentially normal.
 - 30% of patients have had a chest CT scan. No late CT scans (done for dyspnea in long COVID) have revealed PEs.
 - No unexpected abnormalities of thyroid function, nutritional deficiencies..

General Approach to Evaluation and Treatment

- Make sure it's not postural orthostatic tachycardia syndrome
 - If so, referral to Cardiology or Neurology
- Attention to mental health: anxiety, depression, insomnia
 - Psychiatry consultation
 - Neuropsychiatric consultation
 - Emphasis on establishing restorative sleep
 - For depression/anxiety with musculoskeletal symptoms: duloxetine, tricyclics antidepressants
 - For sleep: TCAs, mirtazapine

Approach to Evaluation and Treatment

- Arrange for rehabilitation services: occupational therapy, physical therapy, pulmonary rehabilitation
- National support networks
 - Body Politic
 - Facebook's Women's COVID Long Haulers Support Group and covidCAREgroup
 - Survivor Corps
- Local D-H support groups:
 - D-H facilitated peer to peer video meet-ups, writing groups
 - University of Vermont Health Network COVID-19 Recovery Support Group

Long-term Adverse Health Outcomes from COVID-19

- Worsening pre-existing conditions and disabilities
- Direct organ damage (lung, heart, kidney, CNS), from infection or hypercoagulability events)
- Ongoing debilitating symptoms of unclear pathology
- Impaired mental health due to anxiety, depression, PTSD
- Extent of long-term disability is unknown
 - Gradual improvement over time is experienced by most patients
 - Long COVID can be a disability under Titles II and III of the Americans with Disabilities Act, Section 504 of the Rehabilitation Act of 1973, and Section 1557 of the Patient Protection and Affordable Care Act.

DARTMOUTH HITCHCOCK POST-ACUTE COVID SYNDROME WEBSITE

- Website development. Comprehensive, Dartmouth Health-specific web site about post-acute COVID syndrome
- <https://www.dartmouth-hitchcock.org/long-covid>