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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

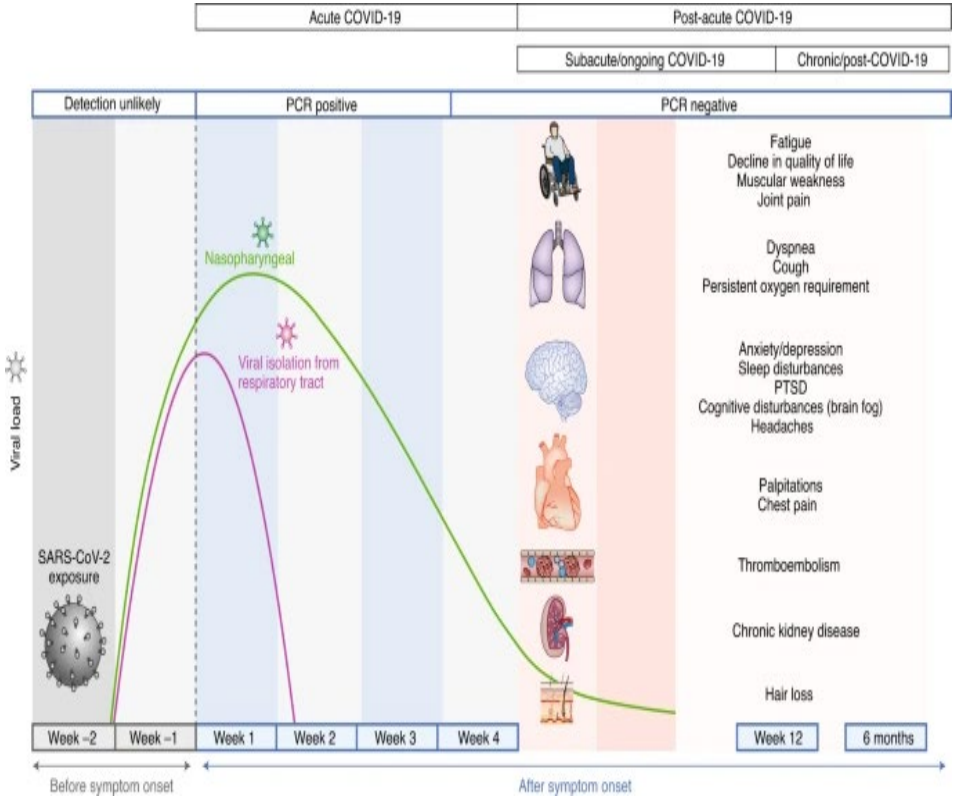
- Pathophysiology of PACS
- Epidemiology
- Care Models
- Challenges
- Summary

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 4weeks
    - Subacute/ongoing COVID-19
    - Chronic/post-COVID-19



Pathophysiology of PASC

Direct mechanisms

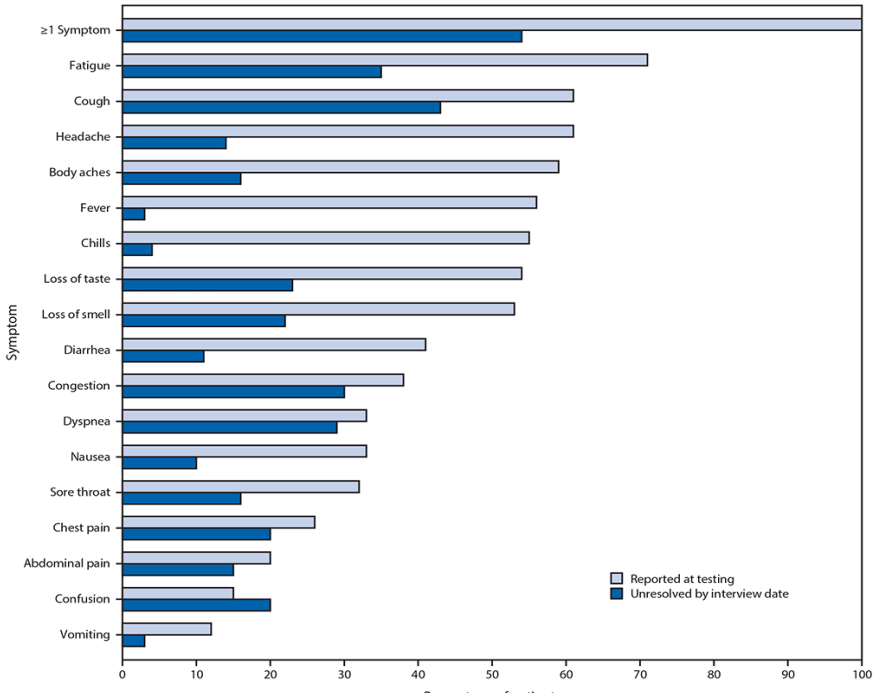
- Persistent immune activation or immune dysregulation?
- Persistent or restricted viral replication?

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

	No O_2 (n=439)	Supplemental O2 (n=1172)	HFNC, IMV or NIV (n=122)
Age	57 (46-65)	57 (48-65)	56 (48-65)
Women	51%	48%	36%
Fatigue or muscle weakness	281/424 (66.3%)	662/1114 (59%)	95/117 (81%)
mRC Dyspnea Score≥ 1 score	102/425 (24%)	277/1079 (26%)	40/111 (36%)
Anxiety or depression	98/425 (23%)	233/1081 (22%)	36/111 (32%)
≥ 1 symptom	344/424 (87%)	820/1114 (74%)	101/117 (86%)
DLCO	18/83 (22%)	48/164 (29%)	48/86 (56%)

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

Davis H et al.. Medrxiv. 5 April 2021. doi: https://doi.org/10.1101/2020.12.24.20248802 (unpublished)

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?

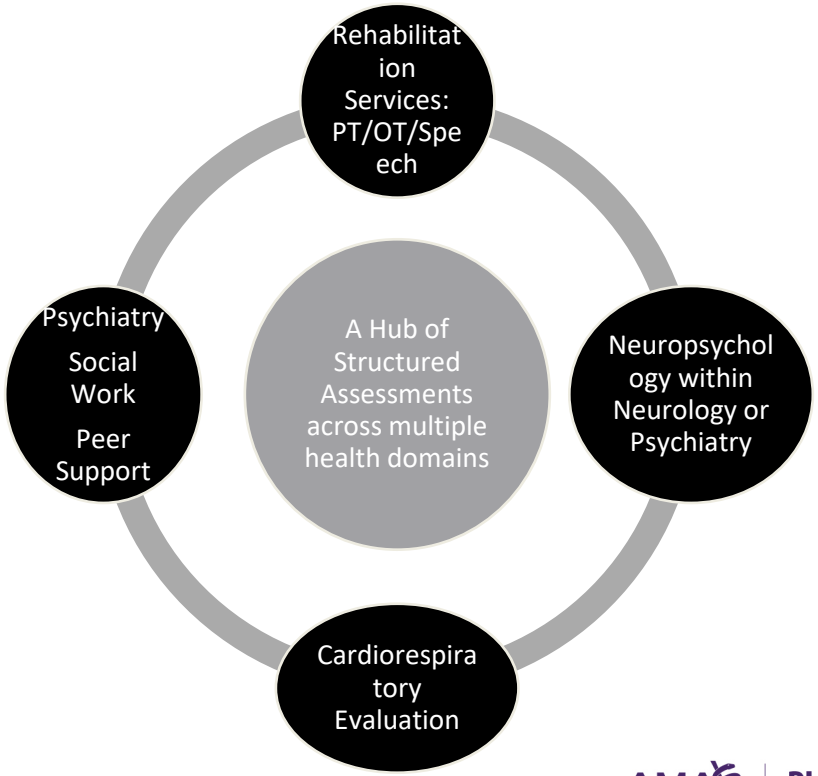
To improve organizational capacity and infra-structure for the clinical care of survivors of COVID-19 illness

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?



Patient Flow through Long COVID Clinic

Eval & Mgt: SOB

Symptoms	Evaluation	Treatment
▪ Dyspnea, sob with exertion ▪ Dry cough ▪ Coughing with phlegm	▪ PFT- Spirometry, Lung Volumes, DLCO ▪ CXR ▪ Chest CT ▪ 6MWT ▪ SPPB ▪ 2 minute step test	• Oxygen • Steroids? • Inhaled corticosteroids • LRTA • Pulmonary rehabilitation • Lung transplantation

Eval & Mgt : Fatigue and Post-Exertional Malaise

Symptoms	Evaluation	Treatment
• 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-morbids • 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: Neuropyschiatric Manifestations

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

Case Update: PASC Evaluation

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:
  - -fludricortisone to retain salt and expand blood volume
  - -Na+ and K+ capsules
  - -ivadrabine (b-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)?

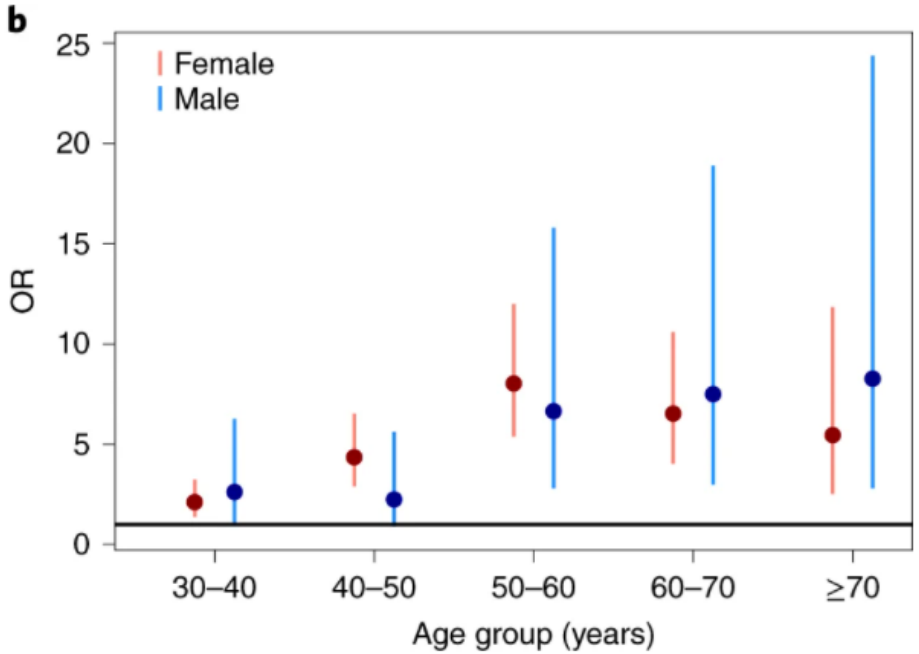
Thank you!

Speaker
Shiwei Zhou, MD

Assistant Professor
University of Michigan

Older Age Associated w/ Subjective Sx Beyond 28 days

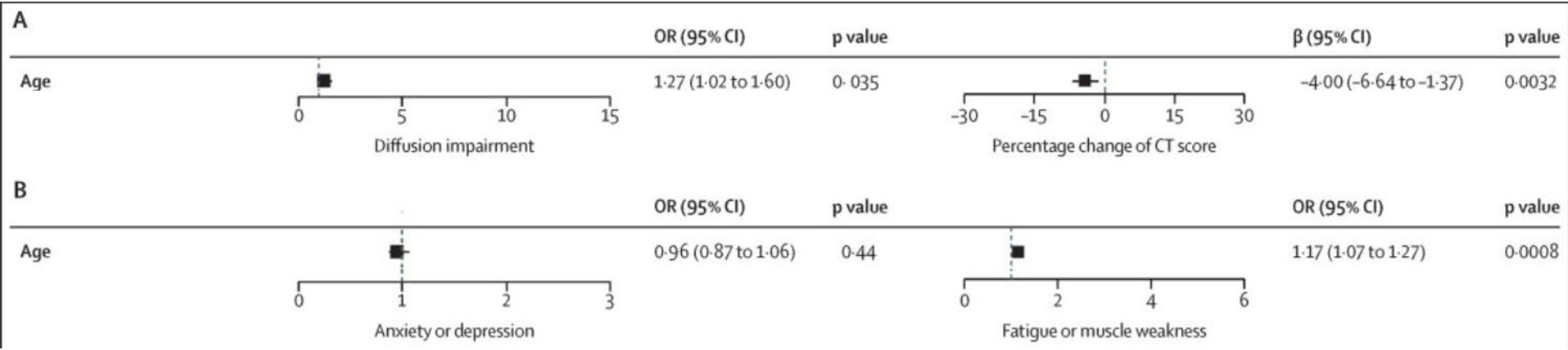
- Symptom > 28 days
  - 18-49 yr: 10%
  - ≥ 70 yr: **22%**
- Women disproportionately affected except in older age group
- Loss of smell most predictive in ≥ 70 yr (OR **7.35**)



**comparison: 20 to 30-year-old age group*

Sudre, C.H., Murray, B., Varsavsky, T. et al. Attributes and predictors of long COVID. Nat Med 27, 626–631 (2021)

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

Huang C, Huang L, Wang Y, et al. *Lancet*. 2021;397(10270):220-232.

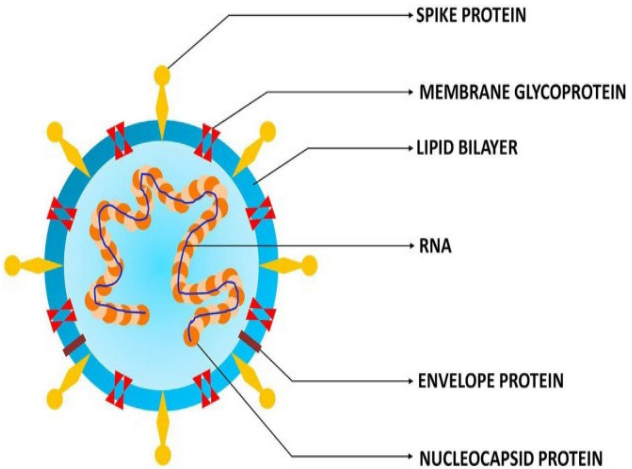
Takeaways

- Older age → 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 12,20201

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.

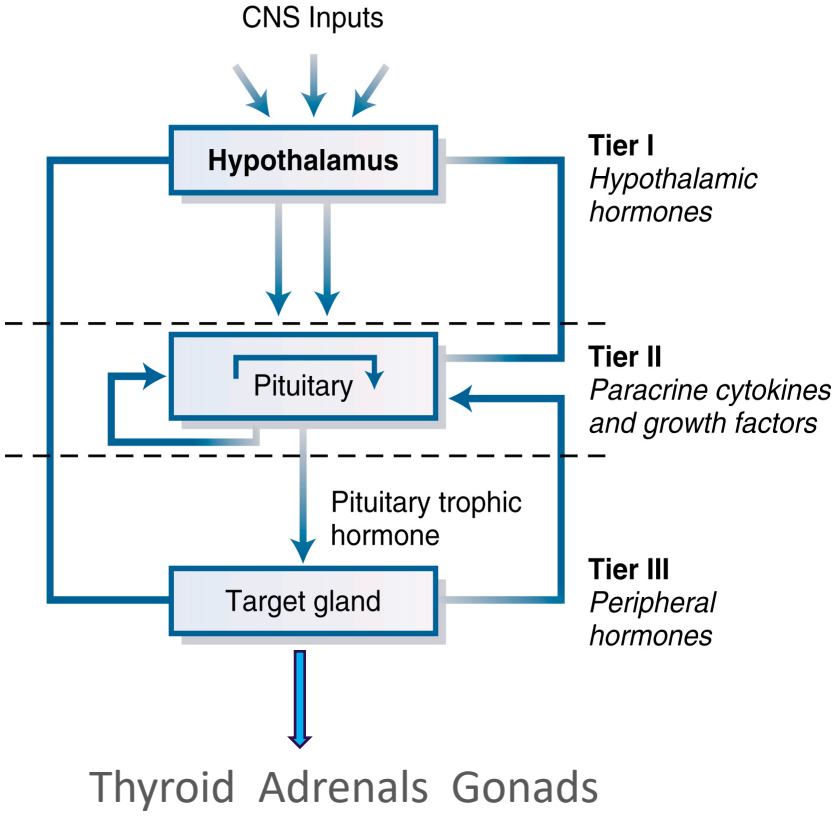
Lundholm MD etal .J of endocrine society;4:2020.https: //doi.org/10.1210/jendso/bvaa144
Singh AK etal Diabetes Metab syndr. 2020;14(4):303-310
Huang,I Diabetes Metab syndr 2020;14(4): 395-403

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”

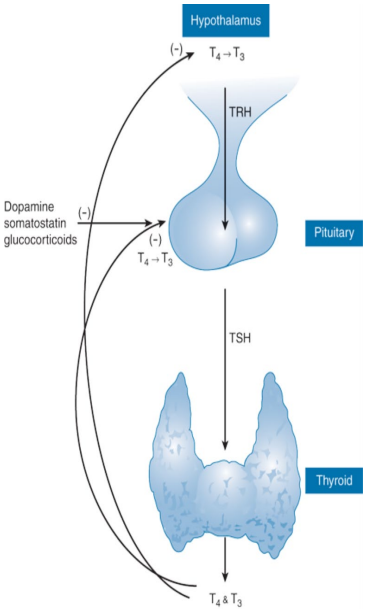
Source : Lundholm M et al .J of endocrine society;4:2020https://doi.org/10.1210/jendso/bvaa144
Singh AK etal Diabetes Metab syndr. 2020;14(4):303-310
Huang,I Diabetes Metab syndr 2020;14(4): 395-403

Endocrine effects of COVID -19 .Hypo –pit –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)



Source: Molina PE: *Endocrine Physiology*, 4th Edition: www.accessmedicine.com

(1) Chen M ,Zhou WB et al.Thyroid .2021;31:8-11.
(2) (2) Lania A, Sandri MT et al Eur J endocrinol 2020;183:381-387

Endocrine Effects of COVID-19:Pit –Thyroid axis

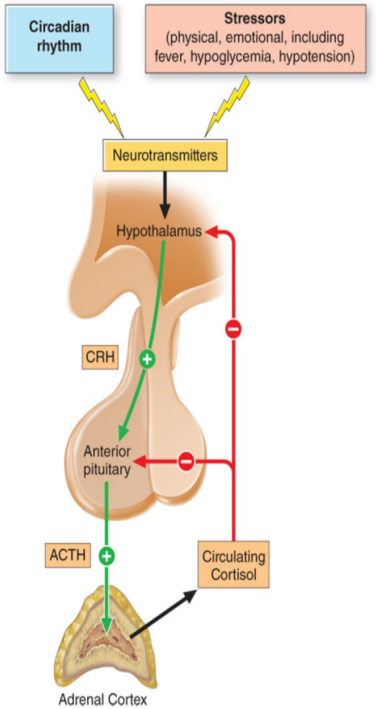
Diagnosis	Thyroid functions	Mechanism
Non-Thyroidal illness	Low TSH ,Low T3 ,low or normal T4	Potential effect of systemic inflammation
Subacute Thyroiditis	Varies by the stage *	Viral infection Thyroid
Central Hypothyroidism **	Low TSH ,Low T4 ,Low T3	Dysfunction of Hypo-Pit axis

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

ChenW,Yuang T,etal .Endocrinology 2021 March 162 (3) bqab004doi 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)



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition
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(1) J of the Endocrine society.2020;4:issue 11.(2).Am J trop Med Hyg 2020;103:1604-1607
(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.

(1)BilezikianJ et al .Eur J Endocrinology 2020;183: R143-R147. (2) Zemb P.Glob Antimicrob Resist.2020;Sept 22:133-134
(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
(5) Periera M et al Crit Rev Food Sci Nutr 2020.Nov 4:1-9 doi:10.1080/10408398.2020.1841090.
(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