

Long Covid: The Lasting Effects of the Pandemic and Pain

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Covid
statistics:
Hopkins
dashboard:
positive and
probable
cases

Worldwide: over half a
billion cases (514 million,
over 6 million deaths

USA over 81 million cases;
992k deaths

Johns Hopkins Daily Dashboard

Global Confirmed

516,913,439

Global Deaths

6,250,172

U.S. Confirmed

81,845,467

U.S. Deaths

997,418

What is PASC (Long Covid)?

- ▶ “A collection of symptoms that develop during or following a confirmed or suspected case of COVID-19, and which continue for more than 28 days.” They found that some of the most common symptoms were fatigue, symptoms that worsened after physical or mental activity, shortness of breath, trouble sleeping, and “brain fog” – trouble thinking clearly.
- ▶ **CDC DEFINITION as 5/5/22**
- ▶ Post-COVID Conditions
- ▶ Some people who have been infected with the virus that causes COVID-19 can experience long-term effects from their infection, known as post-COVID conditions (PCC) or long COVID.
- ▶ People call post-COVID conditions by many names, including: long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID.
- ▶ **Common Symptoms: Fatigue (31%), shortness of breath (15%) in hospitalized patients**
- ▶ **Loss of taste and smell in outpatient patients 16%**
- ▶ Estimated based on various studies to be in 15-70 % patients post-covid
- ▶ One study:
 - ▶ 12.6% experienced chest or throat pain
 - ▶ 11.6% experienced other pain
 - ▶ 3.24% experienced myalgia

History of Viral-related pain syndromes

Virus: Impact on Peripheral and Central Nervous Systems

Cytomegalovirus (CMV)

HIV

Herpes Zoster

Epstein Barr Virus

Influenza A virus

Zika

Attal et al

Virus most commonly responsible for neurological lesions	Neurological lesion
Herpes zoster	Lesion of sensory ganglia (responsible for postherpetic neuralgia) Myelitis
HIV	Painful sensory polyneuropathy Myelitis
Enteroviruses	Myelitis
Poliovirus	Postpolio syndrome
HTLV1	Myelitis
Zika	Guillain–Barré syndrome
Chikungunya	Myelitis
Other viruses*	Guillain–Barré syndrome
COVID-19	Guillain–Barré syndrome Myelitis Stroke Encephalitis

*eg, Epstein–Barr, cytomegalovirus, influenza A, coronaviruses, and hepatitis.

Yale Medicine review: Causes of PASC

- **Residual organ damage.** This theory holds that the symptoms of long COVID are due to residual damage to organs caused by the body's own immune response to SARS-CoV-2 infection.
- **Remaining virus.** This theory suggests that after the immune system eliminates the virus, some remnants of it survive in one or more organs, and it continues to stimulate an immune response.
- **Exaggerated Immune response.** According to this theory, in some people, COVID-19 sparks an exaggerated immune response; the immune system then remains in an overexcited state, resulting in various symptoms.

PASC and Chronic Pain

- ▶ Survivors of acute COVID-19 often exhibit PICS¹
 - ▶ Up to 77% patients may have chronic pain after an ICU stay
- ▶ ICU-acquired weakness can lead to deconditioning, joint pain, and contractures²
- ▶ Neuropathic pain may involve both the central and peripheral nervous system²
- ▶ ACE2 receptors may be involved²
 - ▶ Expressed in both muscle and neural tissue
 - ▶ SARS-CoV-2 has the potential to induce painful para-infectious neurologic disease
- ▶ Infection may lead to prolonged microvascular insufficiency²
 - ▶ May cause injury to nervous tissue and result in persistent pain

Abbreviations: ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; ICU, intensive care unit; PASC post-acute sequelae of COVID-19; PICS, post-intensive care syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

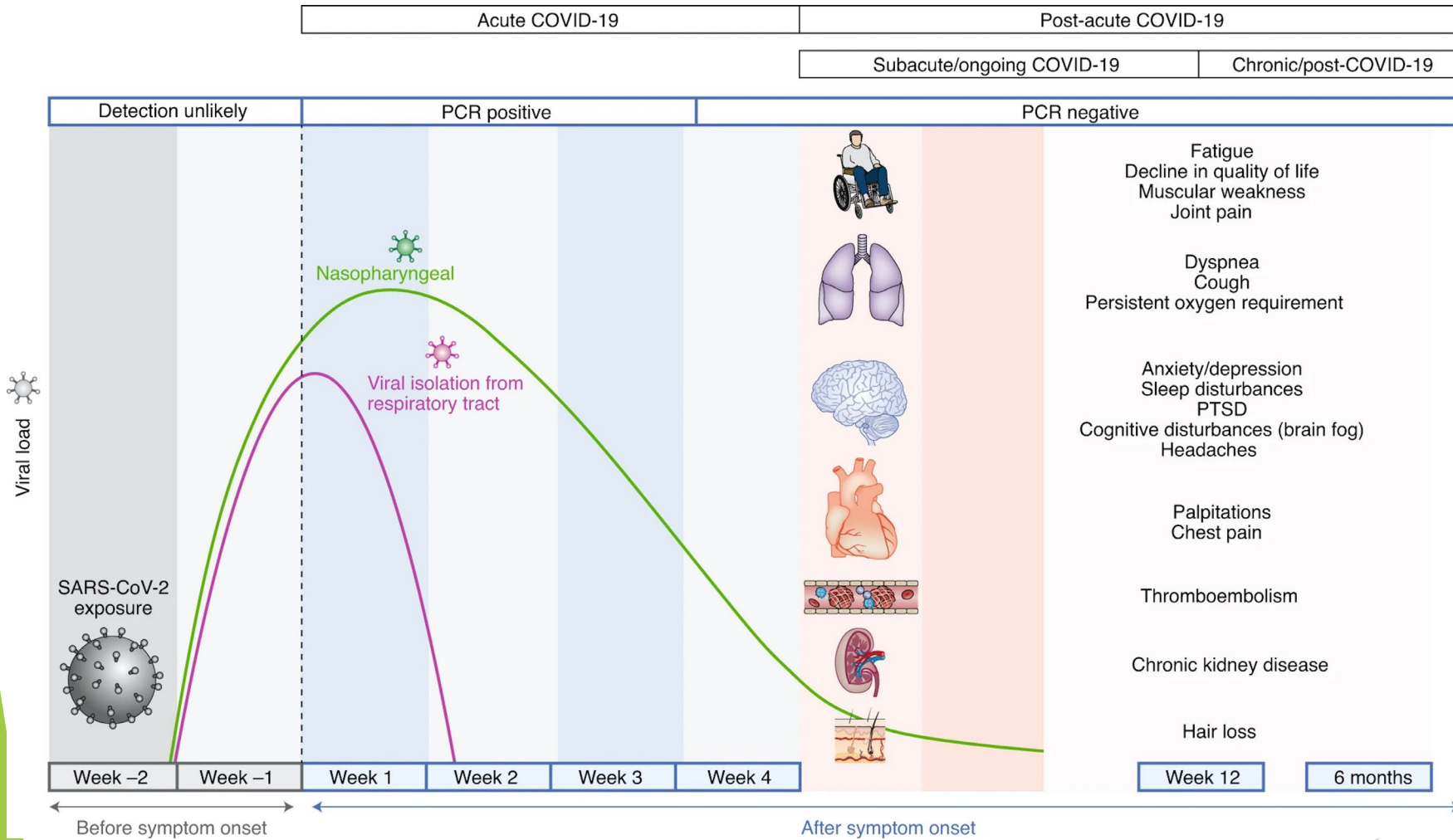
1. Huang Y. Accessed June 29, 2021. <https://dailyvoice.com/new-york/briarcliff/lifestyle/chronic-pain-following-covid-19-infection-is-more-common-than-you-may-think/810436/> 2. Hegarty D. Published September 30, 2020. Accessed June 29, 2021. <https://www.painreliefireland.ie/blog/pain-and-covid-19-acute-challenges-long-term-impact>

Pre-existing, ICU and new pain

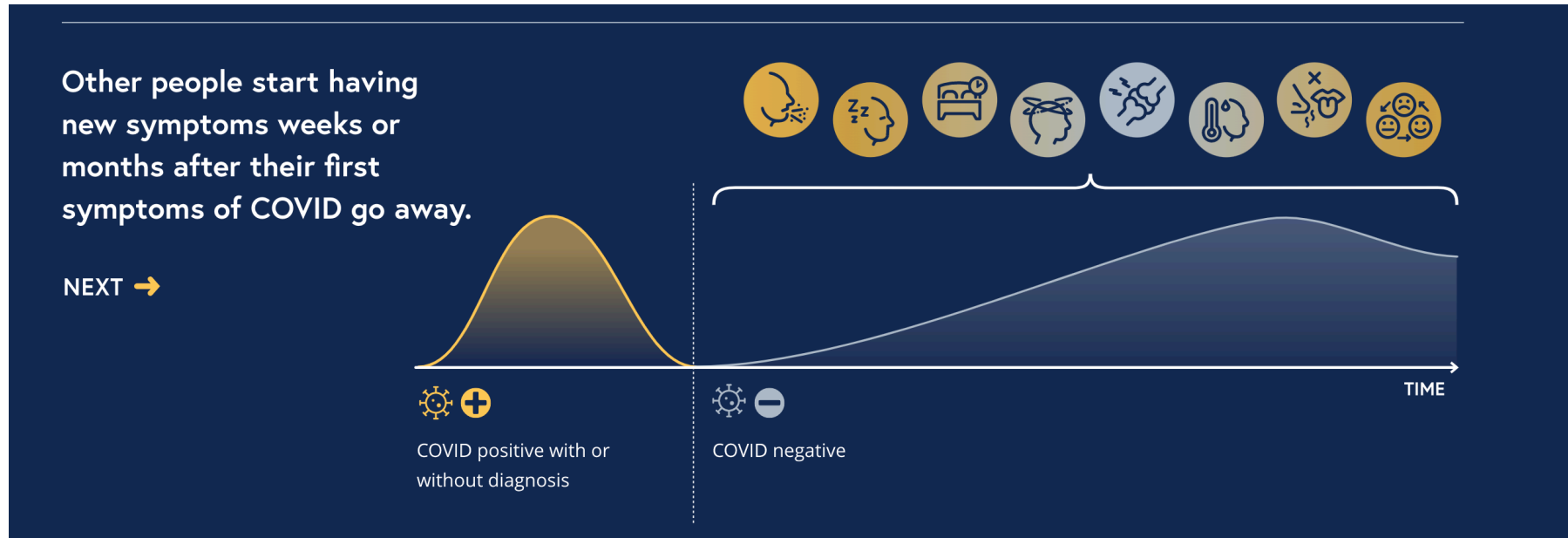
- ▶ "neurotoxic consequences of this virus will be enhanced in patients with pre-existing neurological injury" Attal et al
- ▶ Longer hospitalization. ICU related pain
- ▶ New Pain syndromes (viral and post viral symptoms)

Timeline

-credit: Peter Staats MD



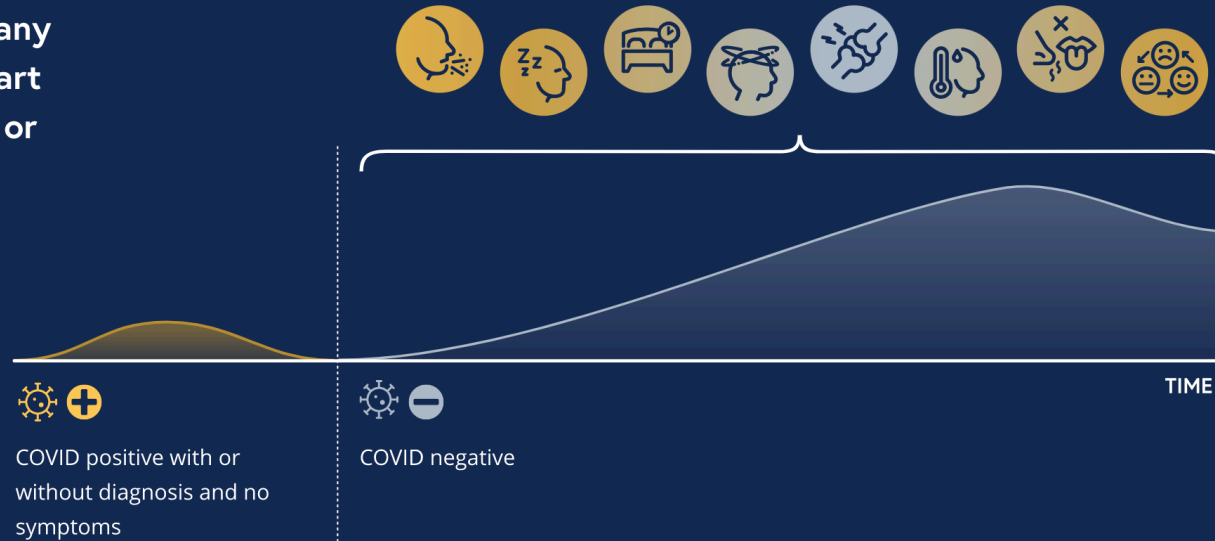
Scenario 1 presentation



Scenario 2 presentation pasc

Some people don't have any symptoms at first but start having symptoms weeks or months later.

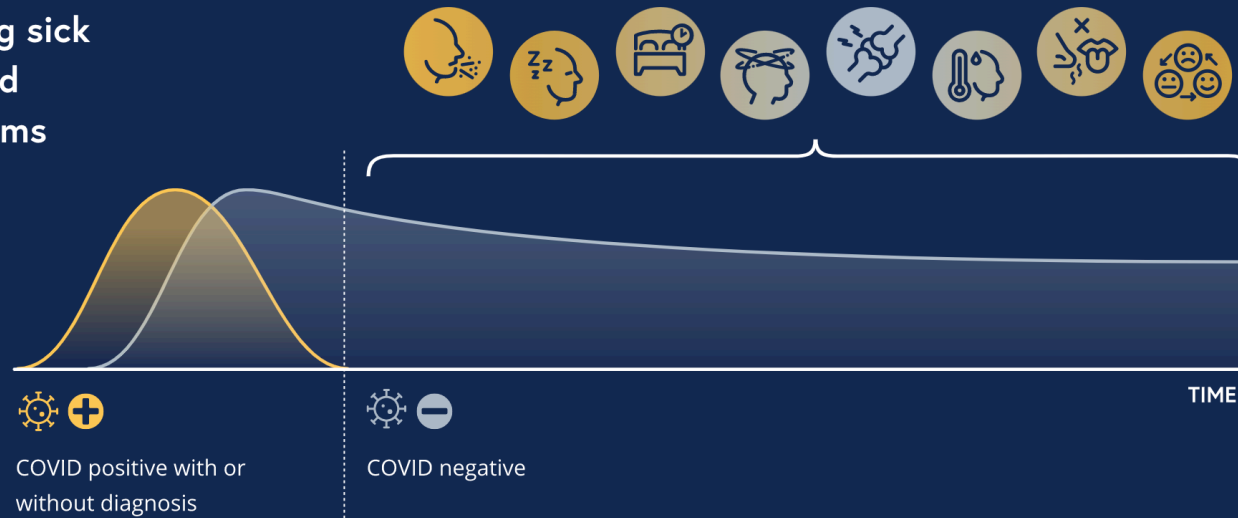
NEXT →



Scenario 3 presentation

Some people start feeling sick when they get COVID and continue to have symptoms for weeks or months.

NEXT →



Any combination

All the long-term effects of COVID together are called post-acute sequelae of SARS-CoV-2 infection, or PASC. People often use the term *Long COVID* to talk about PASC.

← START OVER



COVID positive with or without diagnosis and with or without symptoms



COVID negative



PASC symptoms that are due to hospitalization or ICU stay

- ▶ Acute myelitis
- ▶ Direct & Indirect effects of virus
- ▶ ICU- positioning, supine, prone

- ▶ Post stroke pain

Common Symptoms of Long Covid 19

- ▶ Difficulty breathing
- ▶ Shortness of breath
- ▶ Tiredness
- ▶ Chronic fatigue
- ▶ Heart palpitations
- ▶ Orthostatic symptoms
- ▶ Post-exertional malaise
- ▶ gastroenteritis
- ▶ chest pain, stomach pain, headache, musculoskeletal pain
- ▶ WIDESPREAD Pain

Extensive list

- 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

* [Post-exertional malaise \(PEM\)](#) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks.

Risk Factors

- ▶ Acute COVID-19 has a worse prognosis in older patients (> 65), those with lower socioeconomic status, and those of certain ethnic groups including American Indian, Alaska Native, Hispanic/Latino, South Asian, and African American populations
- ▶ UNCLEAR
- ▶ There is not enough data to determine if this pattern extends to PASC
- ▶ Men are at greater risk for increased symptom severity and death however, PASC is more common in women
- ▶ Women are more likely to have persistent fatigue, anxiety, and depression at 6-month follow-up
- ▶ A study of 128 participants demonstrated 54% of women had fatigue at median of 10 weeks after initial COVID-19 symptoms
- ▶ BMJ study prospective found unclear but may be risk factors may be: >50, having hypertension (odds ratio (OR)=1.3, P=0.018), obesity (OR=2.31, P=0.002), a psychiatric condition (OR=2.32, P=0.007), or an immunosuppressive condition (OR=2.33, P=0.047)

Biopsychosocial factors: may experience exacerbation of their symptoms, which may be due to multiple factors including social threats, limited medical tx: discontinuation of therapy, or reduced access to treatments, anxiety (concerns about health outcomes) (French study)

Incidence of PASC persistent symptoms and risk factors unclear

UCLA Longitudinal Study : April 7, 2022: 1000+ pts

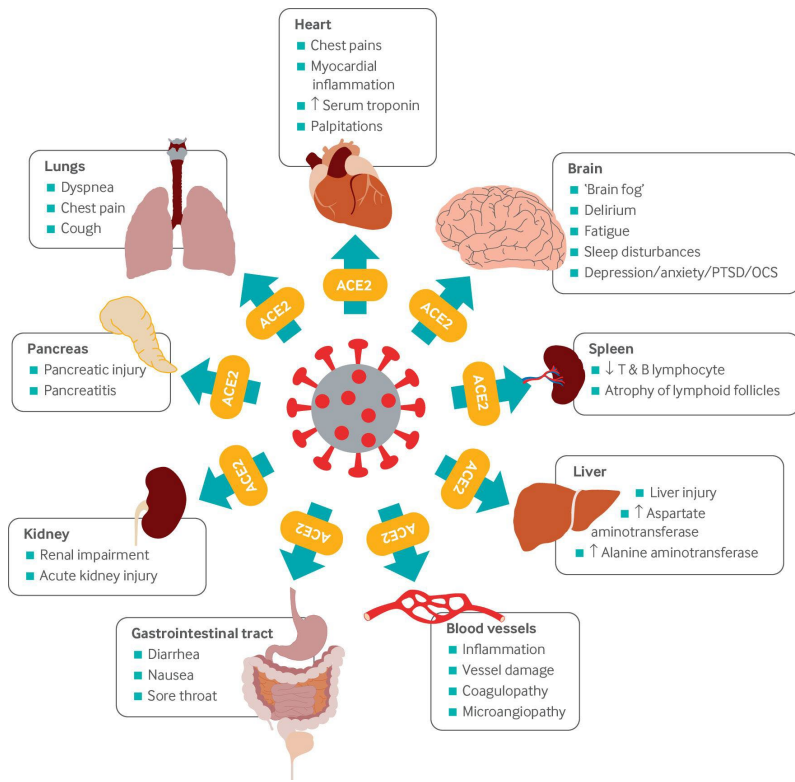
- ▶ **Background:** The incidence of persistent clinical symptoms and risk factors in Post-Acute Sequelae of SARS-CoV-2 (PASC) in diverse US cohorts is unclear. While there are a disproportionate share of COVID-19 deaths in older patients, ethnic minorities, and socially disadvantaged populations in the USA, little information is available on the association of these factors and PASC.
- ▶ **Conclusions:** Three in ten survivors with COVID-19 developed a subset of symptoms associated with PASC in our cohort. While ethnic minorities, older age, and social disadvantage are associated with worse acute COVID-19 infection and greater risk of death, our study found no association between these factors and PASC.
- ▶ Associated with diabetes, longer hospitalization, higher BMI
- ▶ 30% of patients get Long Covid : A person was determined to have the syndrome if they reported persistent symptoms on questionnaires 60 or 90 days after infection or hospitalization.

Post Acute Sars-Cov Symptoms (PASC): predictability at initial diagnosis:

Predictability: possible- study looking at patient phenotypes at initial dx of Covid

- ▶ Four Factors:
- ▶ Autoantibodies
- ▶ Pre-existing Type 2 diabetes immune compromise
- ▶ SARS-CoV-2 RNA levels in the blood (viral load)
- ▶ Epstein-Barr virus DNA levels in blood EBV

- ▶ *severity of symptoms not linked with PASC
- ▶ *early blood viral measurements are strongly associated with certain long COVID symptoms that patients will develop months later
- ▶ *EBV reactivated early on after SARS-CoV-2 infection
- ▶ The current disparities between long covid epidemiology reporting are owing to many reasons, including the length of follow-up period, population assessed, accuracy of self-reporting, and symptoms -



Recent studies out of UK highlighting role of various factors: autoantibodies and immune system

Viral effects on Brain, Autonomic Nervous System:

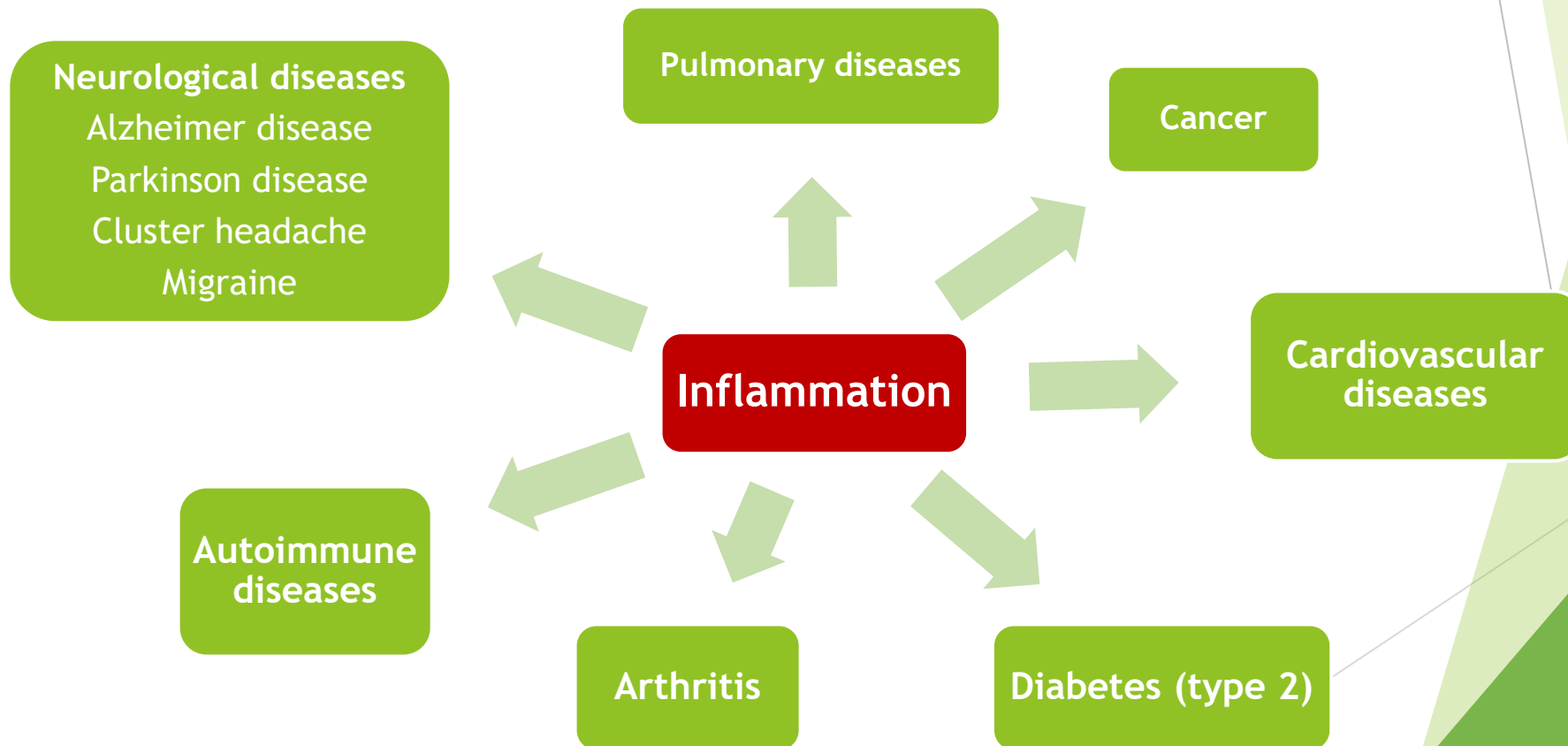
*Persisting viral infection and/or Post-viral immune reaction

*Proinflammatory cytokine-chemokine profile

*Dysautonomia theory underlying pathophysiology of a subset of Long COVID/PASC patients

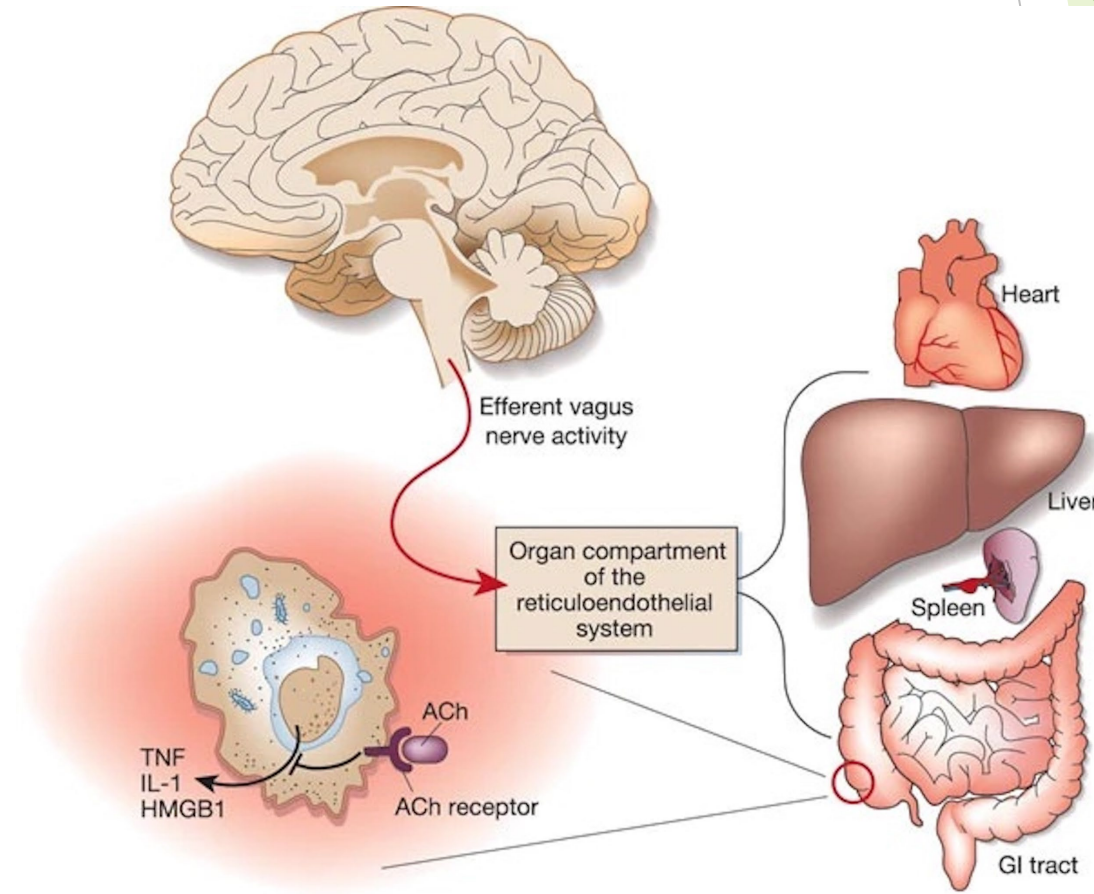
- ▶ Most Common: **Widespread Pain**
- ▶ Joint Pain
- ▶ Treatment: Stellate Ganglion Block looked at with several case studies highlighting improvement
- ▶ Vagal nerve stimulators
- ▶ Neuromodulation
- ▶ Neuropathic agents
- ▶ Anti-inflammatory agents
- ▶ Fatigue,
- ▶ Sleep disorders,
- ▶ Orthostatic intolerance
- ▶ High Heart Rate
- ▶ Respiratory disease
- ▶ Brain Fog
- ▶ Loss of taste and Smell

Need to fight and quiet the inflammatory response triggered by covid and present in PASC



Neuroimmune Mechanism

- ▶ Efferent vagal activity
- ▶ Release of acetylcholine
- ▶ ACh binds receptors
- ▶ Triggers immune inhibition and modulations



Multi-inflammatory system - children

- ▶ MIS-C is an inflammatory response to infection by SARS-CoV-2, the mechanism behind the development of the syndrome is not yet well understood.
- ▶ MIS-C is a serious though rare condition in children in which the body's own immune system overreacts to a SARS-CoV-2 infection, resulting in inflammation of multiple organ systems throughout the body.

Endogenous Control of Inflammation

Immune system control is critical for survival...
 Thus, the body has several “braking” mechanisms for inhibiting inflammation

	<p>Suppressors of cytokine signaling (SOCS) proteins</p>	<p>Anti-inflammatory cytokines (eg, IL-1ra, IL-4, IL-10)</p>	
	<p>Circulating Hormones and cell receptors (corticosteroids)</p>	<p>Neurotransmitters (norepinephrine and acetylcholine)</p>	

Abbreviations: CIS, cytokine-inducible SH2-containing protein; IL, interleukin; JAK, janus kinase; STAT, signal transducer and activator of transcription.

Non-invasive Vagus Nerve Stimulation (nVNS)


- ▶ Relevant mechanisms
 - ▶ Efferent sympathetically mediated catecholamine release → smooth muscle relaxation → bronchodilation
 - ▶ Suppression of inflammatory cytokines via activation of the cholinergic anti-inflammatory pathway

Neuromodulation: Technology at the Neural Interface

Received: April 22, 2020 Revised: April 23, 2020 Accepted: April 23, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13172

The Use of Non-invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated With COVID-19: A Theoretical Hypothesis and Early Clinical Experience

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a pandemic with no specific therapeutic agents and substantial mortality, and finding new treatments is critical. Most cases are mild, but a significant minority of patients develop moderate to severe respiratory symptoms, with the most severe cases requiring intensive care and/or ventilator support. This respiratory compromise appears to be due to a hyperimmune reaction, often called a cytokine storm. Vagus nerve stimulation has been demonstrated to block production of cytokines in sepsis and other medical conditions. We hypothesize that non-invasive vagus nerve stimulation (nVNS) might provide clinical benefits in patients with respiratory symptoms similar to those associated with COVID-19.

Materials and Methods: Information on two case reports was obtained via email correspondence and phone interviews with the patients.

Results: Both patients reported clinically meaningful benefits from nVNS therapy. In case 1, the patient used nVNS to expedite symptomatic recovery at home after hospital discharge and was able to discontinue use of opioid and cough suppressant medications. In case 2, the patient experienced immediate and consistent relief from symptoms of chest tightness and shortness of breath, as well as an improved ability to clear his lungs.

Conclusions: Preliminary observations and a strong scientific foundation suggest that nVNS might provide clinical benefits in patients with COVID-19 via multiple mechanisms.

Keywords: Cholinergic anti-inflammatory pathway, COVID-19, cytokine storm, neuromodulation, non-invasive vagus nerve stimulation, respiratory symptoms

Conflict of Interest: Peter Staats, is an employee and was cofounder of electroCore, Inc., and receives stock ownership. Justyna Blake and Eric Liebler are employees of electroCore, Inc., and receive stock ownership. Georgios Giannakopoulos owns stock in electroCore, Inc. In the previous three years, Robert Levy has served as a consultant for Abbott, Saluda, Nalu, and Mainstay Medical and has stock options with Nalu and Saluda.

Stellate Ganglion Block

- ▶ Jan 2022 case reports
- ▶ Anchorage
- ▶ Impaired CBF is associated with dysautonomia syndromes that share symptoms with Long COVID, namely myalgic encephalitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS).
- ▶ Aberrant network adaptation to sympathetic/parasympathetic imbalance is expected to produce long-standing dysautonomia. Cervical sympathetic chain activity can be blocked with local anesthetic, allowing the regional autonomic nervous system to “reboot.”

The stellate ganglion block has been used for nearly a century to treat a variety of sympathetically mediated medical conditions. Its safety profile is well established. Its application in treating Long COVID/PASC is novel but promising. The lack of effective treatments for Long COVID/PASC makes the SGB an attractive therapeutic modality that deserves further investigation.

Treatment and Management of PASC

- ▶ Symptomatic treatment of various aspects of symptoms
- ▶ Multidisciplinary approach
- ▶ Consider newer treatment : Vagal nerve stimulator to address reversing inflammation mechanism
- ▶ Stellate ganglion block- address autonomic system aspects
- ▶ Anti-inflammatory
- ▶ Anti-viral (paxlovid)

Public Health Measures:

Does Vaccination make a difference?

UK study: vaccination can decrease risk of Long Covid however breakthrough infections and mild symptoms do not preclude the possibility of developing LONG COVID

Vaccines with continued consideration of variants role in Long Covid, vaccines specific or modified, booster recommendation, oral treatments, antibody infusions

Growing number of people with long standing constellation with symptoms including widespread or localized pain syndromes in our society

Continued R & D to establish management and treatment

Case studies, longitudinal studies

Resources and Policy

References

- ▶ Barek A, Aziz A, Safiqueel Islam M. Impact of age, sex, comorbidities, and clinical symptoms on the severity of COVID-19 cases: a meta-analysis with 55 studies and 10014 cases. *Heliyon*. 2020;6(12):e05684
- ▶ Lieberman, NAP, Peddu, V, Xie, H. In vivo antiviral host transcriptional response to SARS-CoV-2 by viral load, sex, and age. *PLoS Biol*. 2020; 18(9)
- ▶ Predicting Long COVID at initial point of COVID-19 diagnosis: Study finds several warning factors." *ScienceDaily*.
www.sciencedaily.com/releases/2022/01/220120165100.htm (accessed May 2, 2022).
- ▶ Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *PAIN* 2020;161:1694-7.
- ▶ Attal, Nadine et al. "Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic." *Pain reports* vol. 6,1 e884. 27 Jan. 2021, doi:10.1097/PR9.0000000000000884

References continue:

- ▶ Office for National Statistics. *Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 16 September 2021* (ONS, 2021)
- ▶ Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management *BMJ* 2021; 374 :n1648 doi:10.1136/bmj.n1648
- ▶ <https://www.yalemedicine.org/conditions/multisystem-inflammatory-syndrome-in-children-mis-c>
- ▶ Liu LD, Duricka DL. Stellate ganglion block reduces symptoms of Long COVID: A case series. *J Neuroimmunol.* 2022 Jan 15;362:577784. doi: 10.1016/j.jneuroim.2021.577784. Epub 2021 Dec 8. PMID: 34922127; PMCID: PMC8653406.