Long COVID-19: Long-Term Complications of COVID-19

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Learning Objectives
After attending this presentation, learners will be able to:

▪ Summarize the current understanding of the epidemiology of post-acute sequelae of COVID-19 (PASC)
▪ Describe the long-term health consequences of COVID-19
Long COVID = Long Hauler = Post COVID Conditions [CDC] = Post Acute Sequelae of SARS-CoV-2 Infection (PASC) [NIH]

Often referred to as "Long COVID," these symptoms, which can include fatigue, shortness of breath, "brain fog," sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and can range from mild to incapacitating. In some cases, new symptoms arise well after the time of infection or evolve over time.

Preliminary reports indicate some patients may develop a so-called "post-acute COVID-19 syndrome," in which they experience persistent symptoms after recovering from their initial illness. The syndrome appears to affect those with mild as well as moderate-to-severe disease. The incidence, natural history and etiology of these symptoms is currently unknown.

State of the Science

• Accepted case definition lacking
• True prevalence not established; multiple published cohort studies but almost all lack control groups without ongoing signs/symptoms
• Reports include patients throughout the age and disease spectrum (mild → severe), previously healthy, pregnant people and children
• Risk factors and pathophysiology under investigation
• Management strategies in evolution; no specific therapies identified to date

Annual Update on HIV Management: State-of-the-Art Updates on HIV, STIs, and COVID-19
April 30, 2021
Definition
• CDC uses the term **post-COVID conditions** to describe health issues that persist **more than four weeks** after first being infected with the virus that causes COVID-19

• **Types of Post-COVID Conditions**
  - **Long COVID** - range of symptoms
  - **Multiorgan effects** - can affect most body systems and include multisystem inflammatory syndrome (MIS) and autoimmune conditions
  - **Effects of COVID-19 Treatment or Hospitalization** – post ICU syndrome, PTSD

ARS Question 1
• **What proportion of patients with confirmed COVID-19 develop long term symptoms/organ dysfunction?**
  - 1. 5%
  - 2. 10%
  - 3. 25%
  - 4. 75%
  - 5. I don’t know

Persistent Symptoms in Patients After Acute COVID-19
• N=143 patients hospitalized in Italy
  - Mean age 56.5y
  - 53% female
  - 12.6% ICU admission

- [Graph showing persistent symptoms after acute COVID-19]
An app into which >4 million people in the US, UK and Sweden have entered symptoms. Data suggest some 10-15% of individuals with COVID-19 – even mild cases – do not recover quickly. In a subset, long COVID was more likely with increasing age and body mass index and female sex. > 5 symptoms in first week associated with long COVID (odds ratio = 3.53 (2.76-4.50)).

https://doi.org/10.1038/s41591-021-01292-y

COVID symptom study

Epidemiology Conclusions

- Incidence/prevalence data cover a broad range, depending on definitions and methods used
- All studies confounded to varying degrees by lack of control groups without lingering signs and symptoms
- Therefore, interpret with caution
- However, US has reported > 32m cases
  - So if prevalence only 10%, this = 3,200,000 people
Clinical Manifestations

- **Manifestations:**
  - Myocarditis
  - Ventricular arrhythmias
  - Cardiomyopathy

- **Pathogenesis:**
  - Direct invasion by the virus
  - Inflammation
  - Blunting of ACE2 receptors

- **Long-term consequences:**
  - Will there be an increase in heart failure as a result?

**COVID-19 and the heart**

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German study, n=100 patients
- Cardiac MRI performed median 71 days after COVID-19 diagnosis
- Cardiac involvement in 78%
- Ongoing myocardial inflammation in 60%
- Presence of chronic comorbidities, duration and severity of acute COVID-19, time since original diagnosis did not correlate with findings

Non-random sample likely biased toward cardiac findings.

Cardiac tissue from 39 consecutive autopsy cases included
- SARS-CoV-2 could be documented in 61.5%
- Viral load above 1000 copies per μg RNA could be documented in 41%
- A cytokine response panel consisting of 6 proinflammatory genes was increased in those 16 patients compared with 15 patients without any SARS-CoV-2 in the heart.
- Comparison of 15 patients without cardiac infection with 16 patients with more than 1000 copies revealed no inflammatory cell infiltrates or differences in leukocyte numbers per high power field.

26 competitive college athletes diagnosed with COVID-19 (RT-PCR)
- None were hospitalized
- Majority did not report symptoms
- 12 (46%) had evidence of myocarditis or prior myocardial injury by cardiac magnetic resonance imaging routinely performed for positive testing results (range, 12-53 days)

Persistent cardiac abnormalities identified not only in the elderly with multimorbidity but also among healthy young athletes.
COVID-19 and the lungs

- Manifestations:
  - Chronic cough
  - Fibrotic lung disease
  - Bronchiectasis
  - Pulmonary vascular disease

- Pathogenesis:
  - Inflammation ➔ Fibrosis
  - Thromboembolic disease

- Long-term consequences:
  - Will there be an increase in cases of COPD and/or pulmonary fibrosis as a result?

Pulmonary sequelae

- Acute manifestations
  - Pneumonia, ARDS, hypoxic respiratory failure

- Post-acute manifestations = Sx/signs of restrictive lung disease
  - After hospital discharge:
    - 30d: 55% decreased DLCO, 49% diminished respiratory muscle strength
    - 3mo: 25% decreased DLCO
    - 3mo: 71% with radiographic evidence of interstitial thickening and fibrosis

- If compounded on cardiovascular comorbidity, persistent decline in pulmonary function could have significant consequences

COVID-19 and the brain

- Manifestations:
  - Headaches
  - Dizziness
  - Trouble concentrating
  - Confusion
  - Hallucinations
  - Stroke

- Pathogenesis:
  - Inflammation
  - Direct viral invasion of brain
  - Hypoxemia

- Long-term consequences:
  - Will there be an increase in “COVID brain?”
Anosmia: SARS-CoV2 receptor: ACE2 in non-neuronal cells

Expression of ACE2 in sustentacular cells

Brann et al., Science Advances 2020

Long Term Neurologic Symptoms

Emotional health & wellbeing

At risk of a global mental and behavioral health crisis given sheer number of COVID-19 cases
New diagnoses of anxiety, insomnia, dementia and mood disorders as well as psychiatric disorders in general, were increased after COVID-19 illness.

Emotional & behavioral concerns

- A diagnosis of COVID-19, and subsequent need for physical distancing, has been associated with feelings of isolation and loneliness.
- COVID-19-related stigma has become pervasive and can result in a sense of hopelessness.
- Increasing reports of lingering malaise and exhaustion akin to chronic fatigue syndrome may leave patients with physical debility and emotional disturbance.
- Individuals recovering from COVID-19 may be at even greater risk (than general population) of depression, anxiety, PTSD, substance use disorder.


Management of Long COVID

- No proven management strategies/therapies yet
- CT.GOV search for “long COVID”
  - 449 studies
  - 217 interventional
- Many comparing various rehab strategies
- Some with cytokine antagonists (monoflukast, IL-7)
- Other random agents eg naltrexone, hyperbaric oxygen
- Anticipate many more to come
ARS Question 2

Can COVID-19 vaccines improve long COVID symptoms?

• 1. yes
• 2. no
• 3. maybe
• 4. I don’t know

Does Vaccination Help?

• Anecdotal reports
• Biologically plausible

UK study of 44 vaccinated pts with 22 unvaccinated controls [preprint]
US health agency will invest $1 billion to investigate ‘long COVID’

The National Institute of Health will fund researchers to study people’s recovery, and will host a biennial summit.

https://covid19.nih.gov/funding/open-funding-opportunities
Conclusions

• Likely large numbers of patients will experience long-term sequelae
• Multidisciplinary care approach will be needed
• Access for underserved populations is critical, including case management support for housing and food
• Listen to patients –
  MH care for anxiety and depression
  Referrals for counseling and peer support
• Rigorous observational and interventional trials required
• Public Health Messaging to avoid infection—it’s not all about COVID Mortality

Question-and-Answer Session

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