Long Covid and Lasting Lung Problems

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The mission of ALLERGY & ASTHMA NETWORK is to end the needless death and suffering due to asthma, allergies and related conditions through outreach, education, advocacy and research.
This will be recorded

The recording will be posted on our website shortly

MEET OUR SPEAKERS

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Conflicts of Interest

LS- I have no disclosures.

SBB- Receives funding for ACTIV-4c Study and RECOVER
COVID-19 Is Still “Down, but Not Out”... Nationally

There’s still a fair amount of COVID around, and I still don’t want to get it... The main reason is the data we see on long COVID is very concerning... Not just the chances that you’re going to feel crummy a few months from now, which is a real number, but the chances that you’re elevating your long-term risk of a heart attack or stroke, or diabetes or...
Roadmap for the Hour

What: What is Long COVID? Pulmonary Symptoms?

Why: What are the Biological Mechanisms?

Who: Do Pulmonary Conditions increase Long COVID Risk?

COVID-19 Is A Multi-Organ System Disease Acutely

- Symptoms
- Pathology
- Heart: Chest pain, Palpitations, Cardiac impairment, Myocardial inflammation, POTS
- Neurological system: Cognitive impairment, Fatigue, Disordered sleep, Memory loss, Tinnitus
- Lungs: Cough, Dyspnea, Abnormal gas exchange
- Immune system: Autoimmunity, MCAS
- Pancreas: Diabetes, Pancreas injury
- Gastrointestinal tract: Abdominal pain, Nausea, Gut dysbiosis, Viral persistence and viral reservoir
- Blood vessels: Fatigue, Coagulopathy, Deep vein thrombosis, Endothelial dysfunction, Microangiopathy, Microdyspla, Pulmonary embolism, Stroke
- Reproductive system: Erectile dysfunction, Reduced sperm count, Increased severity and number of premenstrual symptoms, Irregular menstruation

Davis et al Nat Microbio 2023
Newer Data Reaffirming

Newer & Larger Studies Corroborate This – Even Compared to Influenza
Newer & Larger Studies Corroborate This – Even in the Bay Area (LIINC Study)

Persistent Pulmonary Sx
ARDS Survivors Have Persistent PFT Abnormalities

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

Differential – Persistent Dyspnea

1. Post-viral reactive airways disease
2. Deconditioning
3. Organizing pneumonia
4. Post-ARDS fibrosis
5. PVD

Other: Reflux-associated cough, Pleuritis, NM disease, Vocal cord dysfunction, Tracheal stenosis, Tracheomalacia

Slide Credit: Dr. Kristin Schwab, UCLA
More than 2/3rds of ARDS survivors reported clinically significant fatigue symptoms 1 year after discharge.
The Why?

Pathophysiology

- Immune dysregulation
  - Persistent infection
  - Viral replication
  - Reactivation
  - Immune dysregulation, with or without reactivation of underlying pathogens, including herpesviruses such as EBV and HHV-8

- Microbiota dysbiosis
  - Impacts of SARS-CoV-2 on the microbiota and virome (including SARS-CoV-2 persistence)

- Autoimmunity and immune priming
  - Autoimmunity and primed immune cells from molecular mimicry

- Blood clotting and endothelial abnormalities
  - Microvascular blood clotting with endothelial dysfunction

- Dysfunctional neurological signalling
  - Dysfunctional signalling in the brainstem and/or vagus nerve

*Davis et al. Nature Microbio 2023*
Pathophysiology
Numerous Insights from LIINC Study
https://www.liincstudy.org/en/study-findings

WHO Case Definition: Post-COVID-19 Condition

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 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 (see Table 3 and Annex 2) which 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. A separate definition may be applicable for children.
There is no one “long COVID.” Each patient is unique & there are some common symptom clusters.

RECOVER Initiative - PASC Symptoms

- Observational Cohort Study of 9750 Patients
  - Using PROMIS Questionnaires
- Points Given Based On Specific A Symptoms is for PASC
  - Not most distressing
- 13 Most Common Symptoms
- More to come as imaging, pathology, and labs are collected
It’s extraordinary how many people [with Covid-19] have a post-viral syndrome that’s very strikingly similar to myalgic encephalomyelitis/chronic fatigue syndrome.

— DR. ANTHONY FAUCI
DIRECTOR OF NIAID, U.S. NATIONAL INSTITUTES OF HEALTH
MEMBER OF THE WHITE HOUSE CORONAVIRUS TASKFORCE

At LEAST 3-5 Main Symptom Clusters

- **Joint Pain-Myalgias-HA**
- **Chest Pain-DOE-Palps**

Pulmonary Comorbidities increase Risk?
OSA Increase Long COVID RISK In Adults and Not Children

Obstructive sleep apnea (OSA) has been associated with more severe COVID-19 illness. We explored whether patients with OSA were at higher risk for PASC using EHR data.

Three 'real world' data research networks within the RECOVER initiative (PCORnet, PEDSnet, N3C) participated in this analysis.

Definitions were harmonized across networks, with the exception of PASC, and adjusted for demographic and clinical factors.

Networks examined the risk of probable PASC in SARS-CoV-2 positive patients with and without pre-pandemic OSA diagnoses.

OSA was associated with increased risk of PASC among adult patients after adjusting for other comorbidities and COVID severity.

After adjustment, associations among children were not significant.

The association diminished among all networks after adjustment, suggesting confounding from associations between obesity, or other comorbidities, and PASC.

Adults with pre-existing OSA had increased odds of developing PASC and may benefit from increased monitoring after SARS-CoV-2 infection.

Asthma Associated with Increased Long COVID

- Meta-analysis of 13 studies
- 639 397 patients
- effect size = -0.0001; 95% CI, -0.0003 to -0.0001; P < .001),
- No significant publication bias
Asthma Control Worse After COVID

- Analysis of 10 studies
- 257,340 patients
- COPD was a risk factor associated with persistent symptoms after COVID-19 infection
- Significance may not be seen in all future studies (95% PI, 0.70 to 2.74)
- Concern that the results maybe less at COPD was a RF for death

COPD Likely Associated with Long COVID

- Analysis of 10 studies
- 257,340 patients
- COPD was a risk factor associated with persistent symptoms after COVID-19 infection
- Significance may not be seen in all future studies (95% PI, 0.70 to 2.74)
- Concern that the results maybe less at COPD was a RF for death

Meta-regression analysis for study size (effect size = −0.0002; 95% CI, −0.0003 to 0.0001; \( P = .66 \)) and Egger test (intercept = 0.23; 95% CI, 0.14 to 0.33; \( P = .69 \)) were both nonsignificant

Tanayott Jama 2023
CASE

• 45 yo F with PMHX for COVID in late 2020 who then developed PASC/Long COVID symptoms predominately brain fog, shortness of breath, fatigue, exercise intolerance, and chronic cough.
Work Up for Dyspnea, Fatigue, and Chronic Cough

• Dyspnea
  – Cardiac Pulmonary Evaluation Test
• Fatigue
  – Sleep Evaluation (Could need specialized Evaluation)
  – Exercise evaluation (6 min walk v CPET)
• Chronic Cough
  – Pulmonary Evaluation
Imaging

**Pulmonary**
- Chest X-Ray
- CT Scan
- PFT

**Cardiac**
- EKG/Halter (tilt table?)
- Echocardiogram
- 6 Min Walk Test vs CPET

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CXR

- Helpful screening tool
- About 50% of patients still had CXR abnormalities at 3 months
- But hard to get a lot of information

*Fogante et al Radiology 2022*
CT Scan

- 41 patients
- Gradual recovery after hospital discharge on serial CT scores.
- 47% of the pt with abnormal CT at 1 year
- Predominate Pattern with ground-glass opacity (GGO) with reticular pattern
- Correlated with PFTs
  - decreased total lung capacity and residual volume
- Patients with radiological abnormalities
  - older
  - current smokers
  - hypertensives
  - lower SaO$_2$
  - secondary bacterial infections during acute phase

\[ \text{Chan et al BMC Med 2021} \]

CT Scan

- 144 patients (79 men, median age 60)
- 3 chest CT scans and PFTs at 6, 12 mo and 2 years
- At D/C- fibrosis, thickening, honeycombing, cystic changes and dilation of the bronchi.
- Over two years-> gradually decreased.
- 6m - 54% of patients showed lung abnormalities.
- 2 yr -, 39% (56/144) lung abnormalities,
  - 23% with fibrotic lung
  - 16% with non-fibrotic lung.

\[ \text{Han et al Radiology 2023} \]
### Table 4: Comparison of Clinical Characteristics and Pulmonary Function at Three Follow-up Time Points

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>6 Months</th>
<th>12 Months</th>
<th>2 Years</th>
<th>$P$ Value</th>
<th>Adjusted $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual symptoms ($n=145$)*</td>
<td>43 (30)</td>
<td>36 (25)</td>
<td>32 (22)</td>
<td>.11</td>
<td>.12</td>
</tr>
<tr>
<td>Cough</td>
<td>23 (16)</td>
<td>16 (11)</td>
<td>15 (10)</td>
<td>.04</td>
<td>.06</td>
</tr>
<tr>
<td>Expectoration</td>
<td>18 (13)</td>
<td>15 (10)</td>
<td>15 (10)</td>
<td>.5</td>
<td>.5</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td>29 (20)</td>
<td>27 (19)</td>
<td>20 (14)</td>
<td>.04</td>
<td>.06</td>
</tr>
</tbody>
</table>

#### Pulmonary function

**Ventilation function**
- **Maximum VC**: 102 ± 21, 106 ± 18, 109 ± 18, $P < .001$, $P < .001$
- **FVC**: 103 ± 22, 108 ± 19, 110 ± 18, $P < .001$, $P < .001$
- **FEV₁**: 101 ± 22, 108 ± 19, 108 ± 19, $P < .001$, $P < .001$
- **FEV₁/FVC**: 94 ± 10, 96 ± 9.3, 95 ± 6.7, .007, .02

**Diffusion function**
- **Dco**: 80 ± 17, 82 ± 14, 84 ± 12, .007, .02
- **Dcco severity**: .08, .99
- **Dcco**: 69 (63)*, 73 (71), 91 (71), .02
- **Mild**: 32 (29), 27 (26), 35 (27), .02
- **Moderate**: 9 (8), 3 (8), 5 (2)
- **Severe**: 0, 0, 0
- **DccoVA**: 97 ± 17, 99 ± 18, 99 ± 18, .02, .04

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Notes:
- *Denotes number of participants with percentages in parentheses.
- $P$ values indicate comparisons with 2-year follow-up.

Han et al Radiology 2023

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### Diagrams

- **PFT**
- **DLCO**
- **FVC**
- **TLC**

Lee et al Resp Research 2022
PFT

Lewis et al Eclinical Med 2021

Long COVID and Heart

SIRIPANTHONG JACC 2023
EKG/Halter

- Around 10% of long COVID patients report palpitations.
- Up to 60% who reported tachycardia, with increase in heart rate from standing vs. sitting position in 1/3 of those (may be postural orthostatic tachycardia syndrome (POTS))
- Up to 20% had evidence of QTc prolongation

Cardiac Conditions - Echocardiogram

| Table 4 Cardiac complications and their prevalence in patients with long COVID |
|---------------------------------|------------------|------------------|
| Cardiac complications           | Patients with cardiac complications (%) | Patients included in study (n) |
| Chronic myocarditis            | 0.4-28.9%         | 48-543           |
| Chronic pericarditis           | 1.9-27%           | 26-105           |
| Myocardial oedema              | 15.4%            | 26               |
| Myocardial fibrosis or scar    | 4%               | 26               |
| Systolic or diastolic LV dysfunction | 0.06-35%     | 51-9983          |
| RV systolic dysfunction        | 7-22.6%          | 50-1414          |
| L.V hypertrophy                | 2%               | 51               |
| Coronary artery disease        | 8%               | 51               |
| Acute myocardial infarction    | 1.5-8%           | 51-47780         |
| Persistent systemic endothelial dysfunction | 2.5-6.1% | 72-133 |
| Coronary microvascular disease | 18%              | 22               |
| Heart failure                  | 0.1-2%           | 543-8903         |
| Pulmonary hypertension         | 10-50%           | 102-145          |

Studies with highly selected patient groups (e.g. only hospitalized and/or intensive care unit treatments, older age, or significant comorbidities as inclusion criteria) were excluded. LV, left ventricle; RV, right ventricle.
6 min walk test (6MWT)

a) Step 1: Resting $O_2$ Titration

- Measure $SpO_2$ without $O_2$ supply
- $SpO_2$ drops <85% in 2-3 minutes?
  - Yes: Oxygenate at 2 L/min
  - No: $SpO_2$ drops <85% in 2-3 minutes?
    - Yes: Oxygenate at 4 L/min
    - No: $SpO_2$ drops <85% in 2-3 minutes?
      - Yes: Oxygenate at 6 L/min
      - No: NOT eligible

Go to Step 2: Walking $O_2$ titration with a defined $O_2$ flow rate (of 2, 4, or 6 L/min)

b) Step 2: Walking $O_2$ titration

- $SpO_2$ drops <85% in 2-3 minutes?
  - Yes: Stop 6MWT at defined $O_2$ flow rate
  - No: $SpO_2$ drops <85% in 2-3 minutes?
    - Yes: Stop 6MWT
    - No: Increase $O_2$ to 2 L/min

Cardiopulm Exercise Test

Central Illustration: Development of PASC With Possible Causes and How These Can Be Classified Using CPET

TREATMENT

Pulmonary Trajectory

- Patients have seen improvement for around 1 year
  - This is in most not all patients
  - This improvement was most pronounced between 6-9 months
- Fibrosis is the least likely to improve
  - We have seen some improvement – something we did not think possible before
  - Traction bronchiectasis stayed and in some cases evolved
- Ground Glass persisted for longer
  - in most cases did regress
Pulmonary Treatments

- Persistent Ground Glass Opacities – Steroids or Immunosuppression (NCT04657484)
- Anti-fibrotic agents (pirfenidone and nintedanib) (NCT04541680, NCT04607928)
- Pulmonary Rehab - *post exertional malaise needs to be accounted for*
- Persistent Viral Infection– Paxlovid (NCT05576662).
- Inflammation? – Metformin
- Microthrombi (Decreased DLCO) – Anticoagulation/ASA – small clinical trials

Clinical trials.gov
Autonomic and Respiratory Reconditioning to Improve Health and Performance

Figure 3: Progressive or graded increase in activity to increase functional capacity

All that “Long-Hauls” is not COVID. Avoid anchoring & keep ddx broad throughout.
### Table 1 Summary of candidate treatments and supporting evidence

**From:** [Long COVID: major findings, mechanisms and recommendations](#)  *Davis et al Nature Microbio 2023*

<table>
<thead>
<tr>
<th>Symptoms and/or biological mechanism</th>
<th>Treatments</th>
<th>Supporting evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postexertional malaise</td>
<td>Pacing</td>
<td>ME/CFS literature</td>
<td>Exercise, cognitive behavioural therapy and graded exercise therapy are contraindicated</td>
</tr>
<tr>
<td></td>
<td>Pharmacological: β-blockers, pyridostigmine, fludrocortisone, midodrine</td>
<td>POTS and ME/CFS literature</td>
<td>Options can be prioritized on the basis of a specific constellation of symptoms</td>
</tr>
<tr>
<td>POTS</td>
<td>Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings</td>
<td>POTS and ME/CFS literature</td>
<td>-</td>
</tr>
<tr>
<td>Immune dysfunction</td>
<td>Intravenous immunoglobulin</td>
<td>ME/CFS literature</td>
<td>Consider consulting an immunologist on implementation</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Cognitive pacing</td>
<td>ME/CFS literature</td>
<td>Consider implementation alongside pacing physical exertion</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Postconcussion syndrome protocols</td>
<td>ME/CFS and postconcussion syndrome literature</td>
<td>-</td>
</tr>
</tbody>
</table>

### Possible Treatments Continued

**From:** [Long COVID: major findings, mechanisms and recommendations](#)  *Davis et al Nature Microbio 2023*

<table>
<thead>
<tr>
<th>Pain, fatigue, neurological symptoms</th>
<th>Low-dose naltrexone</th>
<th>ME/CFS and other literature</th>
<th>Substantial anecdotal reports of success within the patient community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, unrefreshing sleep, brain fog</td>
<td>Low-dose aripiprazole</td>
<td>ME/CFS literature</td>
<td>-</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>8C007</td>
<td>Long COVID case report</td>
<td>Neutralizes G protein-coupled receptor autoantibodies</td>
</tr>
<tr>
<td>Abnormal clotting</td>
<td>Anticoagulants</td>
<td>Long COVID pilot study</td>
<td>Additional trials in progress</td>
</tr>
<tr>
<td>Abnormal clotting</td>
<td>Apheresis</td>
<td>ME/CFS literature, long COVID pilot study</td>
<td>-</td>
</tr>
<tr>
<td>Viral persistence and antivirals (COVID-19)</td>
<td>Paxlovid</td>
<td>Long COVID case reports</td>
<td>No active trials, despite strong evidence for viral persistence</td>
</tr>
<tr>
<td>Viral persistence and antivirals (reactivations such as of EBV, HCMV and VZV)</td>
<td>Valaciclovir, famciclovir, valganciclovir and other antivirals</td>
<td>ME/CFS literature</td>
<td>-</td>
</tr>
</tbody>
</table>
Possible Treatments Continued

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Study Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial dysfunction</td>
<td>Sulodexide</td>
<td>Long COVID pilot</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Probiotics</td>
<td>Long COVID pilot</td>
<td>Resolved gastrointestinal and other symptoms</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>Splanchnic ganglion block</td>
<td>Long COVID case report</td>
<td>Effects may wax over time and require repeated procedures</td>
</tr>
<tr>
<td>Endothelial function, microcirculation,</td>
<td>Pycnogenol</td>
<td>COVID-19 pilot</td>
<td>-</td>
</tr>
<tr>
<td>inflammatory markers and oxidative stress</td>
<td></td>
<td>study</td>
<td></td>
</tr>
<tr>
<td>MCAS</td>
<td>$H_2$ and $H_3$ antihistamines, particularly lomustine</td>
<td>Long COVID case reports, MCAS literature</td>
<td>Expected to treat symptoms, not underlying mechanism</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Transcutaneous vagal stimulation</td>
<td>Long COVID pilot study</td>
<td>-</td>
</tr>
</tbody>
</table>

Davis et al. Nature Microbio 2023

Take Home Points

- Disentangling the PASC-E Unibus Pluram (From Many, One) & remember all that Long Hauls isn’t COVID

- Pulmonary or Cardiac Imaging can be helpful but does not tell the whole story

- If there are abnormalities seen inline other conditions then we can treat with medications for those conditions \(\text{fibrosis, obstruction, arrhythmia}, \text{etc}\)

- PASC treatments – will not be right for everyone – need to direct treatment both clinically and as research trials progress

- Listen to everyone in the room. Believe patients.
Thank You!

Questions?

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QUESTIONS

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Thank you!

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3:00 PM ET