LONG COVID

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The Definition

- The many names of COVID
- CDC and WHO Definitions
- Diagnosis of Exclusion
Known by Many Names...

- Long COVID
- Post-COVID Syndrome
- Long-haul COVID
- Post-acute COVID
- Post-acute sequelae of COVID (PASC)

...Still Only One Syndrome (we think)
“The occurrence of new, returning, or ongoing health problems 4 or more weeks after an initial infection with SARS-CoV-2.”

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html
“Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis.”

Common symptoms: include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning.

Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.”

https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
Long COVID

- No diagnostic test
- Diagnosis of exclusion

Long COVID

Many other things
Prevalence

Current prevalence of Long COVID is unclear...
- Lack of clarity over case definition
- Difficult to distinguish from other post-illness conditions
Prevalence:
Difficulty in Differentiation

Difficult to separate what is Long COVID versus what is:

- Post-sepsis syndrome
- Post-intensive care syndrome
- Exacerbation of pre-existing conditions
- Complications of treatments
- Complications of interventions that occurred while hospitalized
Prevalence: Post-Intensive Care Syndrome

Symptoms remaining after critical illness from any cause:

• ICU-acquired weakness: Up to 50% of patients who stay for at least one week
• Cognitive dysfunction: 30-80% of patients
• Post-Traumatic Stress Disorder (PTSD), depression, anxiety, difficulty with sleep

https://www.sccm.org/MyICUCare/THRIVE/Post-intensive-Care-Syndrome
Prevalence: Post-Sepsis Syndrome

Symptoms remaining after critical illness from infection:

• Over 1 million individuals in the U.S. survive an episode of sepsis each year
• One-sixth have persistent physical disability
• Many are readmitted to the hospital
• One-third die in the year following the sepsis episode

Prescott HC and Angus DC. JAMA. 2018.
Iwashyna TJ, et al. JAMA. 2010.
Currently experiencing long COVID, as a percentage of all adults

Data from the U.S. Census Household Pulse Survey

- 40% U.S. adults report having had COVID
- 35% U.S. adults who had COVID report ever having long COVID symptoms
- 7.5% U.S. (1 in 13) adults report current long COVID symptoms

https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm
Prevalence of Long COVID may be higher

• Data from international surveys
• 35-54% of patients with mild acute COVID had persistent symptoms at 2-4 months
• 50-76% reported new symptoms not present during acute COVID or that resolved then reappeared
• 9% reported symptoms as severe

Salmon-Ceron et al. J. Infect. 2020.
Petersen et al. Clin Infect Dis. 2020
Nehme et al. Ann Intern Med. 2020.
The Risk Factors for Long COVID

- Not well-known
- Hospitalization during acute infection
- Females > males
- Middle-aged adults > older adults
- High viral load during active infection
- Unvaccinated > vaccinated
| Phase          | Jun 1 - Jun 13, 2022 |
|---------------|----------------------|
|               | Percent | 95% CI     |
| National Estimate |        |            |
| United States  | 7.5      | 7.1 - 7.9  |
| By Age         |          |            |
| 18 - 29 years  | 8.4      | 7.0 - 9.9  |
| 30 - 39 years  | 7.8      | 7.0 - 8.6  |
| 40 - 49 years  | 8.8      | 7.9 - 9.7  |
| 50 - 59 years  | 8.5      | 7.4 - 9.7  |
| 60 - 69 years  | 6.6      | 5.8 - 7.5  |
| 70 - 79 years  | 5.0      | 4.0 - 6.2  |
| 80 years and above | 2.8 | 2.0 - 3.8  |
| By Sex         |          |            |
| Female         | 9.4      | 8.9 - 10.0 |
| Male           | 5.5      | 5.0 - 6.0  |
| By Gender identity |      |            |
| Cis-gender male | 5.3      | 4.8 - 5.8  |
| Cis-gender female | 9.4      | 8.8 - 10.0 |
| Transgender    | 14.9     | 9.5 - 21.8 |
| By Sexual orientation | |            |
| Gay or lesbian | 6.6      | 4.6 - 9.1  |

Data from the U.S. Census Household Pulse Survey

https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm
One in five patients not requiring supplemental oxygen during hospitalization had abnormal lung function after 6 months.
Long COVID

Highly variable symptoms
Pathophysiology
Evaluation/Treatment
Long COVID Symptoms

Most common:
Fatigue
Headache
Attention Disorder
Dyspnea/Altered breathing
Depression/Anxiety

Lopez-Leon S, et al. Sci Rep. 2021.
Angiotensin-converting enzyme 2 (ACE2) receptor

- Point of entry for SARS-CoV-2
- Elicits a downstream pro-inflammatory response, oxidative stress

Crook H, et al. BMJ. 2021.
SARS-CoV-2 and the Renin Angiotensin System (RAS)

- Virus upregulates the harmful and downregulates the protective arms of RAS
- High levels of Ang II
- Low levels of Ang 1-7, Ang 1-9

Latil M, et al. Drug Discovery Today. 2021.
Viral mediated parenchyma damage; immune mediated microvascular damage

a) Virus binds to ACE2 → cells release DAMPs/PAMPs
b) Macrophages release IL1 and TNF-alpha → neutrophils attracted to site
c) Neutrophils release chemokines → vascular permeability increased, differentiation of fibroblasts into myofibroblasts
d) Release of protein-rich exudate to interstitial space
e) Myofibroblasts release collagen, fibronectin, and ECM in response to TGF-beta → excess scar tissue deposition despite infection resolution

Dyspnea, hypoxia, fatigue, ground glass opacities and pulmonary fibrosis

Pathophysiology: Pulmonary

*DAMP = Damage Associated Molecular Patterns
*TNF = Tumor Necrosis Factor *ACE2 = Angiotensin-Converting Enzyme 2
*PAMP = Pathogen-Associated Molecular Pattern *ECM = Extracellular Matrix

Joshee S, et al. Mayo Clin Proc. 2022.
### Long COVID Symptoms: Pulmonary

| Presentation                                                                 | Evaluation/Treatment                                                                 |
|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| • Cough, shortness of breath, fatigue, chest pain, decreased exercise tolerance | • 6-minute walk test, Timed Up and Go (TUG) Test                                       |
| • Secondary symptoms of palpitations, dizziness, anxiety can be exacerbated by shortness of breath | • Pulmonary function tests                                                            |
| • Chest myopathy from COVID-19 skeletal muscle injury and viral airway hyperresponsiveness contribute | • CT scan – ground glass opacities or fibrotic changes                                   |
| • Vagal nerve inflammatory mediators and vocal cord dysfunction may be implicated | • Evaluate for sleep apnea – especially those with fatigue                             |
|                                                                              | • Pulmonary rehabilitation                                                              |
|                                                                              | • Drugs used to treat idiopathic fibrosis (pirfenidone, nintedanib, prednisolone)      |

Joshee S, et al. Mayo Clin Proc. 2022. www.sandiegocounty.gov/COVIDHealthProfessionals.
Pathophysiology: Cardiovascular

**Immune-mediated myocardial and microvascular destruction.**

a) Endothelial cell disruption similar to pulmonary
b) Increased cardiometabolic demand → myocardial injury via hypoxia and overuse
c) Chronic myocarditis and IL6 → fibrofatty replacement
d) Fibrofatty replacement → reentrant arrhythmias and sudden cardiac arrest and death
e) Medications also induce cardiotoxicity and electrolyte imbalances

_Chest pain, palpitations, pericarditis, myocarditis, fibrosis, arrhythmias/death_

*Joshee S, et al. Mayo Clin Proc. 2022.*

*IL = Interleukin*
## Long COVID Symptoms: Cardiovascular

| Presentation                                                                 | Evaluation/Treatment                                                                 |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| • Chest discomfort and palpitations, exercise Intolerance                    | • EKG may show tachycardia or PVCs                                                   |
| • Dysautonomia (tachycardia and orthostasis)                                 | • Echocardiogram typically normal                                                   |
| • Postural Orthostatic Tachycardia Syndrome (POTS); occurs typically in females of childbearing age | • Orthostatic vital signs and, if needed, tilt-table testing                          |
| • Increased troponin, myocarditis, cardiac fibrosis                           | • Continue ACE-inhibitors, ARBs                                                      |
| • Important to evaluate for hypertrophic cardiomyopathy, particularly in young athletes | • For POTS: propranolol, ivabradine being studied                                    |
| • Resolution of symptoms generally a very slow process                       |                                                                                      |

Joshee S, et al. Mayo Clin Proc. 2022.  
www.sandiegocounty.gov/COVIDHealthProfessionals.
Pathophysiology: Neurological

*BBB = Blood Brain Barrier *PNS = Peripheral Nervous System *HIF-1 = Hypoxia-Inducible Factor I

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Immune-mediated damage to BBB & thromboembolism; viral mediated hypoxia and damage to PNS

- a) inflammatory markers increase leakage and allow leukocyte infiltration and basement membrane modification
- b) Megakaryocytes in the parenchyma of alveolar tissue which may travel into the brain tissue due to endothelial disruption
- c) Hypoxia due to hypercoagulable state → HIF-1 increase → increase in BBB permeability and prolonged cytokine release

**Neuropsychiatric, cognitive and peripheral nerve pathologies**

Joshee S, et al. Mayo Clin Proc. 2022.
## Long COVID Symptoms: Neuropsychiatric

| Presentation | Evaluation/Treatment |
|--------------|----------------------|
| • Symptoms often disabling but poorly defined | • Standard noninvasive screening tools |
| • Headache, poor cognitive performance, attention deficit, memory deficit, abnormal sensation, ataxia, chronic fatigue | • Several drugs in trial |
| • Anosmia, olfactory symptoms | • Vaccine may be protective against neurologic sequelae |
| • Females at greater risk | • For anosmia: nasal steroids |
|                           | • Many improve in 6 to 12 months |

www.sandiegocounty.gov/COVIDHealthProfessionals
## Long COVID Symptoms: Rheumatology

| Presentation                                                                 | Evaluation/Treatment                                           |
|----------------------------------------------------------------------------|---------------------------------------------------------------|
| • Fatigue and pain: joint pain, localized pain - especially back and neck   | • Acupuncture, graduated exercise program                      |
| • Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: post exertion worsening of symptoms, unrefreshing sleep, cognitive impairment | • Electrotheraphy - TENS for localized pain                    |
| • Fibromyalgia: pain generalized, fatigued, unrefreshing sleep (female & prior use of corticosteroids increases risk) | • Replace low vit D, Mg (may help with HA and pain)           |
| • Relapse Triggers: physical activity, stress, exercise, mental activity, menstruation | • Amitriptyline (good w/poor sleep), duloxetine                |
| • Exclude autoimmune disorders that mimic Long COVID                       | • For neuropathic symptoms:                                   |
|                                                                            | • gabapentin, pregabalin                                       |

www.sandiegocounty.gov/COVIDHealthProfessionals.
Long COVID Symptoms: Emotional & Mental Health

| Presentation                                                                 | Evaluation/Treatment                                      |
|-----------------------------------------------------------------------------|-----------------------------------------------------------|
| • Traumatized with memories of illness, PTSD                                | • Cognitive Behavioral Therapy                            |
| • Disturbed by cognitive symptoms – brain fog                               | • Breath retraining and relaxation                        |
| • Frustrated, angry, sleep-deprived and frightened                          | • Physical activity                                       |
| • May feel that symptoms will never resolve                                 | • Natural sunlight helps regulate mood and sleep          |
| • Anxiety and depression may occur or be triggered in patients with previous history | • Address sleep hygiene                                   |
| • Important to address cognitive impairments                                | • Compensatory cognitive training for brain fog            |

www.sandiegocounty.gov/COVIDHealthProfessionals.
Long COVID in children is less well-studied but can occur
Long COVID in Children and Teens

Post-viral airway hyperresponsiveness – exacerbated in those with history of asthma, atopia, smoking parent

Increased anxiety and depression

Cognitive changes most challenging

May unmask diabetes

www.sandiegocounty.gov/COVIDHealthProfessionals
Multisystem Inflammatory Syndrome in Children (MIS-C)

- Presents 2-6 weeks after initial infection
- Diagnostic Criteria – age ≤21 years, fever ≥38°C or ≥24 hours, lab evidence of inflammation, multiorgan system dysfunction
- Fever, rash, GI symptoms, shock
- Increase in inflammatory mediators, "cytokine storm"
- Frequent cardiac involvement

American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/
Long COVID
Treatments

- Supportive/rehabilitative services most useful at this point
- Medications - many ongoing trials, nothing with strong evidence
- Most aimed at re-balancing RAS – antioxidant and anti-inflammatory properties
Melatonin

- Hormone released by pineal gland and other organs
- Good safety profile
- Activator of nuclear factor erythroid 2-related factor (NRF2)
- Promotes production of intracellular antioxidants such as glutathione

Jarrott B, et al. Pharmacol Res Perspect. 2022.
Other Drugs under Review

- Statins
- Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)
- Monoclonal antibodies that block inflammatory mediators (TNF, IL-6)
- Antivirals used to treat mild-moderate COVID-19 (nermatrelvir/ritonavir)
- COVID-19 vaccine

Ayoubkhani D, et al. BMJ. 2022.
Carson E, et al. American J Therapeutics. 2022.
Crook H, et al. BMJ. 2021.
Jarrott B, et al. Pharmacol Res Perspect. 2022.
Longitudinal Study of hospitalized COVID-19 patients from Wuhan, China

At 6 months:
• 68% had at least one persistent symptom
  • Fatigue, muscle weakness (52%)
• 30% reported dyspnea
• 23% reported anxiety or depression

At 1 year:
• 49% had at least one persistent symptom
  • Fatigue, muscle weakness (20%)
• 26% reported dyspnea
• 26% reported anxiety or depression
• 88% of those formerly working had returned to work

Huang L, et al. Lancet. Jan 2021.
Huang L., et al Lancet. Aug 2021.
Much that we don't know
Lessons from prior pandemics:

• H1N1 Pandemic of 1918-1919
  • Individuals born during the pandemic had increased cardiovascular disease in adulthood compared to other birth cohorts
  • They also achieved a lower mean height in young adulthood compared to surrounding birth cohorts

• Influenza A2 outbreak in Helsinki, Finland of 1952
  • Maternal viral infection during the 2nd and 3rd trimester may have increased the risk of adult schizophrenia

• Mouse studies – viral infections affect brain cell development
  • Mazumder B, et al. J Developmental Origins of Health and Disease. 2010.
  • Mednick SA, et al. Arch Gen Psychiatry. 1988.
Influenza Pandemic 1918-1919

Cardiovascular Disease at 60-82 Years of Age by Birth Cohort

Mean Height at 19-27 Years by Birth Cohort at Enlistment 1941-1942

Mazumder B, et al. Journal of Developmental Origins of Health and Disease. 2010.
What is being done to help?

- $1.15 Billion in NIH grants for Long COVID research – Researching COVID to Enhance Recovery (RECOVER)
- Coverage for affected patients under American Disabilities Act 1990
- Some may qualify for Social Security Disability Insurance
COVID-19 Vaccine is the Best Prevention against Long COVID

• CDC recommends COVID-19 primary series vaccines for everyone ages 6 months and older, and COVID-19 boosters for everyone ages 5 years and older, if eligible

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/expect.html
https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html?s_cid=11747:covid%20vaccine%20schedule:sem.ga:p:RG:GM:gen:PTN:FY22
Key Points

Many patients who experience acute COVID-19 have lingering symptoms weeks to months after recovery from initial illness.

Risk of Long COVID is not directly linked to severity of acute COVID infection.

Inflammation appears to play a key role in the etiology of long COVID symptoms.

Multidisciplinary approach to treatment is important, emphasizing nonpharmacologic therapies.

Research is ongoing on possible drug treatments.