The COVID-19 “long-hauler” syndrome – facts, fallacies and the unknown

Sunday, June 6 | 12N – 1 pm CDT
Moderator
Louis Weinstein, MD

Immediate Past Chair, AMA Senior Physicians Section Governing Council
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Speakers’ Disclosure

The content of this activity does not relate to any product of a commercial interest as defined by the ACCME; therefore, there are no relevant financial relationships to disclose at this time.
Objectives

Upon completion of this activity, the physician will be able to:

• Define the term long-hauler for COVID-19 post viral syndrome.
• Assess the range of long-lasting symptoms patients have reported.
• Describe how long hauler syndrome specifically affects the senior population.
• Relate experiences, symptoms, and successful practices of those treating these patients.
• Compare the differences between older and younger people experiencing long-hauler syndrome.
Speaker
Aluko A. Hope, MD

Associate Professor, Pulmonary and Critical Care, Oregon Health and Sciences University
Understanding & Improving COVID-19 Recovery

Associate Professor, Pulmonary/Critical Care, Oregon Health and Science University (OHSU)
Adjunct Associate Clinical Professor of Medicine, Division of Critical Care Medicine, Montefiore-Einstein
Outline

- Pathophysiology of PACS
- Epidemiology
- Care Models
- Challenges
- Summary
Case AB with Acute COVID-19

- 55 year old woman
- PMHx: hypertension, pre-diabetes, obesity, depression
- Works as an elementary school teacher
- In May 2020, PCR+ COVID-19
- Fever, headache, anosmia, difficulty breathing, and chest pains, myalgia
- Admitted to hospital 6 days into symptoms
  - Psat 92% on with bilateral reticular infiltrates
  - Remdesivir x 5 days: 200mg x 1 → 100mg x 4
  - Decadron 6mg IV x 5 days
  - Treated with NC 2-3 L
Defining PASC

- Definition is still evolving
- Acute COVID-19 lasts ~ 4 weeks
- Persistent symptoms and/or delayed or long-term complications beyond 4 weeks
  - Subacute/ongoing COVID-19
  - Chronic/post-COVID-19
Pathophysiology of PASC

Direct mechanisms
- Persistent immune activation or immune dysregulation?
- Persistent or restricted viral replication?

Indirect mechanisms
- Residual organ damage from acute infection?
- Unmasking of underlying comorbidities after infection?
- Post-hospital or post-ICU syndromes
COVID-19 symptoms persist in outpatients

- 292 adults tested at outpatient sites at 14 academic centers in 13 U.S. cities
  - Telephone interview regarding symptoms
  - 94% reported ≥ 1 symptom at initial testing
  - 35% not at usoh at interview (median 16 days from initial testing)
  - Cough, fatigue and shortness of breath were most common symptoms to persist
  - Older age and multi-morbidity were factors associated with persistent symptoms

Tenforde MW et al. MMWR Morb Mortal Wkly Rep 2020
Sixty-Day Outcomes Among Patients Hospitalized With COVID-19

- Observational cohort study
- Hospitalized patients admitted with COVID-19 March-July 2020
- 38 hospitals in Michigan
- 1250 survived/1648 eligible
  - 975 (78.0%) discharged home
  - 158 (12.6%) subacute rehab

### Mortality and rehospitalization (total 1250)
- Died in the 60 day after discharge, n (%) 84 (6.7)
- Rehospitalization, n (%) 189 (15.1)

### New or Worsened Symptoms (total = 488)
- Persistent Symptoms 159 (32.6)
- New or worsening symptoms 92 (18.9)
- Continued loss of taste and/or smell 64 (13.1)
- Cough 75 (15.4)
- SOB/ chest tightness/ wheezing 81 (16.6)
- Difficulty ambulating due to chest problems 44 (9.0)
- Oxygen use 32 (6.6)
- Breathlessness walking up stairs 112 (23.0)
- New use of CPAP or other breathing machines during sleep 34 (7.0)
Long-term consequences of discharged COVID-19 patients

- 1733 adults underwent follow-up questionnaires, physical exam, 6mwt
  - 516 chest CT, PFT
  - Hospital LOS, median (IQR) 14·0 (10·0–19·0) days
- Time from symptom onset to follow-up visit, median (IQR) 186·0 (175·0–199·0) days
- Fatigue or muscle weakness, anxiety or depression were the most common symptoms
- The risk of presenting ≥ 1 symptom
  - Higher in HFNC/IMV/NIV (OR 2·42, 95% CI 1·15–5·08)
  - Women more likely to report ≥ 1 symptom (81% versus 73% in men, p=0.0046)
- Risk of dyspnea higher in HFNC/IMV/NIV
  - OR 2·15, 95% CI 1·28–3·59

<table>
<thead>
<tr>
<th></th>
<th>No O2 (n=439)</th>
<th>Supplemental O2 (n=1172)</th>
<th>HFNC, IMV or NIV (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 (46-65)</td>
<td>57 (48-65)</td>
<td>56 (48-65)</td>
</tr>
<tr>
<td>Women</td>
<td>51%</td>
<td>48%</td>
<td>36%</td>
</tr>
<tr>
<td>Fatigue or muscle weakness</td>
<td>281/424 (66.3%)</td>
<td>662/1114 (59%)</td>
<td>95/117 (81%)</td>
</tr>
<tr>
<td>mRC Dyspnea Score≥ 1 score</td>
<td>102/425 (24%)</td>
<td>277/1079 (26%)</td>
<td>40/111 (36%)</td>
</tr>
<tr>
<td>Anxiety or depression</td>
<td>98/425 (23%)</td>
<td>233/1081 (22%)</td>
<td>36/111 (32%)</td>
</tr>
<tr>
<td>≥ 1 symptom</td>
<td>344/424 (87%)</td>
<td>820/1114 (74%)</td>
<td>101/117 (86%)</td>
</tr>
<tr>
<td>DLCO</td>
<td>18/83 (22%)</td>
<td>48/164 (29%)</td>
<td>48/86 (56%)</td>
</tr>
</tbody>
</table>

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Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact

- BodyPolitic
- The Patient-Led Research group via social media and digital tools like Slack.
- 3,752 participants from 56 countries.
- Questionnaire include 205 symptoms.
  - Fatigue, PEM, cognitive dysfunction were the most common symptoms
  - Relapses with exercise, physical/mental activity, stress
  - Average of about 13 symptoms

Long Covid Symptoms

- **Most Common:** Fatigue & dyspnea
- **Neurocognitive:** Brain fog, HA, insomnia, anosmia, dysautonomia, ageusia, vertigo, chronic fatigue syndrome (ME), stroke, neuropathy
- **Behavioral Health:** Depression, anxiety, PTSD
- **Pulm:** dyspnea, interstitial thickening, fibrosis,
- **Cardiac:** chest pain, palpitations and/or tachycardia, mycarditis, cardiomyopathy, arrhythmias, thromboembolism
- **GI:** Abd pain, diarrhea, wt loss
- **MS:** Myalgias, arthralgias, fatigue
- **Skin:** Rashes, COVID toe, alopecia
- **Socioeconomic:** Unemployment, impaired daily function and mobility
- **Other:** Fevers, Chills, mast cell activation syndrome
Case Update: PASC Course

3 months after COVID-19:

- Chest tightness
- Palpitations
- Dizziness and lightheadedness
- Dyspnea, 2 block exercise tolerance limited also by palpitations
- Brain fog
  - Decreased attention/concentration
  - Memory challenges – repeating herself, feels emotionally labile
  - Executive functioning impairment
- Anxiety and post-traumatic stress symptoms
Why a post-COVID-19 clinic?

To improve organizational capacity and infra-structure for the clinical care of survivors of COVID-19 illness

To provide diagnosis and assessment services for COVID-19 survivors with lingering symptoms

To provide care management and coordination for chronic symptoms in survivors of COVID-19 illness

To provide training and education in the management of COVID-19 prolonged symptoms
What Happens at a post-COVID clinic?

- Rehabilitation Services: PT/OT/Speech
- Neuropsychology within Neurology or Psychiatry
- Cardiorespiratory Evaluation
- Psychiatry
- Social Work
- Peer Support

A Hub of Structured Assessments across multiple health domains
Patient Flow through Long COVID Clinic

- Internal LIPs
  - Long COVID HUB
  - PCP/PCMH manages all specialty needs in scope

- C4 Self Referral
  - LC SPOKE: Diagnostics

- External LIPs
  - LC SPOKE: Defined Specialty need out of scope of primary care management

- PCMH: Plan of Care for PCP to manage

# Eval & Mgt: SOB

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Evaluation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, sob with exertion</td>
<td>PFT- Spirometry, Lung Volumes, DLCO</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Dry cough</td>
<td>CXR</td>
<td>Steroids?</td>
</tr>
<tr>
<td>Coughing with phlegm</td>
<td>Chest CT</td>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>6MWT</td>
<td>LRTA</td>
</tr>
<tr>
<td></td>
<td>SPPB</td>
<td>Pulmonary rehabilitation</td>
</tr>
<tr>
<td></td>
<td>2 minute step test</td>
<td>Lung transplantation</td>
</tr>
</tbody>
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## Eval & Mgt: Fatigue and Post-Exertional Malaise

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Evaluation</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| • Severe exhaustion after minimal exertion  
• Prolonged post-exertional malaise and recovery  
• Lack of restorative sleep  
• Weighed down by lead weight all day  
• “Crash” after having a “good day.” | • Assess co-morbid issues  
• Assess sleep  
• Assess deconditioning  
• Assess impact of mental activities  
• Pulmonary workup: CXR, CT (if CXR abnl), PFTs  
• Directed serologic eval: CBC, CMP, TSH, Vit B12 / D, Iron/Ferritin, ESR, CRP, Cortisol, etc. | • Treat co-morbid issues  
• Physical therapy  
• 4Ps to break self-reinforcing cycle of fatigue – Posture, Pace, Plan, Prioritize  
• Leverage energy window  
• Medications?  
• Support SDoH  
• Mind-body exercises |
### Eval & Mgt: Neuropsychiatric Manifestations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Evaluation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Brain fog</td>
<td>• Screen for psychiatric co-morbidities (GAD-7 / PHQ-9)</td>
<td>• OT / Speech for brain fog</td>
</tr>
<tr>
<td>• Difficulty concentrating</td>
<td>• Assess sleep (ISI)</td>
<td>• Avoid overstimulating environments and tasks with divided attention</td>
</tr>
<tr>
<td>• Losing train of thought</td>
<td>• Neuropsychology referral for complex presentations of neurological, sleep, BH</td>
<td>• Treat headaches</td>
</tr>
<tr>
<td>• Short term memory lapses</td>
<td>• Brain imaging for headaches with “red flags”</td>
<td>• Treat psychiatric conditions</td>
</tr>
<tr>
<td>• Word finding difficulties</td>
<td></td>
<td>• Hydration/nutrition recommendations</td>
</tr>
<tr>
<td>• Overwhelmed (multitasking)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Post traumatic stress symptoms</td>
<td></td>
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</tbody>
</table>
Case Update: PASC

Evaluation

• Symptom Assessment
  • Endorsed 6 symptoms: fatigue, breathlessness, sleepiness, anxiety, depression, appetite changes
• GAD-7 score 21
• PHQ-9 score 10
• Post Traumatic Stress questionnaire – difficult to complete because of multiple “stressful events”

Interventions Offered:

• Neuropsychology/Psychology
• Physical Therapy
• Peer Support group for Women COVID-19 survivors
Challenges in PASC care

• Dearth of literature on health disparities in PASC
• Testimonial Injustice
• Hermeneutic Injustice
Resisting Injustice in PASC

- Peer support for patients/caregivers
- Care coordination
- Skillful communication
- Patient and family engagement in research
Speaker
Shannon G. Caspersen, MD
Assistant Professor
Weill Cornell Medical College/New York Presbyterian Hospital
38 year old female psychiatrist

- No chronic medical conditions
- Past Medical Hx of preeclampsia with HELLP (despite absence of risks factors), some unusual ID occurrences
- Active: full-time practice, exercise 5+ days/week, many volunteer activities, busy mom, etc
- Chronic fatigue/fibromyalgia/chronic Lyme/migraine “skeptic”
- Anti-Dr. Google crusader
Timeline

Monday, March 9, 2020

- Symptoms of acute covid begin (malaise, myalgias, sore throat)
- Miss a day of work (rare), begin telemedicine with all patients
- See primary care and ED physicians via telemed over the course of the week
- Finally instructed to come to ER on Friday, March 13 due to chest pain and dyspnea
- Labs in ER were significant only for lymphocytopenia. EKG and CXR wnl
- Permission obtained from Department of Public Health to administer a covid test (neg)
- Acute symptoms resolve after about 10 days
“Phase I”: March-July 2020

- Neurological: numbness and tingling in extremities, cold feet (socks needed in 90°F), tremor, new-onset migraines, visual disturbance, mild short-term memory and word-finding difficulties
- CV: dyspnea on mild exertion, HR increase 2x-3x going from supine to erect position, dizziness and pre-syncope when erect
- General: extreme fatigue, requiring 10+ hrs/sleep per night, general malaise, neck pain
- Lab findings: April, May, June wnl
- Functional status: able to see patients full time (essentially supine), manage remote kindergarten
“Phase II”: Diagnosis and Treatment

- Reading about other patients on Body Politik, who have similar symptoms and are being diagnosed with POTS/dysautonomia.
- Perform my own “quick and dirty” POTS test: positive
- See my primary doctor, tells me before doing a physical exam that I have “pandemic anxiety” and “deconditioning”
- Performs orthostatic vitals, proclaims he has “never seen someone so orthostatic”
- Referred to cardiologist: EKG, echo, labs wnl, orthostatics consistent with POTS
Phase II continued:

• Pharmacology:
  - Fludrocortisone to retain salt and expand blood volume
  - Na+ and K+ capsules
  - Ivadrabine (β-blocker-like rate control)

• Lifestyle Modifications:
  - Supine living
  - Fluid intake (2-3L/day)
  - Reduce sugar, red meat, cholesterol, no alcohol

• Exercise:
  - Dallas Protocol (8 months of supine→erect exercise)
“Phase III”: Flares and Functioning

• Still sleeping 9-12 hours per night
• Still following Dallas protocol, but due to flares, have had to repeat months and am only on month 4, 11 months later
• Still on medications, but have reduced doses
• Able to cook, clean, go out to dinner, pick up daughter from school
• HR still goes to 150s occasionally
• “flares” of systemic symptoms, usually triggered by acute stress, menstrual cycle (when estrogen is lowest) or possibly dietary indiscretions
Takeaways/Questions

• Some patients wish that their symptoms were caused by anxiety, but be careful about framing it as such (oops)
• Have humility and empathy for patients who consult Dr. Google
• Who “owns” dysautonomia and long-haulers?
• Why does getting vaccinated make some of us feel better (temporarily)?

Thank you!
Speaker
Shiwei Zhou, MD
Assistant Professor
University of Michigan
Older Age Associated w/ Subjective Sx Beyond 28 days

- Symptom > 28 days
  - 18-49 yr: 10%
  - ≥ 70 yr: 22%
- Women disproportionately affected except in older age group
- Loss of smell most predictive in ≥ 70 yr (OR 7.35)

Older Age Associated w/ PFT & CT changes at 6 Mo.

At 6 months post discharge among 1,733 patients in Wuhan, China, older age was
- **Positively (+) associated** w/diffusion impairment, fatigue/muscle weakness
- **Negatively (-) associated** w/ percentage change in chest HRCT score
- No significant association w/ anxiety/depression
- No Covid negative group

Takeaways

• Older age $\rightarrow$ higher association w/ PASC symptoms
• Many questions remain
• Validate the patient’s experience
• Vaccination: the only way to prevent PASC
Speaker
Ved V. Gossain, MD

Professor, Emeritus,
Michigan State University
Endocrine effects of COVID-19

• SARS-CoV2 (COVID-19) is a single stranded RNA virus.
• So far > 160 million cases and more than 3 million deaths have occurred worldwide*
• 33.8 million cases and 583K deaths in the USA
• ACE-2 is the binding site for the virus entry into the host cell.
• ACE-2 is expressed in lungs, CV system GI System and also many endocrine tissues including, Pancreas, Testis, Ovaries, Adrenal, Pituitary and Thyroid glands

*SOURCE: WHO dashboard. May 12, 2020
Endocrine effects of COVID-19: Diabetes

- Worldwide 415 million adults have diabetes
- By the year 2040 this will increase to 642 million
- 34.2 million Americans (just over 1 in 10) have diabetes
- 88 million Americans (Approx 1 in 3) have prediabetes

Source: IDF Atlas 7th edition
Endocrine effects of COVID-19: Diabetes

• DM is a “Risk factor” for increased morbidity and mortality with COVID-19.
• COVID-19 has been associated with direct β cell damage.
• A significant number of COVID-19 patients present with hyperglycemia (Not previously known DM), Including DKA and mixed DKA + HHS.
• Hyperglycemia: dysfunction of phagocytosis, impaired neutrophil chemotaxis and impaired cell mediated immunity.

Singh AK et al Diabetes Metab syndr. 2020;14(4):303-310
Huang,I Diabetes Metab syndr 2020;14(4): 395-403
Endocrine Effects of COVID-19: Diabetes

- Increased incidence of COVID-19 among hospitalized patients with DM.
- In a meta-analysis (n=6452) DM was associated with increased severity, increased frequency of ARDS and higher mortality in patients with COVID-19.
- Tight glucose control in the outpatient and inpatient settings is crucial to prevent complications and poor outcomes.
- DM may persist in “long haulers”

Source: Lundholm M et al. J of endocrine society;4:2020https://doi.org/10.1210/jendso/bvaa144
Singh AK et al Diabetes Metab syndr. 2020;14(4):303-310
Huang, I Diabetes Metab syndr 2020;14(4): 395-403
Endocrine effects of COVID-19. Hypothalamic-pituitary-end organ axis
Endocrine Effects of COVID-19 – Pituitary thyroid axis

• In postmortem studies, no pathological change was found in Thyroid gland except lymphocytic infiltration in one study.

• SARS Co-V-2 was not found in the thyroid by immunohistochemistry or polymerase chain reaction analysis in the Thyroid tissue.

• 64% patients had abnormal thyroid functions 3 months after the diagnosis of COVID 19.(1)

• 247 noncritical hospitalized patients for COVID-19 -20.2% had thyrotoxicosis and 5% had Hypothyroidism(2)

(1) Chen M ,Zhou WB et al.Thyroid .2021;31:8-11.
(2) Lania A, Sandri MT et al Eur J endocrinol 2020;183:381-387
## Endocrine Effects of COVID-19: Pit–Thyroid axis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Thyroid functions</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Thyroidal illness</td>
<td>Low TSH , Low T3 , low or normal T4</td>
<td>Potential effect of systemic inflammation</td>
</tr>
<tr>
<td>Subacute Thyroiditis</td>
<td>Varies by the stage *</td>
<td>Viral infection Thyroid</td>
</tr>
<tr>
<td>Central Hypothyroidism **</td>
<td>Low TSH , Low T4 , Low T3</td>
<td>Dysfunction of Hypo-Pit axis</td>
</tr>
</tbody>
</table>

- Initially hyperthyroidism, followed by Hypothyroidism and recovery
- ** may be associated with low cortisol levels also

Chen W, Yang T, et al. Endocrinology 2021 March 162 (3) bqab004 doi 10.1210 endocr/bqab004
Endocrine Effects of COVID-19. Pituitary adrenal axis

- ACE-2 is expressed in Pituitary and Adrenal glands (1).
- Microscopic changes of adrenal necrosis, hemorrhage and vascular thrombosis in adrenal glands has been reported (2).
- 32% patients with COVID had evidence of adrenal insufficiency (3).
- The benefit of Steroids may be related to adrenal insufficiency (1).
- Pts with Adrenal insufficiency can be assumed to be high risk for COVID-19 and complications including Adrenal crisis (1).

(3). Endo Pract .2021;27(2) 83-89
Endocrine effects of COVID-19.-Vit D

• Lower levels of 25-OH D are associated with higher risk of Respiratory infections.\(^1\),\(^2\)

• The role of Vit D in COVID-19 is controversial.\(^3\),\(^4\)

• An association of Vit D deficiency and increased risk of hospitalization and mortality from COVID-19 has been described\(^5\)

• A single high dose of Vit D among Hospitalized patients did not reduce length of hospital stay\(^6\)

• Trials are underway – await results.

\(^3\)Hastle CE et al. Diabetology and Metab Syndrome 2020;14:561-565.
\(^4\)Meltzer DO et al. JAMA 2020.3(9) e 219722.doi.10.1001/jamanetworkopen.2020.19722
\(^6\)Murai IH. JAMA 2021;325(11) 1053-1060 .doi.10.1001/jama .202026848
Endocrine effects of COVID-19- Summary

• Diabetes mellitus is a “risk factor” for increased morbidity and mortality with COVID-19.
• Plasma glucose levels should be determined in all patients with COVID-19 requiring hospitalization because pts may present with new onset of Diabetes.
• Optimal control of hyperglycemia should be maintained to avoid complications and poor outcomes.
• Other glands (Adrenals, Thyroid, gonads) may be affected directly by virus (Primary defect) or secondarily through the effects on Pituitary/Hypothalamus.
• More data is needed for the long-term effects of COVID-19 on the endocrine system.
Questions from Audience Members
Physicians’ powerful ally in patient care