Long COVID

Zanthia Wiley, MD, FHM, FIDSA
Associate Professor of Medicine
Emory Division of Infectious Diseases

Alex Truong, MD, MPH
Assistant Professor of Medicine
Emory Division of Pulmonary, Critical Care, Allergy and Sleep Medicine

Case

A 48 yo woman presents to the ED with ~ 3 yrs of extreme fatigue with “heart racing” with minimal exertion (mostly after walking short distances or cleaning homes). Forgets appointments. Hard to concentrate to help her children with homework. Takes 2 naps daily due to fatigue. Decreased her work hours.

- Had COVID Sept 2020, got one dose of a COVID vaccine in Spring 2021, and had COVID Jan 2022
- No chest pain, SOB, N/V, F/C
- A visiting family member (RN) was worried about her s/s and encouraged her to seek care. She presents to nearby ED (no PCP).

PMHx: None (only hospitalized for childbirth – last 9 yrs ago; recalls neg HIV test)

Medications: Occasional multivitamin

(not actual case)

Case

Social History: Married, 3 school-aged children, husband works as a painter. They are self-employed high school graduates. She has never travelled outside of Georgia. Pet dog (vaccinated/from shelter). Has never used IV illicit drugs. Marijuana in her 20s. Occasional wine or beer on the weekends. Her husband is her only sexual partner. They live in an apartment. She and her husband are unable to afford health insurance for family.

Vaccination History: Received all childhood vaccinations. Got one dose of COVID vaccine (she does not recall which one) Spring 2021.

Family History: HTN (mother)

(not actual case)

Physical Exam

Vital Signs: Temp – 36.8, P - 110, BP – 120/60 (not orthostatic), 99% on ambient air

General: no acute distress, well-developed, lying on the stretcher

HEENT: normal, no thyromegaly

Cardiovascular: tachycardic and regular

Abdomen: soft, nontender, no organomegaly

Extremity: no rashes or edema

Neuro: non-focal

Psych: normal affect

(not actual case)

Case – Diagnostic Studies

8 \ 13 / 250

/ 39\ Auto Diff - normal

MCV – 85

136 | 96 | 10 / 90

3.7 | 25 | 0.9 \

AST/ALT - normal

Extended chemistry - normal

Serum lactate – normal

(not actual case)

Case – Diagnostic Studies

EKG – sinus tachycardia

PA/Lateral Chest X-ray – normal

UA and Urine pregnancy test – negative

Rapid RSV/Flu/COVID – negative

Rapid HIV Ag/Ab – negative

TSH - normal

(not actual case)

Case Recap

A 48 yo woman with prior COVID (Sept 2020, COVID Jan 2022) presenting to the ED with ~ 3 yrs of post-exertional malaise, palpitations, brain fog, and fatigue that has significantly affected her quality of life. EKG with sinus tachycardia (benign labs and PA/Lat CXR).

(not actual case)

Final Diagnosis: Presumptive Long COVID

(not actual case)

Long COVID epidemiology

18–19% (nearly 1 in 5) of U.S. adults who reported ever having had COVID-19 currently have symptoms of long COVID, defined as symptoms lasting 3 or more months that were not present prior to having COVID-19.

8% (nearly 1 in 13) of U.S. adults (those with and without a previous COVID-19 diagnosis) currently have post-COVID conditions.

Women are more likely than men to currently have post-COVID conditions.

Percentages of adults reporting post-COVID conditions among those who had COVID-19 were not significantly different across racial/ethnic groups.

Bisexual adults and transgender adults were more likely to report currently having post-COVID conditions than adults of other sexual orientations and gender identities.

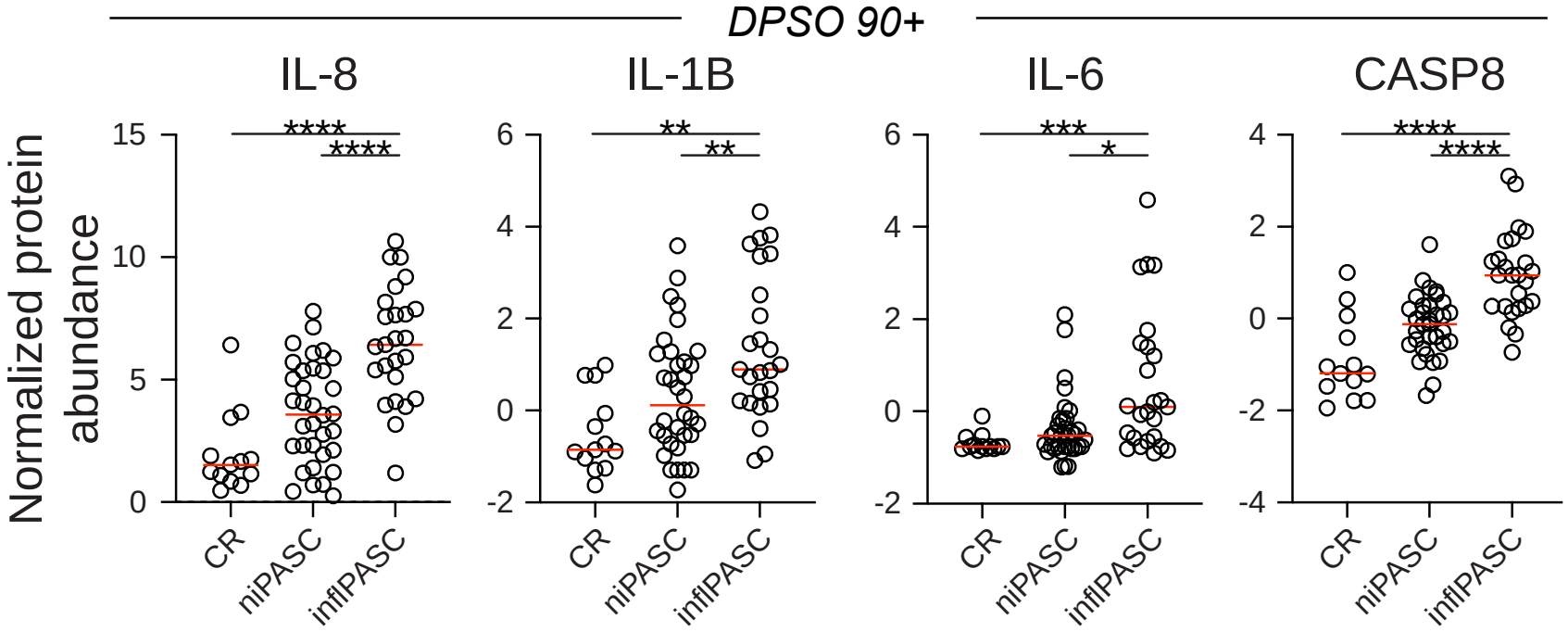
Adults with disabilities were more likely to report currently having post-COVID conditions than those without.

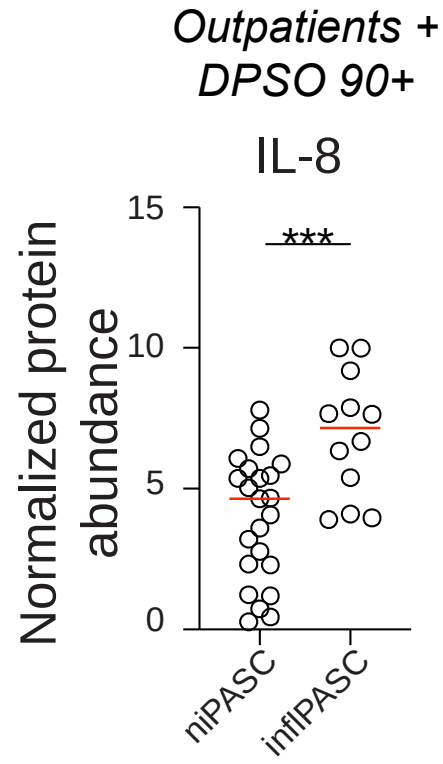
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

Proposed pathology

- Persistent inflammation
- Autoimmunity
- Persistent viremia
- Decreased serotonin levels
- Mast Cell activation syndrome
- Microthrombi

Long-COVID and inflammation





Woodruff and Bonham et. al. MedRxiv, 2022

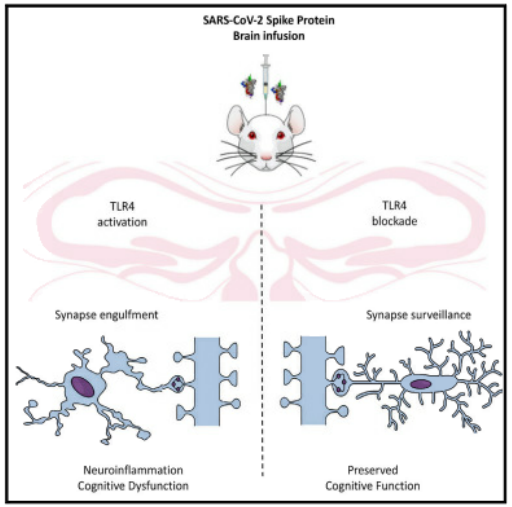
Long-COVID and Persistent Viremia

Article

Cell Reports

SARS-CoV-2 Spike protein induces TLR4-mediated long-term cognitive dysfunction recapitulating post-COVID-19 syndrome in mice

Graphical abstract



Authors

Fabricia L. Fontes-Dantas, Gabriel G. Fernandes, Elisa G. Gutman, ..., Soniza V. Alves-Leon, Giselle F. Passos, Claudia P. Figueiredo

Correspondence

dapoian@bioqmed.ufrj.br (A.T.D.P.), sonizavieiraalvesleon@gmail.com (S.V.A.-L.), gfazzioni@yahoo.com.br (G.F.P.), claudia@pharma.ufrj.br (C.P.F.)

In brief

Cognitive impairment is frequent in post-COVID-19 syndrome patients, but its underlying mechanisms are unclear. Fontes-Dantas et al. show that Spike brain infusion in mice induces late neuroinflammation and synapse loss, leading to long-term cognitive impairment mediated by TLR4 signaling. In patients, genotype GG TLR4-2604G>A was associated with poor cognitive outcome.

Highlights

- Spike protein infusion into mouse brain induces late cognitive dysfunction
- Spike protein induces late hippocampal microgliosis and synapse loss
- Blockage of TLR4 renders mice resistant to Spike-induced cognitive dysfunction
- *TLR4*-2604G>A GG genotype was related to poor cognitive outcome in COVID-19 patients

Cell Reports 42, 112189, March 28, 2023

- Rats showed cognitive decline after infusion of SARS-CoV2 spike proteins
- Increased ionized calcium binding adaptor molecule immunoreactivity, TNF-α, IFN-β, and IL-6
- Increased synaptic phagocytosis/synaptic pruning by microglial cells
- Spike protein induces TLR4 activation, which in turns actives microglial cells
- Blockage of TLR4 receptors mitigates effects

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Long-COVID and Decreased Serotonin Levels

ARTICLE | VOLUME 186, ISSUE 22, P4851-4867.E20, OCTOBER 26, 2023 Download Full Issue

Serotonin reduction in post-acute sequelae of viral infection

Andrea C. Wong • Ashwarya S. Devason • Iboro C. Umana • ... Sara Cherry • Christoph A. Thaiss • Maayan Levy [21] • Show all authors • Show footnotes

Open Access • Published: October 16, 2023 • DOI: https://doi.org/10.1016/j.cell.2023.09.013 •

Check for updates

Highlights
Summary
Graphical abstract
Keywords
Introduction
Results

Highlights

- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

- Long COVID patients have reduced circulating serotonin levels
- Driven by viral RNA induced type 1 interferon (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Reduced serum serotonin impairs cognition via reduced vagal nerve signaling

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Long-COVID and Mast Cell Activation Syndrome

Int J Infect Dis. 2021 Nov; 112: 217–226. Published online 2021 Sep 23. doi: 10.1016/j.ijid.2021.09.043

PMCID: PMC8459548 | PMID: 34563706

Mast cell activation symptoms are prevalent in Long-COVID

Leonard B. Weinstock,[a,*] Jill B. Brook,[b] Arthur S. Walters,[c] Ashleigh Goris,[d] Lawrence B. Afrin,[e] and Gerhard J. Molderings[f]

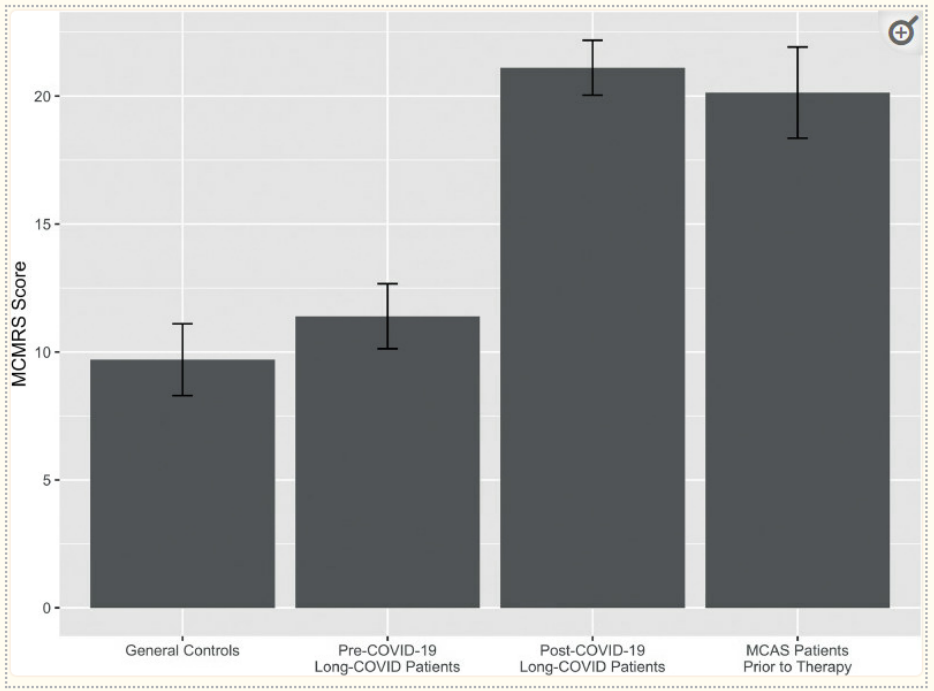

Figure 1

Mean mast cell mediator release syndrome scores for each group, with whiskers showing 95% confidence intervals.

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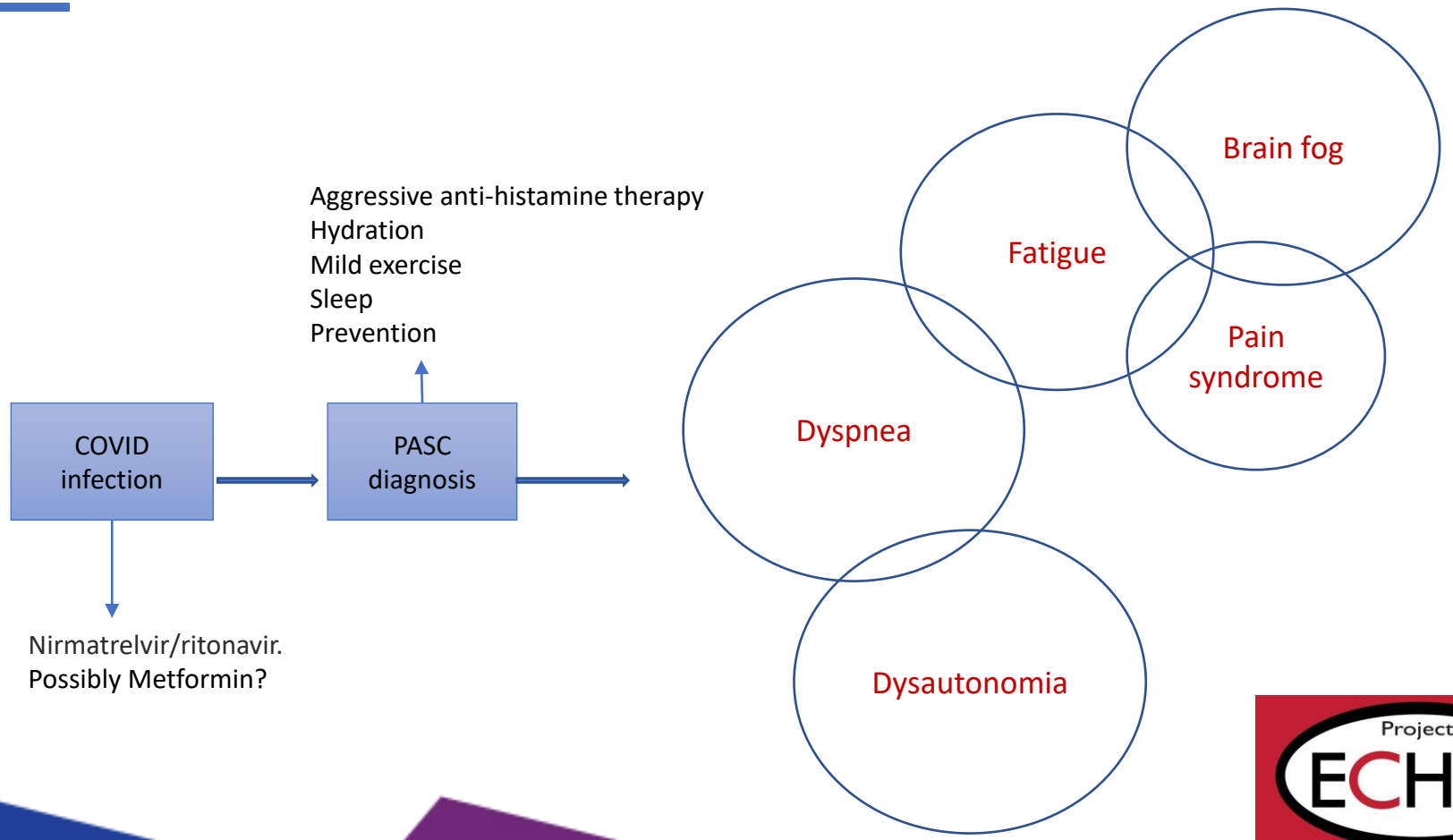
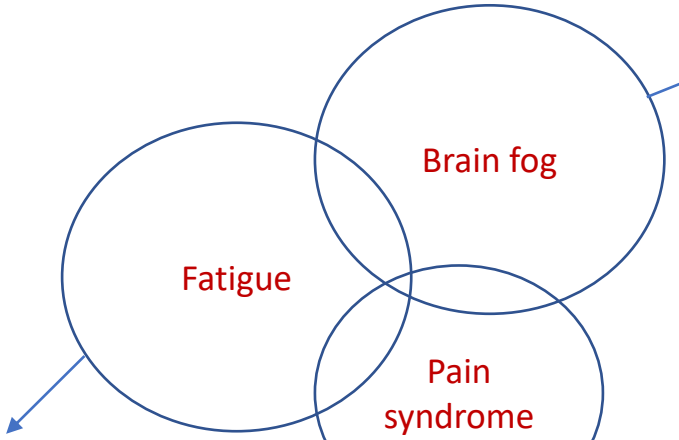
PROPOSED TREATMENT ALGORITHM



TREATMENT

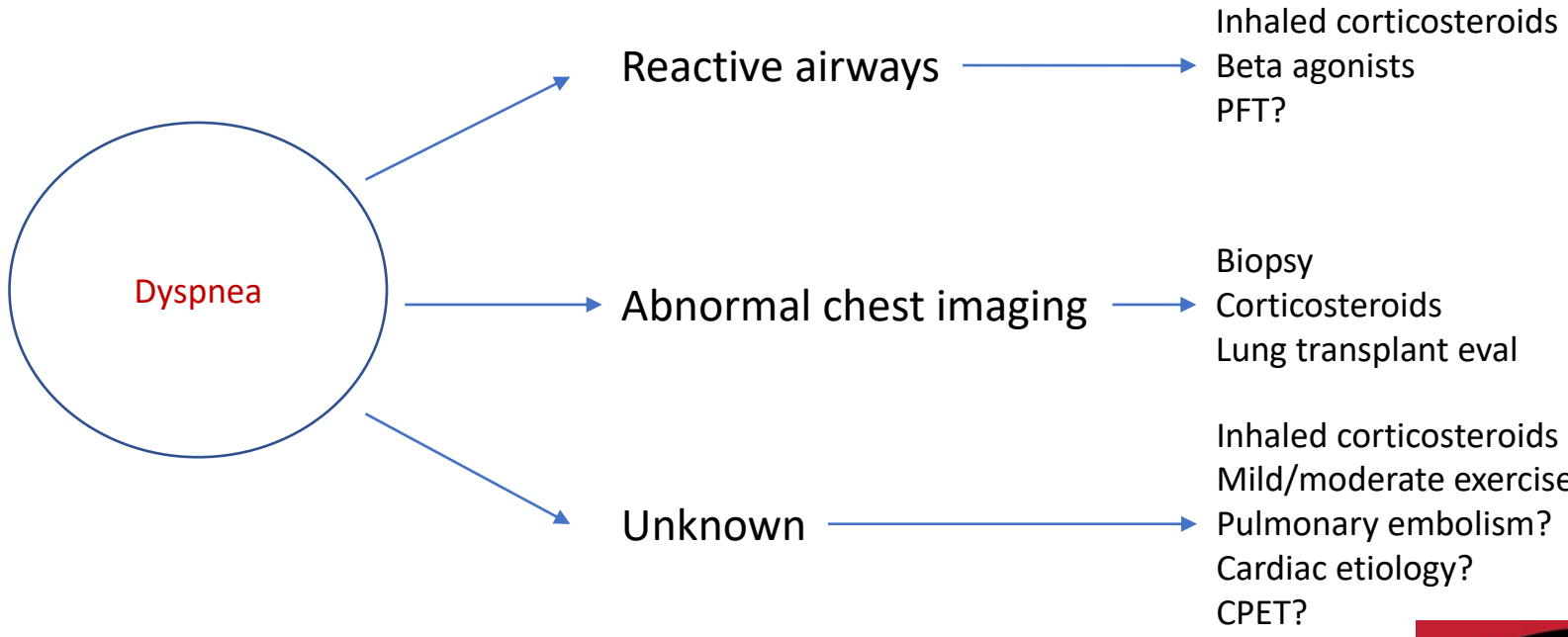


- Neuropsychological testing
- Stimulant vs. non-stimulant ADD medication
- SSRI/SNRI
- Brain imaging not helpful (unless there is focal pathology)

- Physical therapy
- Stimulants vs. non-stimulant ADD medication
- SSRI
- Tryptophan supplementation?

- High dose NSAIDS
- Gabapentin/pregabalin
- Duloxetine
- Low dose naltrexone
- Pain referral

TREATMENT


Dyspnea
Reactive airways
Inhaled corticosteroids
Beta agonists
PFT?
Abnormal chest imaging
Biopsy
Corticosteroids
Lung transplant eval
Unknown
Inhaled corticosteroids
Mild/moderate exercise
Pulmonary embolism?
Cardiac etiology?
CPET?

MEDICATIONS/INTERVENTIONS UNDER INVESTIGATION

- Naltrexone
- Nirmatrelvir
- High dose antihistamines
- Stellate ganglion blockade
- Anticoagulation
- Iliac vein stenting

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FUTURE DIRECTIONS AND THE GREAT UNKNOWN

- Is there one underlying pathology explaining post COVID syndrome?
- Are there multiple phenotypes and are the pathologies different depending on phenotypes?
- What potential roles do anti-inflammatory medications have?
- Will addressing attention help with brain fog?
- Does COVID infection change neurochemistry in ways we have yet to understand?

CONCLUSION

- Post-COVID syndrome is multi-system dysfunction that often limits patient's ability to work and function
- It is real. It is under recognized and under diagnosed.
- Inflammation may play a role, though we're still very early in our understanding of this.
- Lack of a central pathology to explain the syndrome.
- At this point, treatment centers around addressing individual symptoms.
- Still so much we don't know
- We need more physicians to take on this work

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