Post-COVID Syndromes: What Can We Do?

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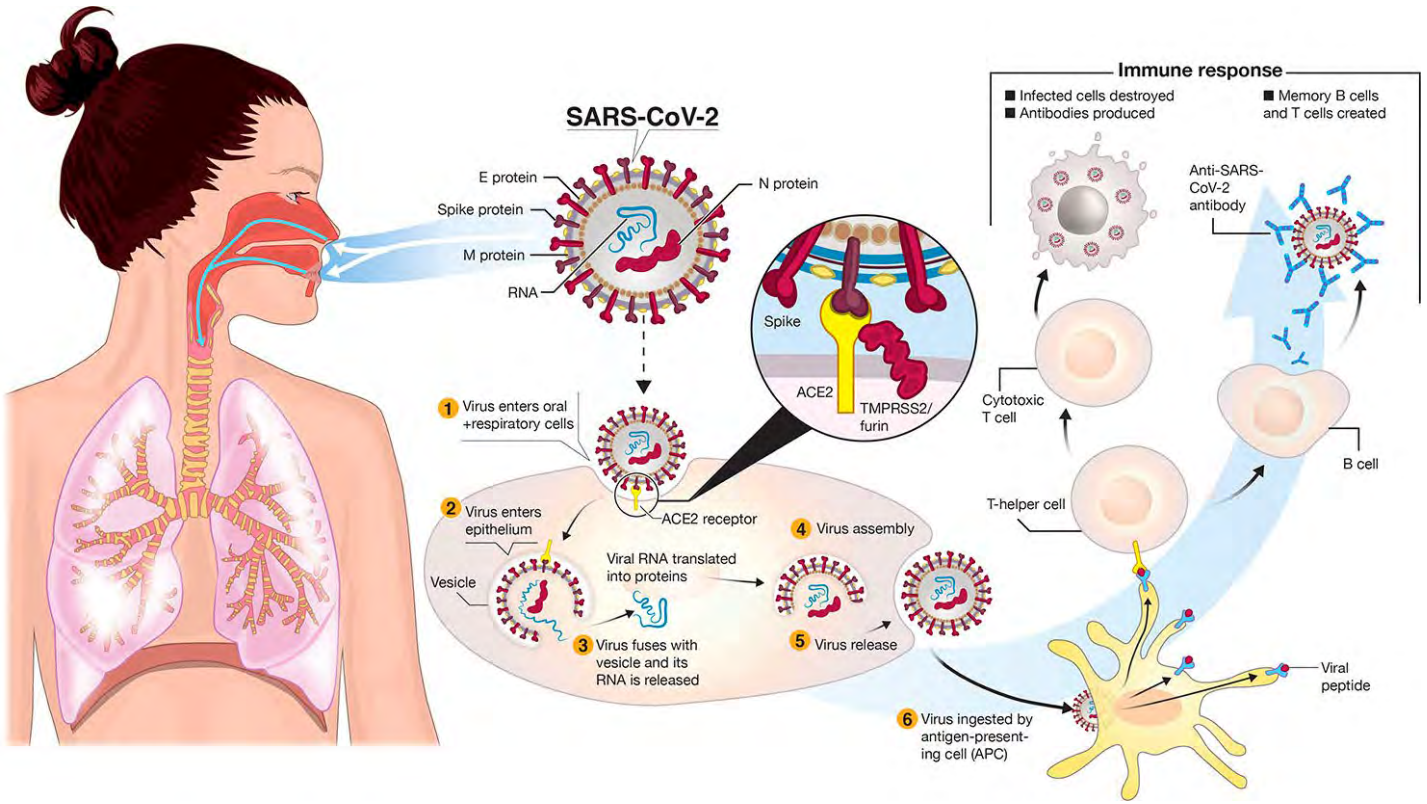
UT Health San Antonio

Disclosures

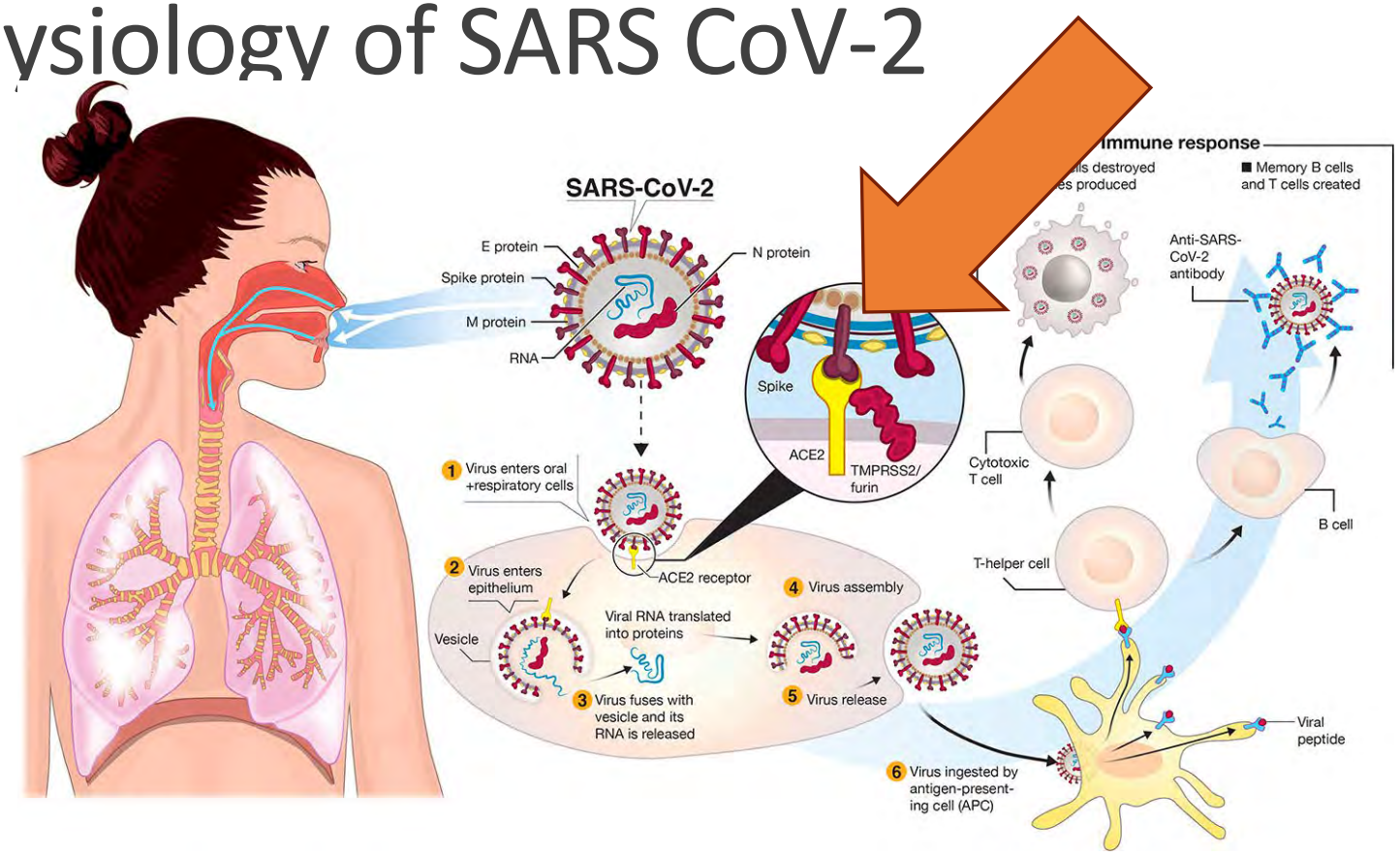
I have no conflicts of interest to disclose (I wish!!)

Physiology of SARS CoV-2



Funk CD, Laferrière C and Ardakani A (2020) A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic. Front. Pharmacol. 11:937.

Physiology of SARS CoV-2



Funk CD, Laferrière C and Ardakani A (2020) A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic. Front. Pharmacol. 11:937.

ACE2 Receptors

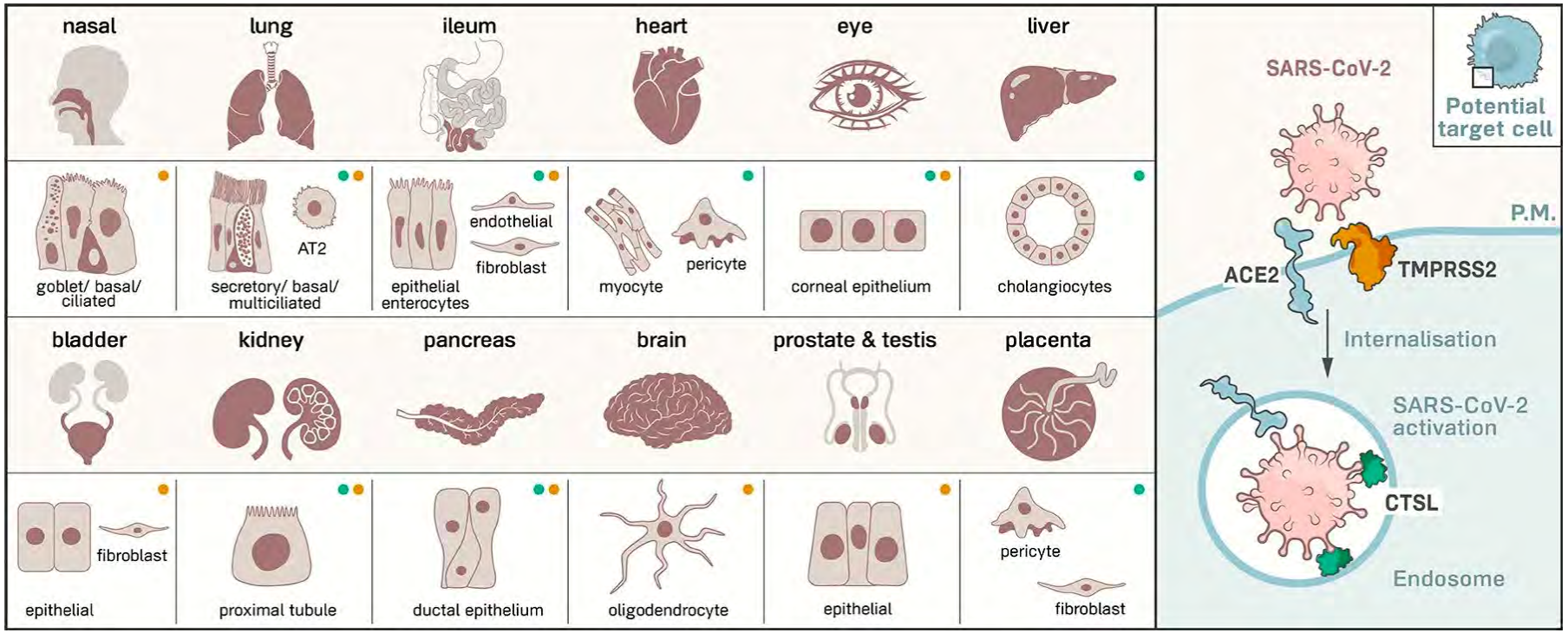


Image: https://www.the-scientist.com/news-opinion/receptors-for-sars-cov-2-present-in-wide-variety-of-human-cells-67496

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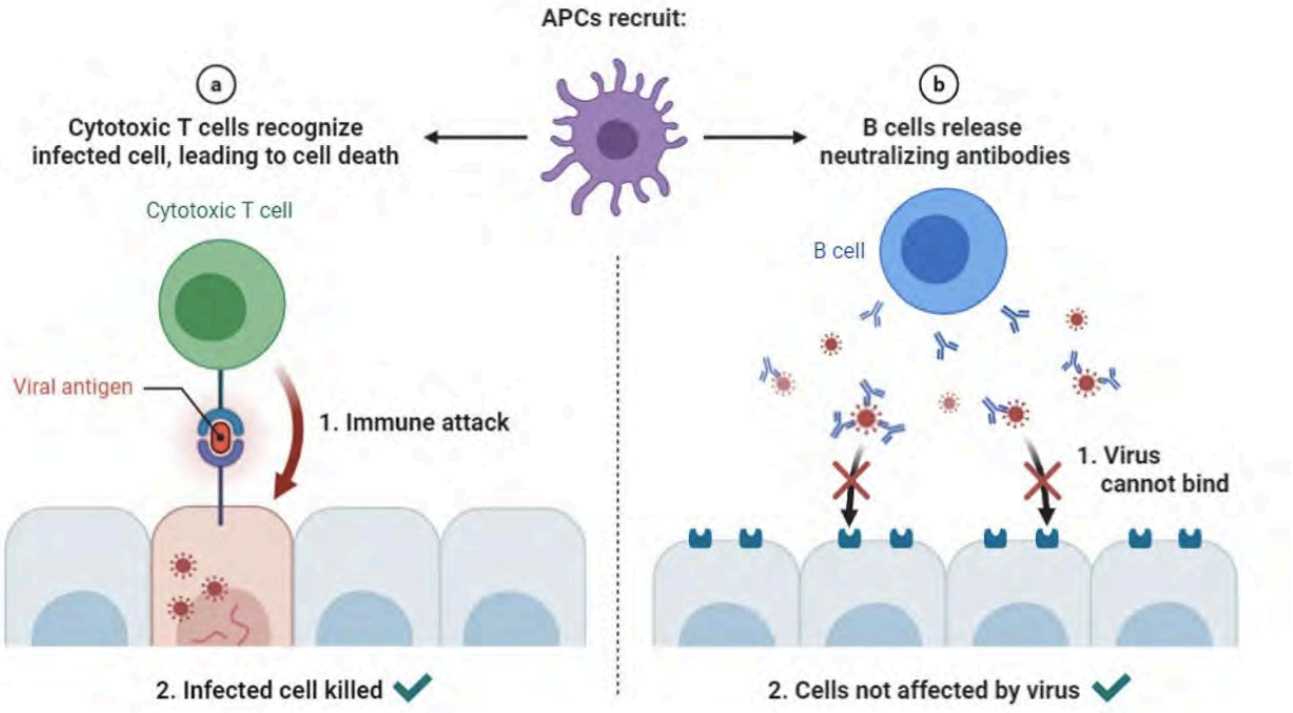
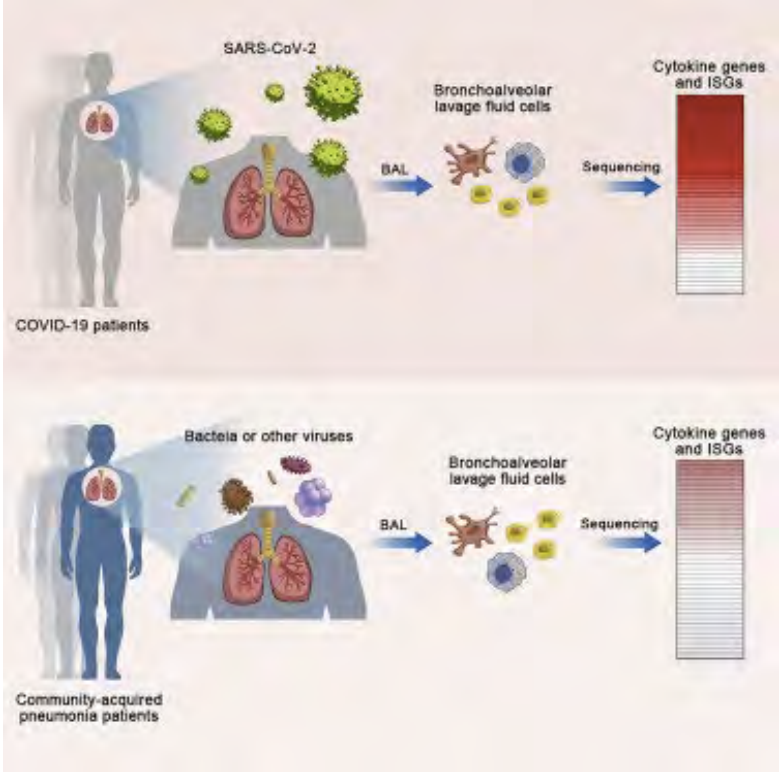
Immune Response to SARS-CoV-2 Infection



Akiko Iwasaki, MD, https://app.biorender.com/biorender-templates/t-5f178d344f5fad00a7792332

Immune Response to SARS-CoV-2 Infection

- Cytokine storm associated with severe respiratory disease
- Cellular immune responses (CD4+ lymphocytes) coordinate immune responses
  - Secrete cytokines
  - Down-regulation
- Persistent activation, or inappropriate responses, may lead to prolonged disease
- No evidence for persistent viral infection (or is there?)



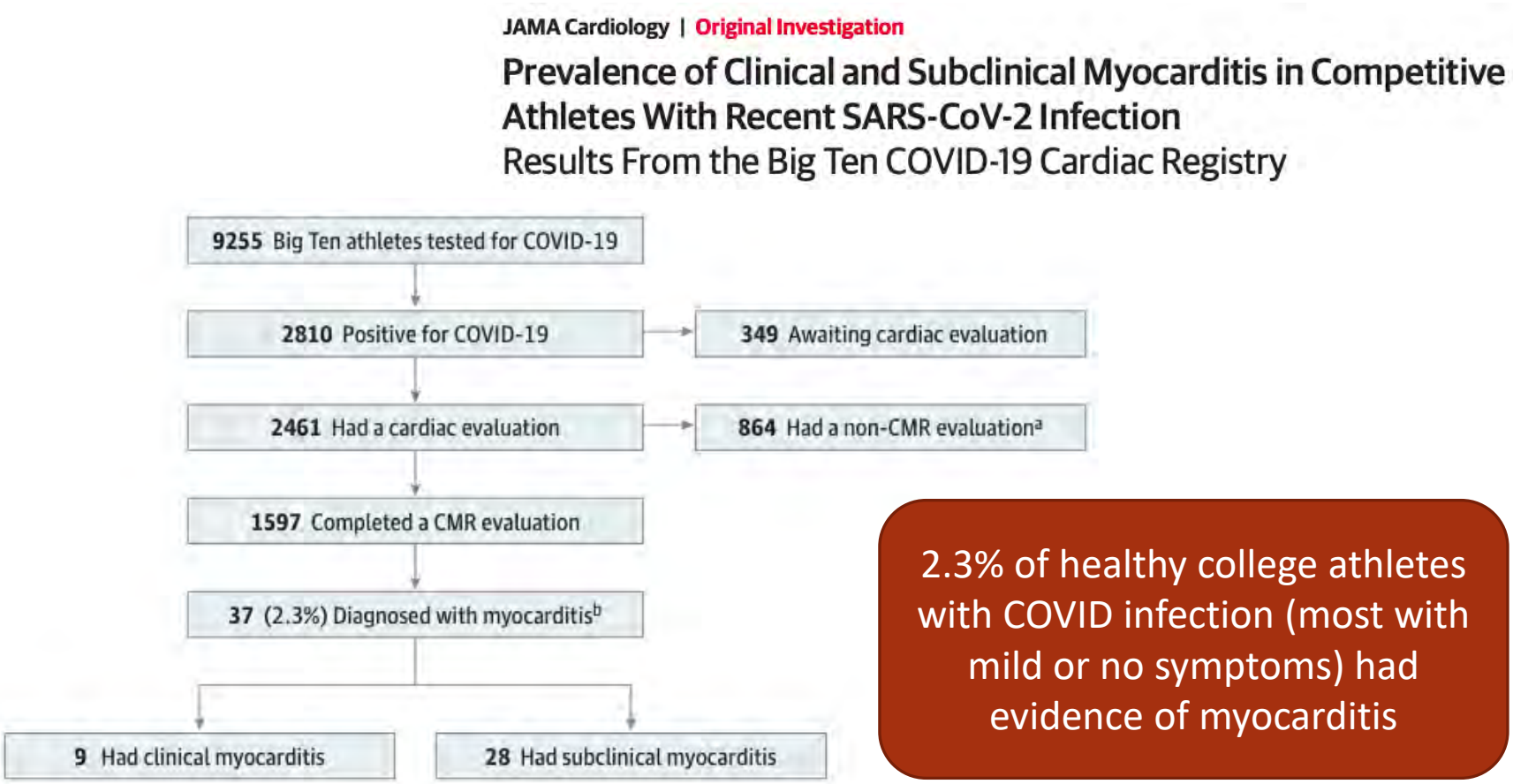
Zhou Z, et al. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. Cell Host Microbe. 2020 Jun 10;27(6):883-890.e2.

Thromboembolic Complications

Myocarditis

Autoimmune Diseases

Big Ten Study

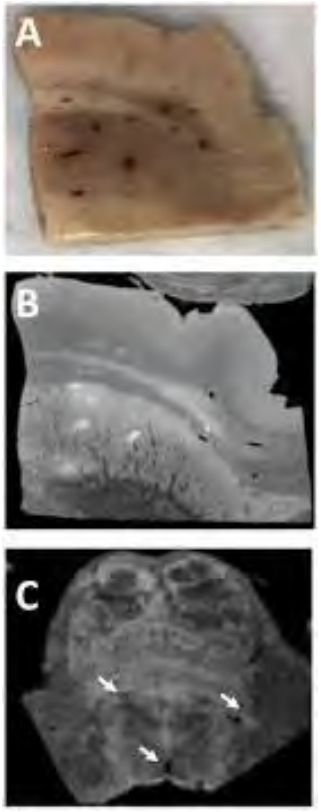


2.3% of healthy college athletes with COVID infection (most with mild or no symptoms) had evidence of myocarditis

Daniels CJ, Rajpal S, Greenshields JT, et al. Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol.* Published online May 27, 2021. doi:10.1001/jamacardio.2021.2065

Neuropathogenic Mechanisms

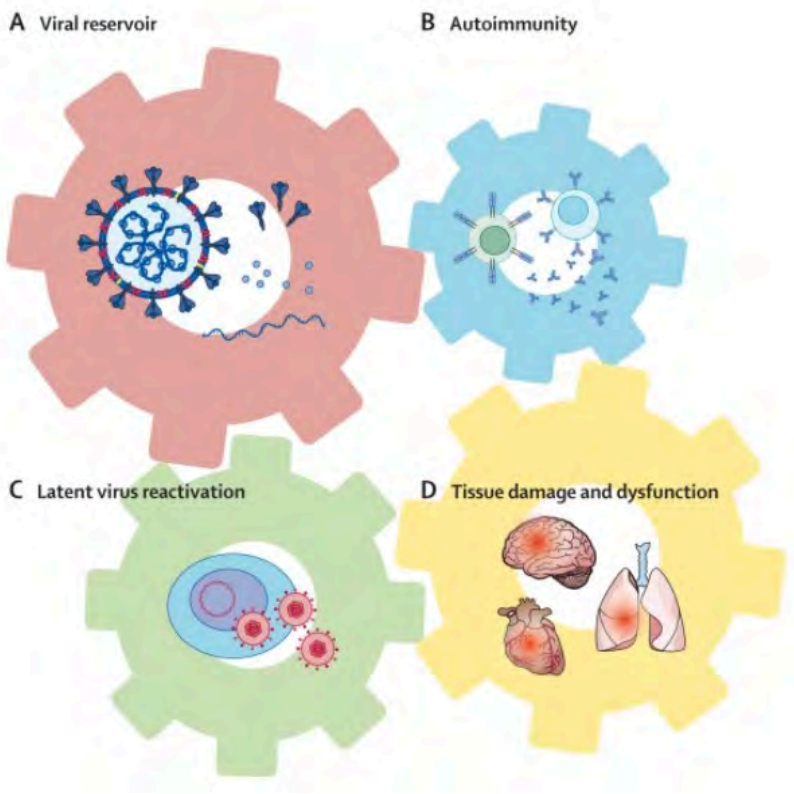
Acute Neurologic Syndromes	Proposed Mechanism
Anosmia/ageusia	Direct viral infection of olfactory bulb
Stroke	Hypercoagulability Endothelial damage
Encephalitis	Viral neuro-invasion Autoimmunity
Encephalopathy	Metabolic derangements Hypoxia/ischemia Cerebral microthrombi Cytokine storm
Peripheral neuropathy	Molecular mimicry
Myositis	Autoimmune Cytokine storm



Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576-3588.

How Can This Lead to Long COVID?

1. Viral reservoirs: areas in the body where Sars-CoV-2 virus is persisting
2. Autoimmunity: dysregulated immune system reacting against the body's own components
3. Latent virus activation: other dormant viruses (like EBV or HSV) may be triggered id
4. Long-term inflammation caused by tissue damage.



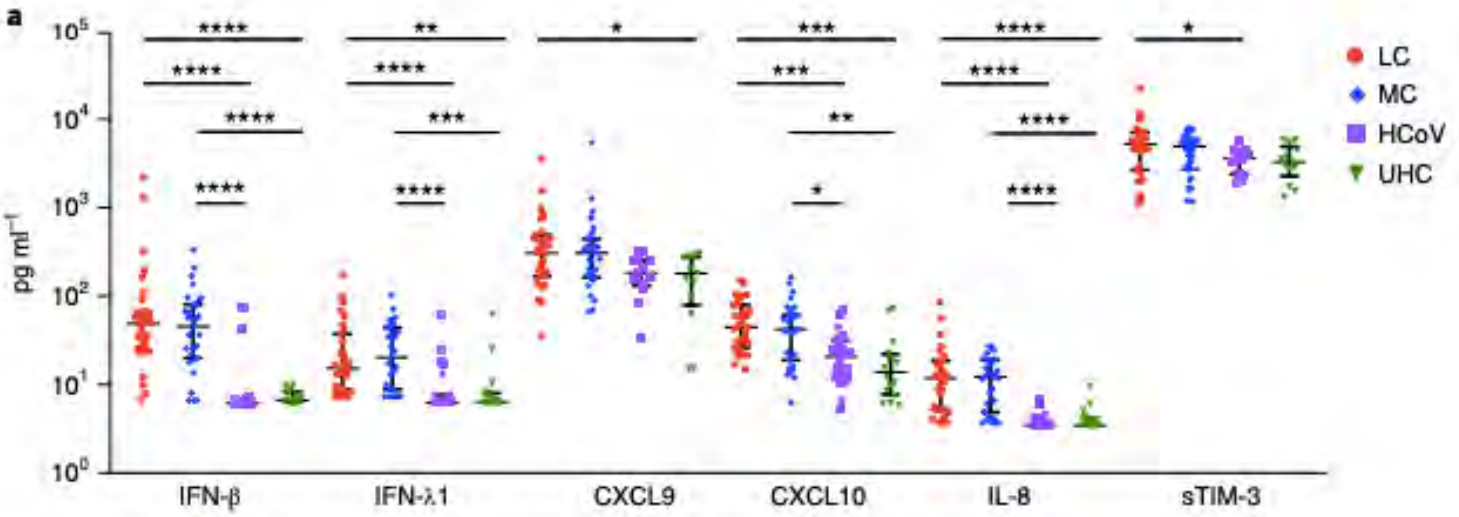
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00053-1/fulltext#articleInformation

LETTERS
https://doi.org/10.1038/s41590-021-01113-x
nature immunology

Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh[1,7], David R. Darley[2,7], Daniel B. Wilson[3], Annett Howe[1], C. Mee Ling Munier[1], Sheila K. Patel[4], Jennifer A. Juno[5], Louise M. Burrell[4], Stephen J. Kent[5,6], Gregory J. Dore[1,2], Anthony D. Kelleher[1,2,7] and Gail V. Matthews[1,2,7]

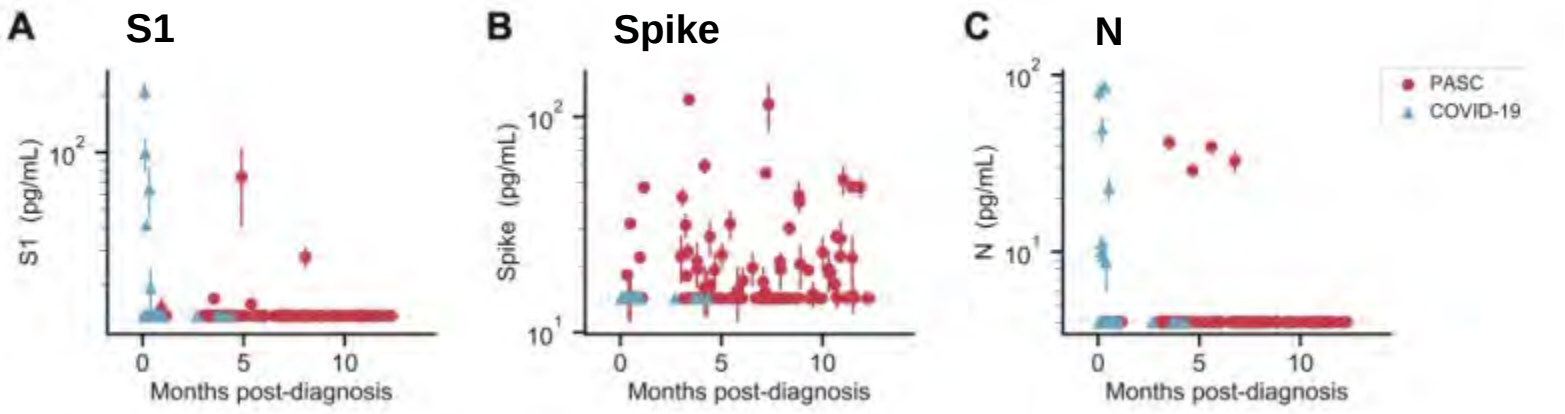
LC = Long COVID
MC = COVID Asymptomatic matched controls
HCoV = Other coronaviruses
UHC = Unexposed/uninfected



Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022 Feb;23(2):210-216.

Persistence of SARS CoV-2 Antigens

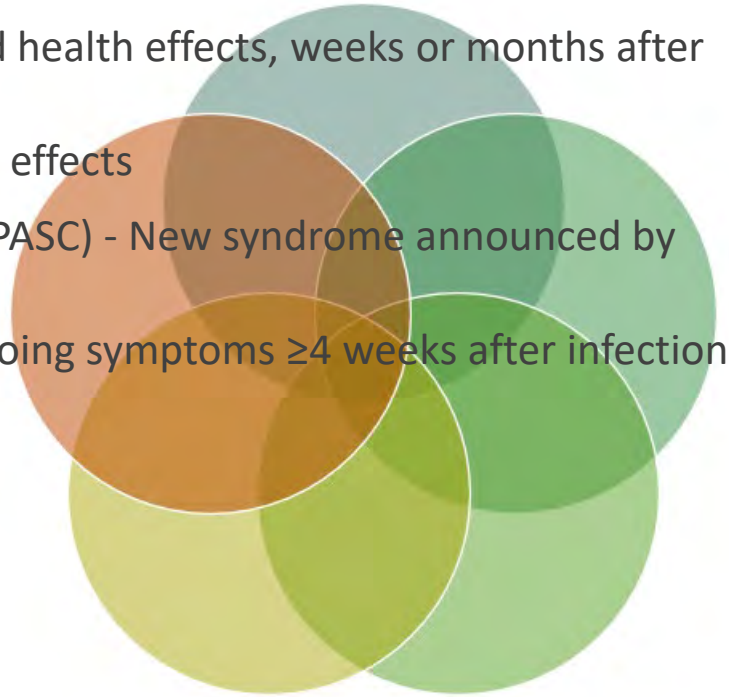
60% of PASC subjects (n=63) vs. none of the non-PASC subjects (n=26) had detectable spike protein antigen ≥5 months after infection



Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, Walt DR. Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae. Clin Infect Dis. 2022 Sep 2:ciac722. doi: 10.1093/cid/ciac722.

What Is “Long COVID?”

- Long COVID – Various persistent symptoms and health effects, weeks or months after infection
- Long Hauler – COVID-19 survivor with lingering effects
- Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) - New syndrome announced by NIH in 2021
- Post-COVID Condition – New, returning, or ongoing symptoms ≥4 weeks after infection
- Post-Viral Fatigue Syndrome
- Chronic Fatigue Syndrome
- Myalgic Encephalitis



Post-Acute Sequelae of SARS-CoV-2 Infection (PASC, pPASC)

Symptom onset or persisting ≥4 weeks after COVID-19 infection

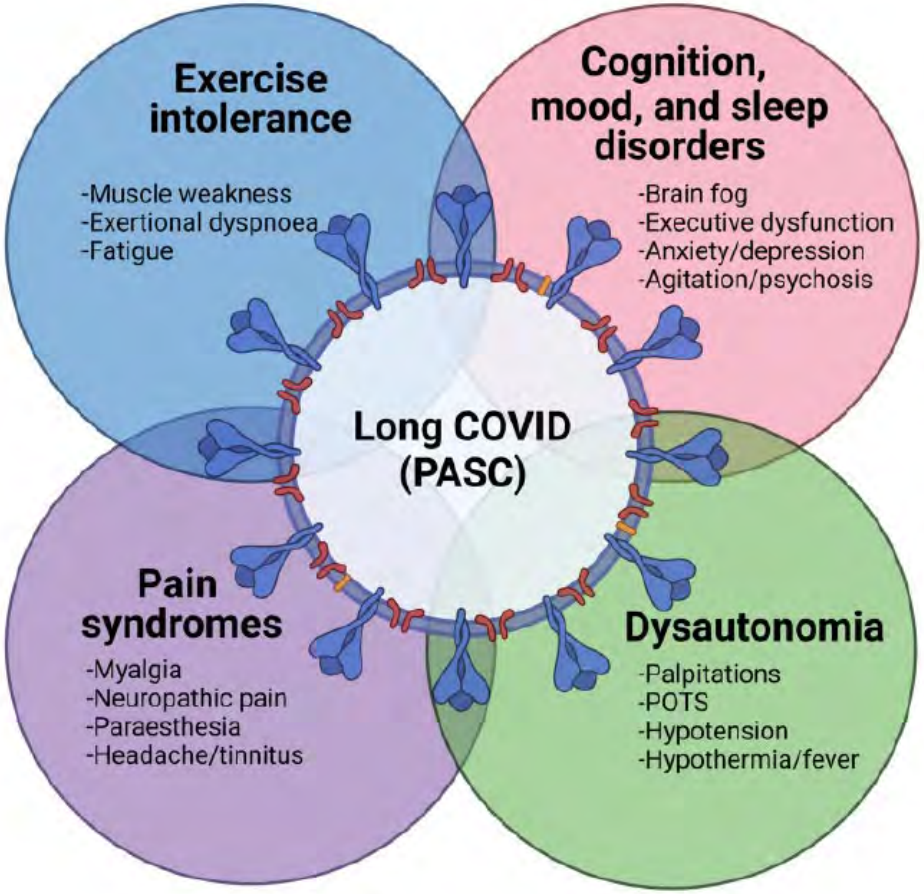
Fatigue + various other symptoms

- Post-exertional fatigue a dominant feature

Intrusive into daily activities

Not explained by other conditions

Neurologic Features of PASC



Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576-3588.

Are There Predictive Factors?

Maybe?

Severe disease

ICU stay

Pulmonary embolism

Myocardial dysfunction

MIS-C

Unvaccinated status

Incidence of PASC in Children & Adolescents

Pediatric studies report 8–58% of SARS-CoV-2 infected children experience “long COVID” symptoms

- Uncontrolled studies may over-estimate by not accounting for other illnesses, or pandemic stress

Controlled cohort studies consistently show higher prolonged symptoms, but wide variability

- 1.7% vs 4.6%
- 0.9% vs 4.4%
- 53.4% vs 66.5%

Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents. *World J Pediatr WJP.* 2021;17:495–499.

Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, et al. Long COVID in children: observations from a designated pediatric clinic. *Pediatr Infect Dis J.* 2021

Buonsenso D, Munblit D, De Rose C, et al. (2021) Preliminary evidence on long COVID in children. *Acta Paediatr Oslo Nor.* 1992;110:2208–2211.

Brackel CLH, Lap CR, Buddingh EP, et al. Pediatric long-COVID: an overlooked phenomenon? *Pediatr Pulmonol.* 2021;56:2495–2502.

Blomberg B, Mohn KG-I, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med.* 2021;27:1607–1613.

Miller F, Nguyen V, Navaratnam AM et al (2021) Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales

Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health.* 2021

Osmanov IM, Spiridonova E, Bobkova P et al (2021) Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study.

Say D, Crawford N, McNab S, et al. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health.* 2021;5:e22–e23.

Smane L, Roge I, Pucuka Z, Pavare J. Clinical features of pediatric post-acute COVID-19: a descriptive retrospective follow-up study. *Ital J Pediatr.* 2021;47:177.

Stephenson T, Shafran R, De Stavola B, et al. Long COVID and the mental and physical health of children and young people: national matched cohort study protocol (the CLoCk study) BMJ Open. 2021;11:e052838.c

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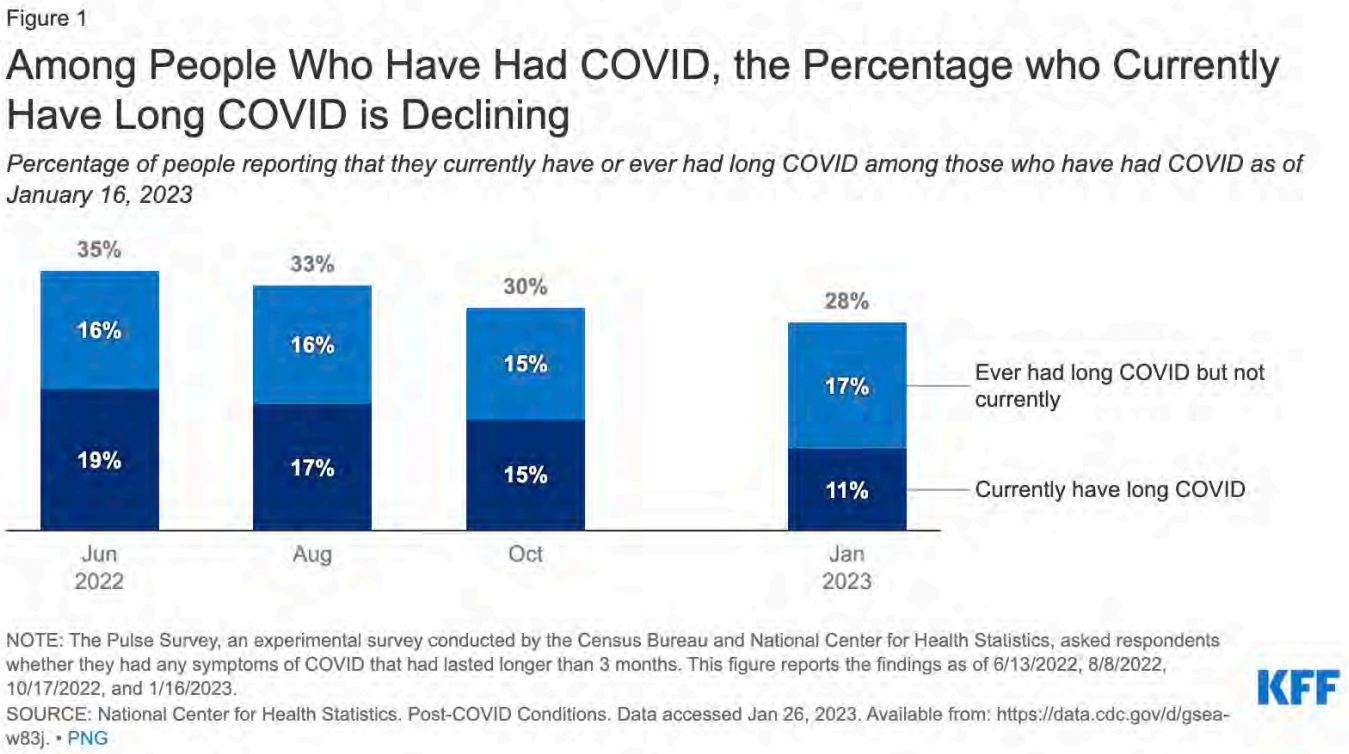
Long COVID: US Population (1/26/23)



https://www.kff.org/policy-watch/long-covid-what-do-latest-data-show/

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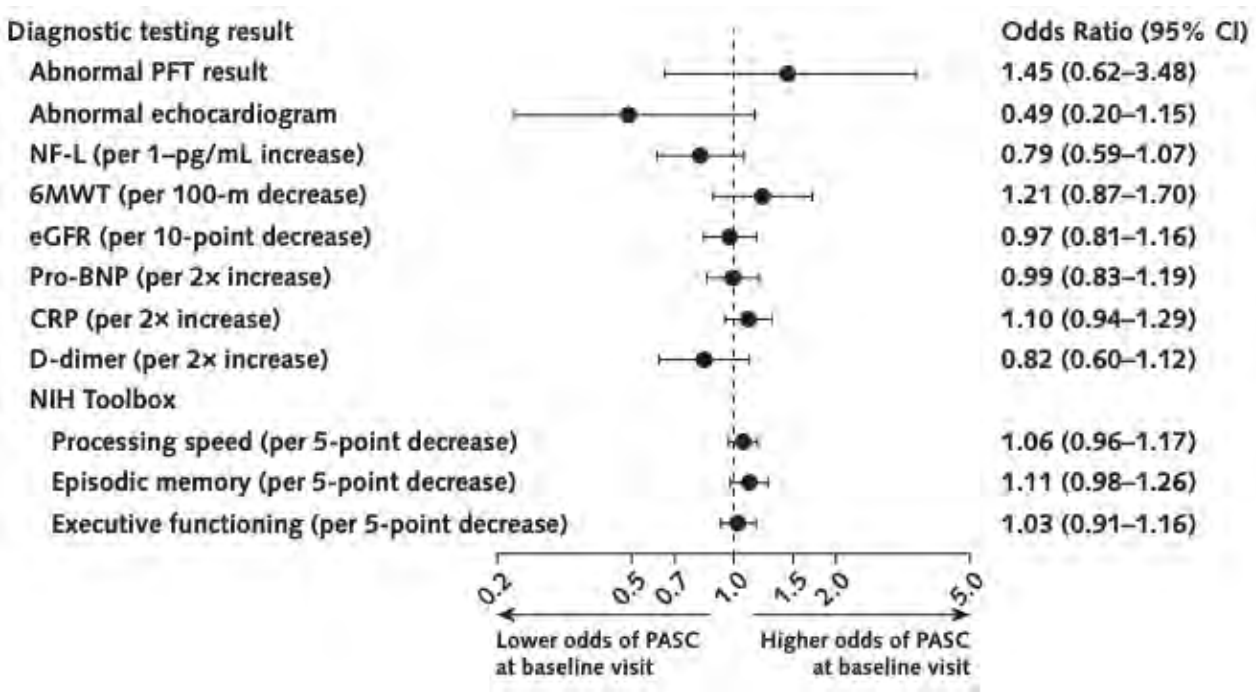
Evaluations to Consider

- Rule-out cardiomyopathy
- Rule-out thromboembolic complications (CVA, PE)
- Screen for autoimmune diseases
- Think about mimics (hypothyroidism, diabetes, depression)
- Mental heath assessment

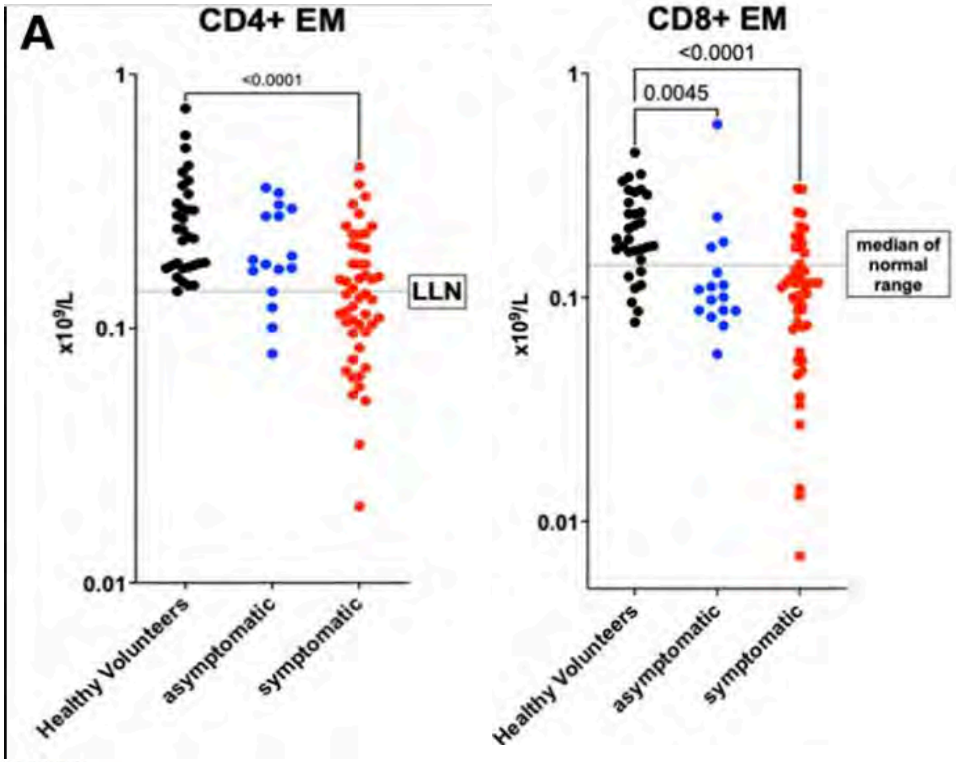
Lab Values, PASC vs Control



No major differences in inflammatory labs, pulmonary function, cardiac function, cognitive function

Sneller MC, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med. 2022 May 24:M21-4905.

CD4 and CD8 cells

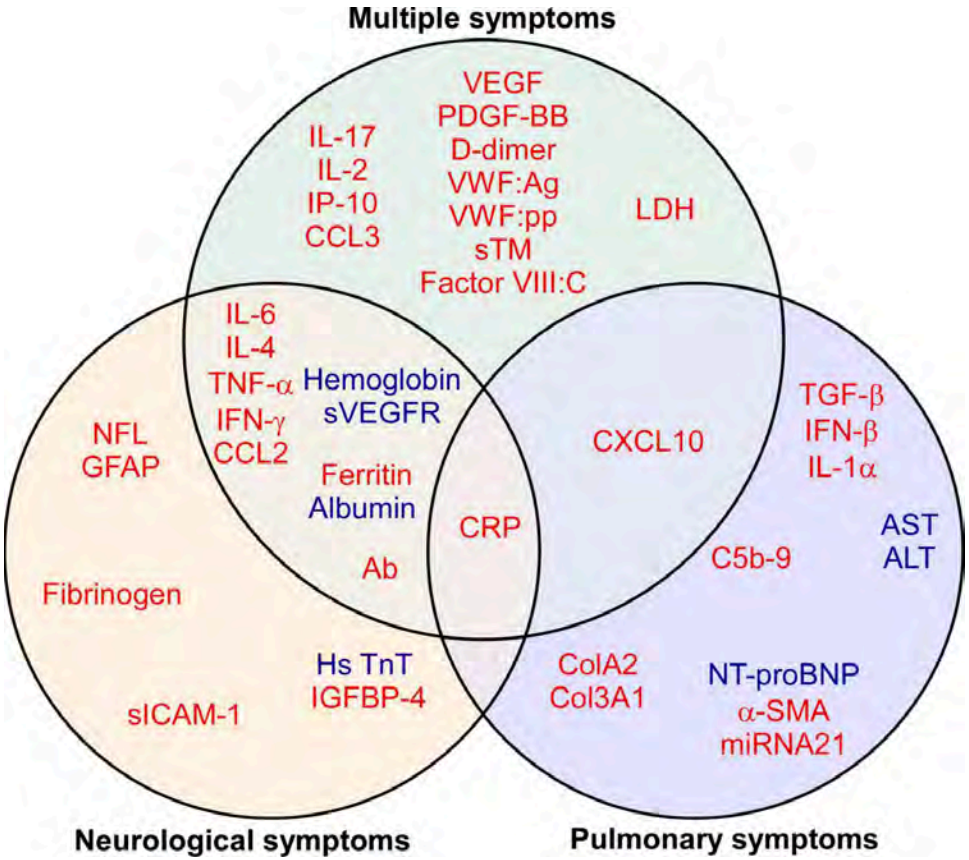


- Antihistamine study
- Essentially no differences in CD4 and CD8 cell populations in PASC vs. COVID+ but not PASC subjects
- Observational study, not randomized

Glynne P, Tahmasebi N, Gant V, *et al*
Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines
Journal of Investigative Medicine 2022;**70:**61-67.

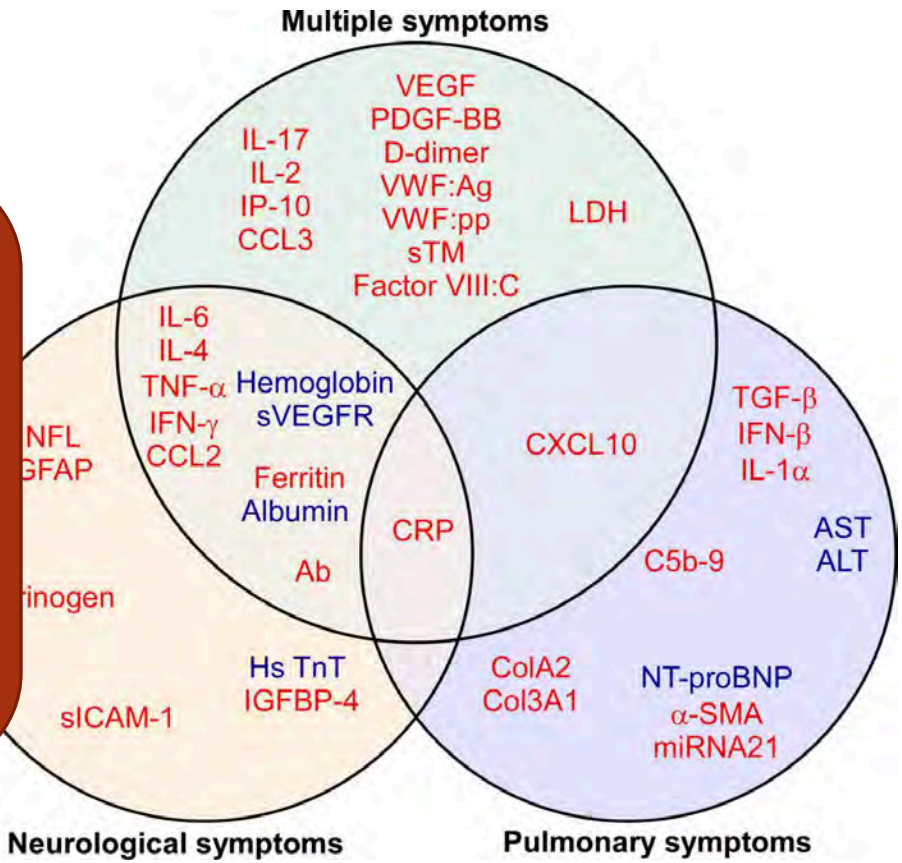
Biomarkers

Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: A systematic review. Front Med. 2023 Jan 20;10:1085988.



Biomarkers

- Any individual patient may have a different mixture of these findings.
- Not diagnostic
- Save your copay



Management

PM&R

WILEY

Clinical Guidance Free Access

Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients

Correction(s) for this article

Joseph E. Herrera DO, William N. Niehaus MD, Jonathan Whiteson MD, Alba Azola MD, John M. Baratta MD, MBA, Talya K. Fleming MD, Soo Yeon Kim MD, Huma Naqvi MD, Sarah Sampsel MPH, Julie K. Silver MD, Monica Verduzco-Gutierrez MD, Jason Maley MD, Eric Herman MD, Benjamin Abramoff MD, MS

Herrera JE, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. PM&R. 2021 Sep;13(9):1027-1043.

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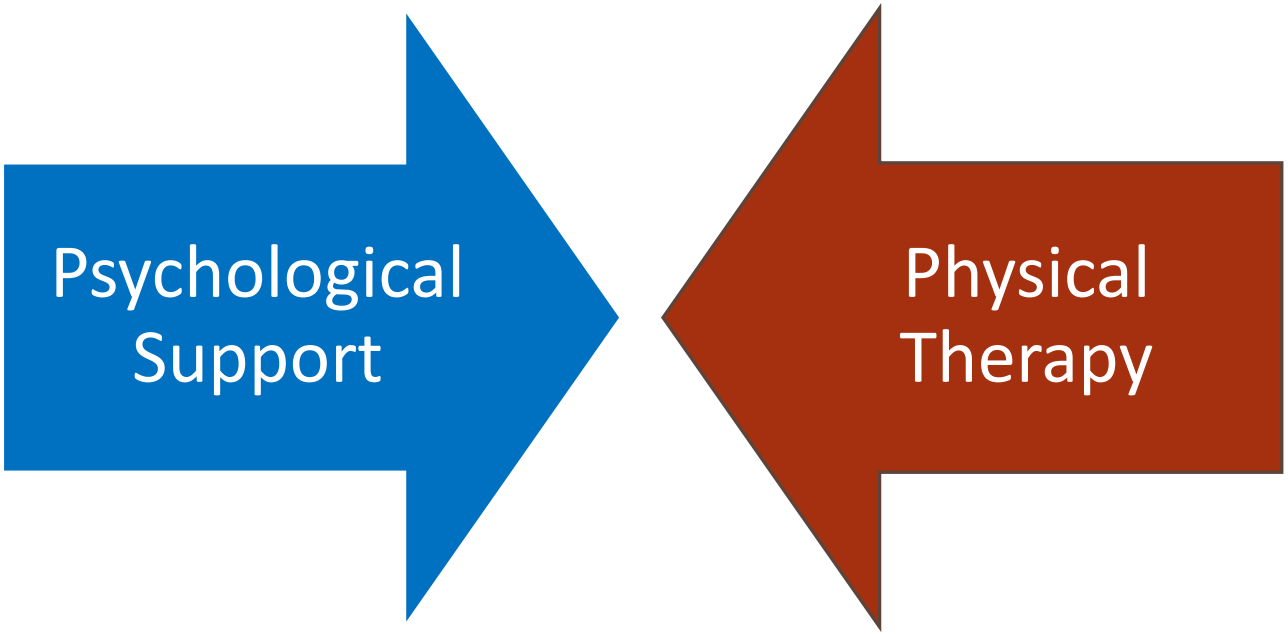
Management

- Set achievable goals
- Focus on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia)
- Improving physical, mental, and social well-being

Supportive Care – Sleep/Wake Cycle

Coping & Restoring Normal



PEDIATRIC ANNALS

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A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19

Alexandra Brugler Yonts, MD, Justin Burton, MD, and Linda Jones Herbert, PhD

Published Online: November 01, 2022 · https://doi.org/10.3928/19382359-20220913-08

Pediatric PASC (pPASC) Management

Specialty	Indications for evaluation	Assessment tools	Management strategies
Primary care	Diagnosed with acute COVID-19	Initial post-COVID follow-up (4 weeks)	Validation, early pacing discussions, referral to multidisciplinary pPASC clinic
		Subsequent post-COVID follow-up (12 weeks)	
		Basic screening laboratory tests: CBC with differential, CMP, CRP, ESR, Ferritin, TSH ± Free T4, vitamin D, Epstein Bar virus antibody panel	Olfactory retraining

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

Pediatric PASC (pPASC) Management

Physical rehabilitation	All pPASC	Orthostatic vitals	Aerobic exercise or reconditioning program
		Functional history and examination	Energy conservation strategies
		6-minute walk test	Dietary counseling
Psychology	All pPASC	Comprehensive psychosocial history	Anxiety management strategies (relaxation, cognitive-behavioral therapy techniques)
		Validated self-report and parent proxy psychosocial questionnaires (eg,	Behavioral activation
		PROMIS Pediatric Profile)	Support groups

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

Pediatric PASC (pPASC) Management

Cardiology	Hospitalized for acute COVID-19		
	Persistent palpitations or syncopal episodes	ECG, troponin, CRP, brain natriuretic protein for myopericarditis symptoms	Dysautonomia syndrome management: fluids, electrolytes, compression, midodrine, fludrocortisone, propranolol
	Chest pain that occurs with exercise; radiates to the back, jaw, left arm, or shoulder; and/or increased when lying down	Echocardiogram, cardiac MRI, stress test if appropriate	Admission and supportive care for myopericarditis if applicable

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

Pediatric PASC (pPASC) Management

Neurology	New or worsening persistent or daily headaches	MRI ± EEG	Headache management (fluids, sleep hygiene, abortive or preventive medications)
	Focal neurological signs	Vitamin and heavy metal levels ± lumbar puncture for CSF cytokines, cell count, neuroimmune studies	Coenzyme Q10, vitamin B complex, magnesium
Pulmonary	Hospitalization for acute COVID-19 infection	Pulmonary function tests ± Chest x-ray	Bronchodilators as applicable
	Persistent cough, wheezing or increased work of breathing	CT chest if studies abnormal	

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

Pediatric PASC (pPASC) Management

Otolaryngology	Hoarseness, stridor, or change in vocal quality	Laryngoscopy	Breathing exercises
	Shortness of breath in the absence of pulmonary findings	Spirometry	Speech pathologist referral
			Vocal retraining
Pain medicine	Paresthesias	Quantitative sensory testing	Tricyclic anti-depressants
	Dysautonomia	Skin biopsy for small fiber neuropathy	Anti-epileptics
	Chronic pain		Topical lidocaine, other analgesics IVIG

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

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A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19

Alexandra Brugler Yonts, MD, Justin Burton, MD, and Linda Jones Herbert, PhD

Published Online: November 01, 2022 · https://doi.org/10.3928/19382359-20220913-08

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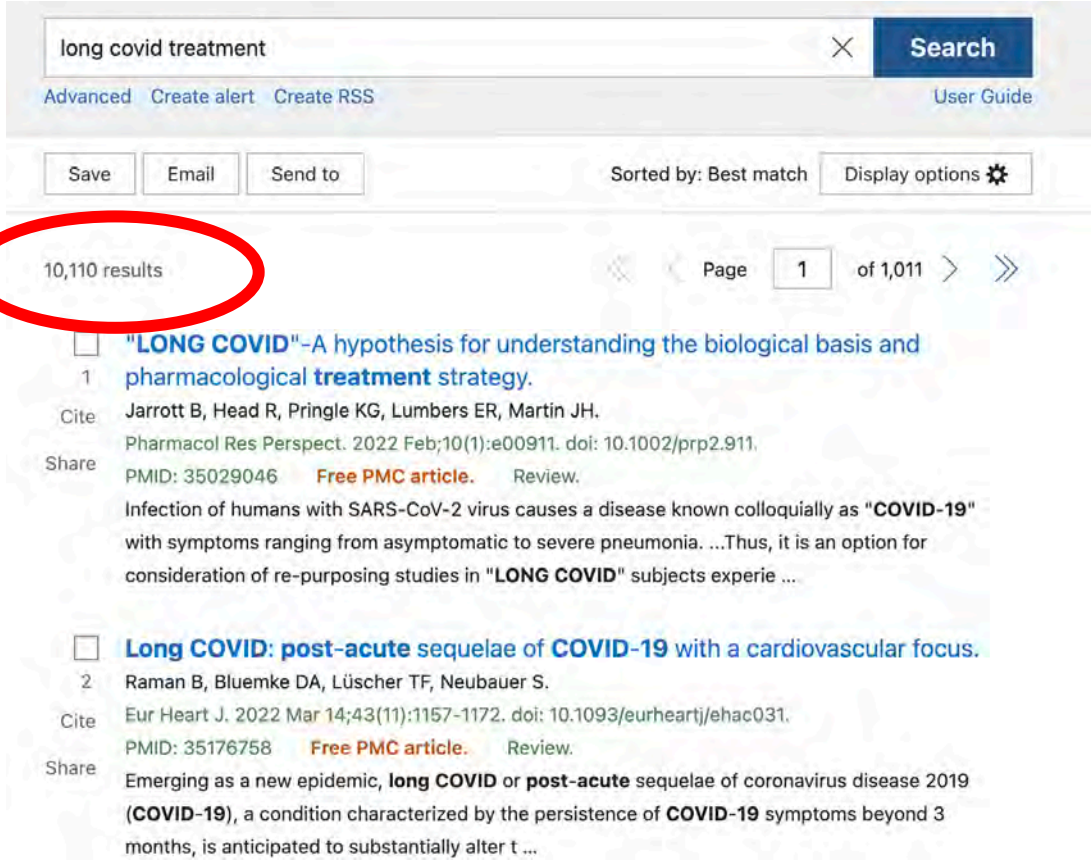
Overwhelming Publications



Deciphering Useful Data

This is a preprint.

It has not yet been peer reviewed by a journal.

The National Library of Medicine is running a pilot to include preprints that result from research funded by NIH in PMC and PubMed.

> medRxiv. 2022 Dec 23;2022.12.21.22283753. doi: 10.1101/2022.12.21.22283753. Preprint

Outpatient treatment of Covid-19 with metformin, ivermectin, and fluvoxamine and the development of Long Covid over 10-month follow-up

FULL TEXT LINKS

medRxiv

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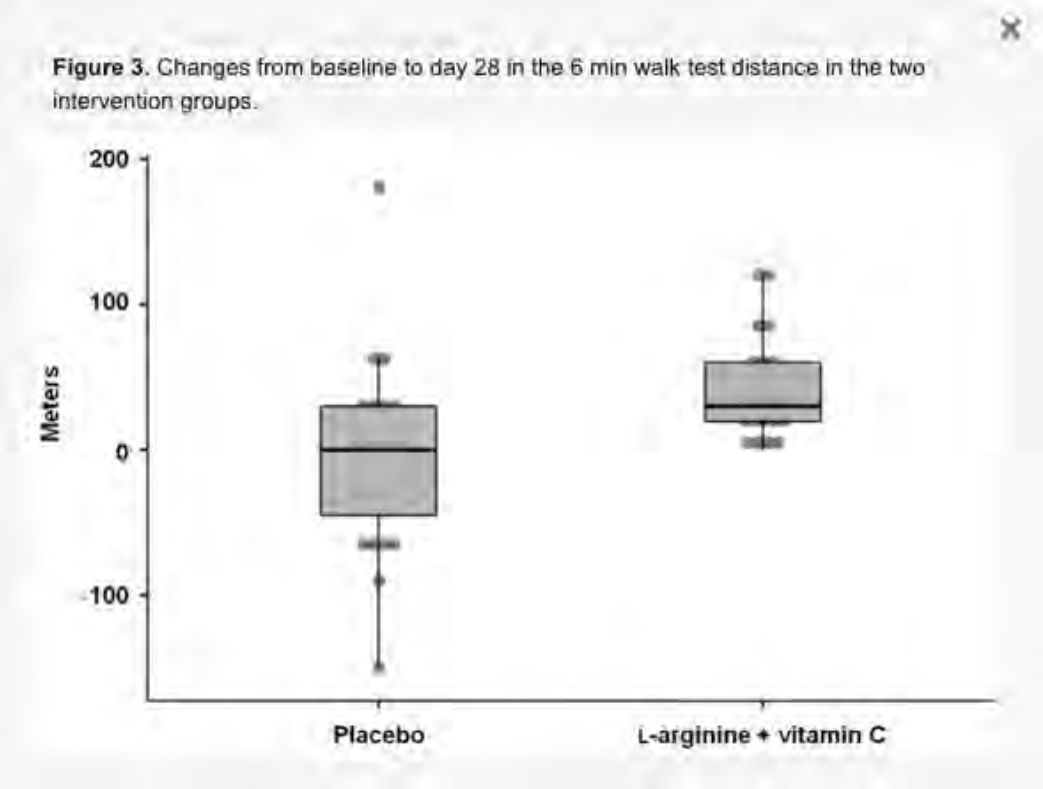
Supplements?

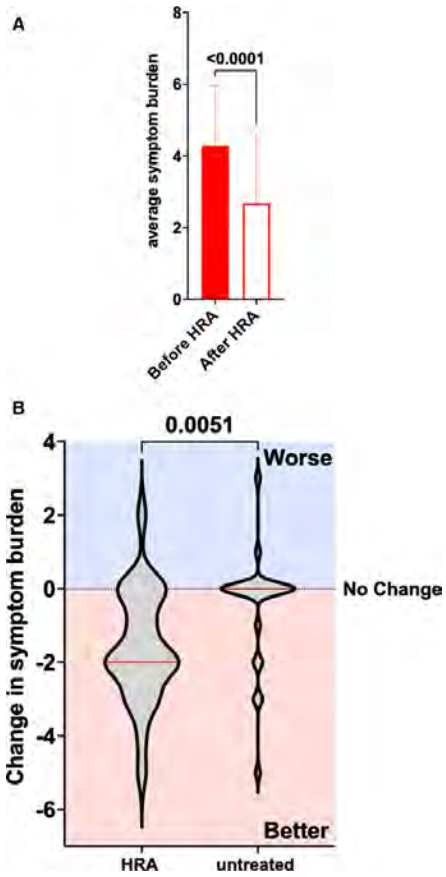


- Randomized 1:1 (n=46, 23 per group)
- BID 1.66 g L-arginine + 500 mg liposomal vitamin C vs. placebo for 28 days
- Improved 6-minute walking distance, hand grip, fatigue at 28 days

Tosato M, et al. Nutrients. 2022; 14(23):4984. https://doi.org/10.3390/nu14234984

Antihistamines?

- Prospective observational study
- **(Loratadine or foxfenadine) + (famotidine or nizatidine)**
- Single clinical practice, not randomized, not blinded
- Based on self-reported symptom scoring system
  - Fatigue, constitutional upset (sweats, fever, arthralgia, myalgia), breathlessness, post-exertional malaise (PEM), chest pain, neurologic (headaches, neurosensory, brain fog), neuropsychiatric (anxiety, insomnia), dysautonomia (postural tachycardia), ear, nose and throat symptoms, gastrointestinal disturbance (food intolerance, diarrhea, bloating), and dermatological manifestations (rashes, flushing, urticaria)
  - Maximum possible symptom score of 11.
- 26% of untreated patients reported improvement at average 8 weeks follow-up



Glynne P, Tahmasebi N, Gant V, *et al*
Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines
Journal of Investigative Medicine 2022;**70:**61-67.

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Antihistamines?

- Prospective observational study
- (Loratadine or foxfenadine) + (famotidine or nizatidine)
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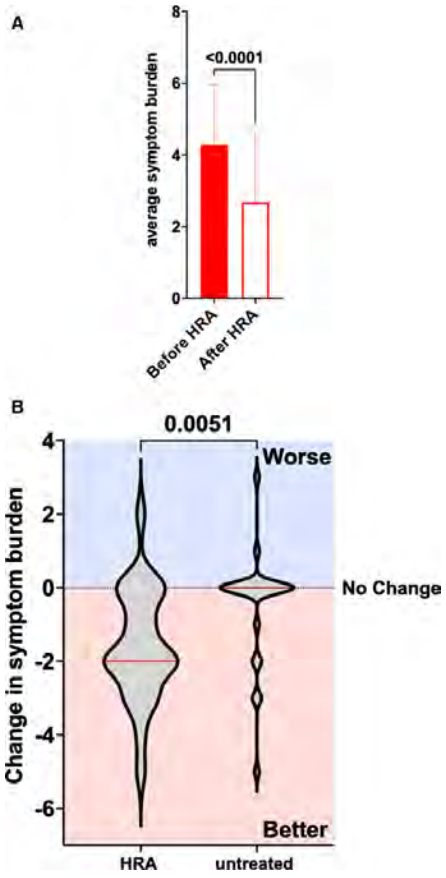
  -)
  - Maximum possible symptom score of 11.
- 26% of untreated patients reported improvement at average 8 weeks follow-up

- Some patients may experience improvement with combination H1 + H2 blockers
- Poor quality data
- Low risk intervention



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Expected Timing of Remission

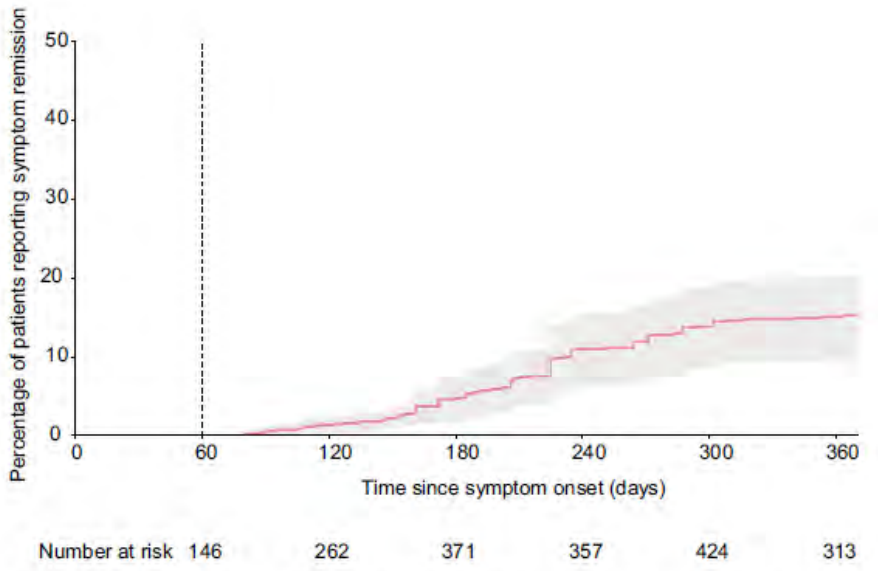
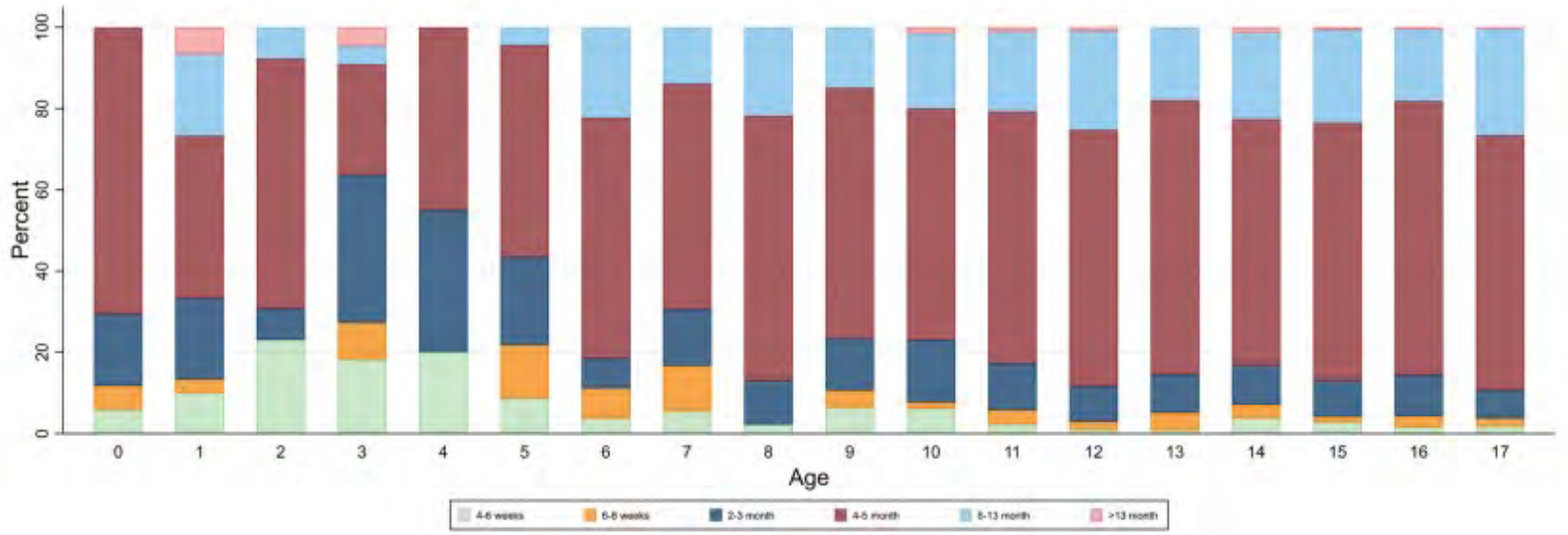


Fig. 2 Cumulative event curve for remission of post COVID-19 symptoms.

Tran, VT., Porcher, R., Pane, I. et al. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun 13, 1812 (2022).

Ongoing Prolonged Symptoms in Children (Danish Cohort)



54-75% had symptom resolution within 1-5 months. About 20% had symptoms 6-13 months.

Borch L, et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. Eur J Pediatr. 2022 Apr;181(4):1597-1607.

News | February 9, 2023

MediciNova gains approval from Health Canada for long Covid therapy trial

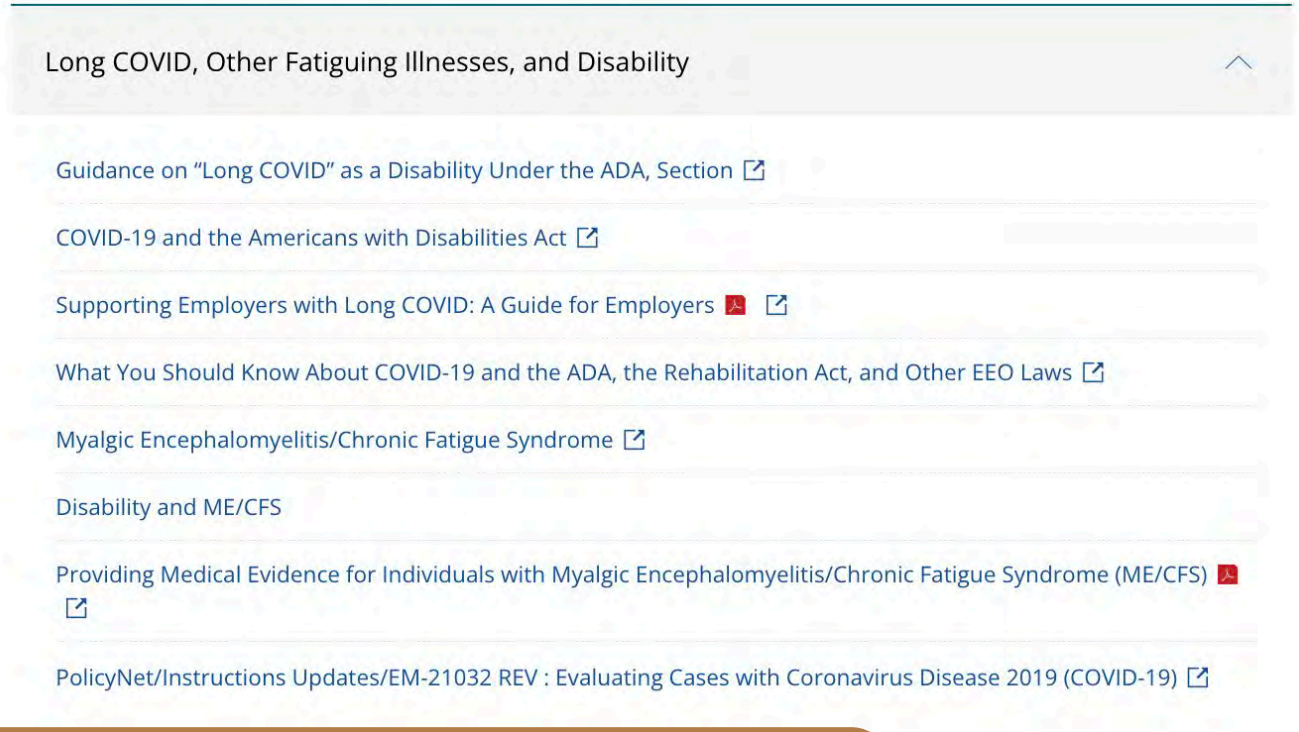
The trial will assess MN-166 and other therapies for the treatment of long Covid patients.

https://www.clinicaltrialsarena.com/news/medicinova-long-covid-therapy/

- Recovering from Covid-19 Lingering Symptoms Adaptive Integrative Medicine (RECLAIM) trial, the placebo-controlled, adaptive, randomized, prospective (Canadian trial)
- **MN-166 = Ibidulast:** Approved in Japan in 1989, used for asthma and dizziness in post-cerebral infarction
- Inhibits phosphodiesterase (PDE4) ad toll-like receptor 4 (TLR4) patheways
- Crosses blood-brain barrier to suppress glial cell activation
- 2019: granted fast track trial status for ALS
- Trials for MS, reducing neurotoxicity from alcohol, tacrolimus, opioids, etc

Disability?

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



Yes, long COVID can be a disability under the ADA, Section 504, and Section 1557 if it substantially limits one or more major life activities.

Summary

- Immune response to SARS-CoV-2 is complex and can lead to varying sequelae of infection in different body systems
- Screen for tissue damage effects in patients with PASC (Long COVID)
- Holistic restorative measures are crucial
  - Sleep-wake cycles
  - Physical therapy for re-conditioning
  - Psychological support
- Good quality data on therapies is difficult to find
- Advocating for recovery time is a key way we can support our patients

Thank you!

HEALTH CONFIANZA

UT Health San Antonio

Project ECHO