Long COVID

What do we understand?

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APIC Nebraska Fall Conference

October 11, 2024

There are no potential conflicts of interest relevant to this presentation.

Slides presented are my own and those modified and referenced from various experts.

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I will discuss studies and reviews of off-label therapies for long COVID. There are no therapies specifically approved by the FDA for the treatment of long COVID, yet based on basic science studies, various medications or supplements may offer benefit.

Outline/Objectives

- Understand the basic concepts ascribed to Long COVID
- Describe the current understanding of the immunopathogenesis of Long COVID
- Review current treatment and prevention strategies for Long COVID

Case Presentation – Jane

August 2020

- 38-year old female with multiple medically unexplained symptoms
- COVID-19 infection March 2020
- URI symptoms x1 week, then afterwards she could not run, had palpitations, dyspnea, insomnia, anxiety, and panic attacks
- She is married, three young children, and had to quit her job
- Seen in ID office consultation

Case Presentation - Jane

- 39-year old female with multiple medically unexplained symptoms – “MUS”
  - Fatigue
  - Dyspnea on exertion
  - Paroxysmal tachycardia
  - Palpitations
  - Insomnia
  - Brain fog
  - Anxiety


I'M SICK AND TIRED OF
BEING SICK AND TIRED!

Case Presentation - Jane

- Comprehensive history and physical
  - Antecedents
  - Triggering events
    - Infections, allergies, toxins, stress, foods
  - Mediators/Perpetuators
- Comprehensive lab evaluation
- Educated and counseled on optimal nutrition and modifiable lifestyle habits
- A diagnostic test was performed

BASIC CONCEPTS OF LONG COVID

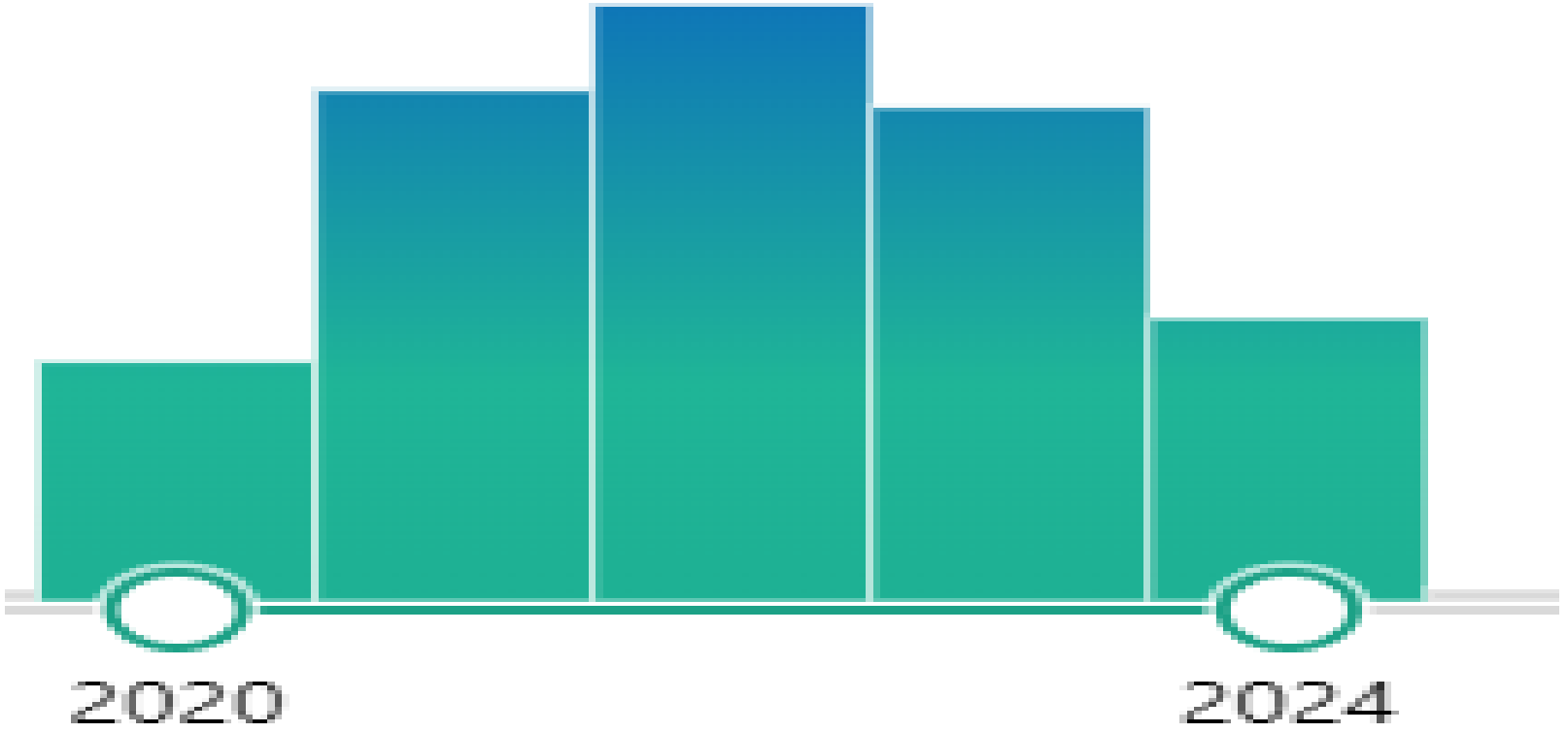
National Library of Medicine
National Center for Biotechnology Information

robertpenn@idmidwes...

PubMed®

long COVID

Search



4,337 **9,504** **11,123** **9,175** **5,168 = 35,212**

September 9, 2024

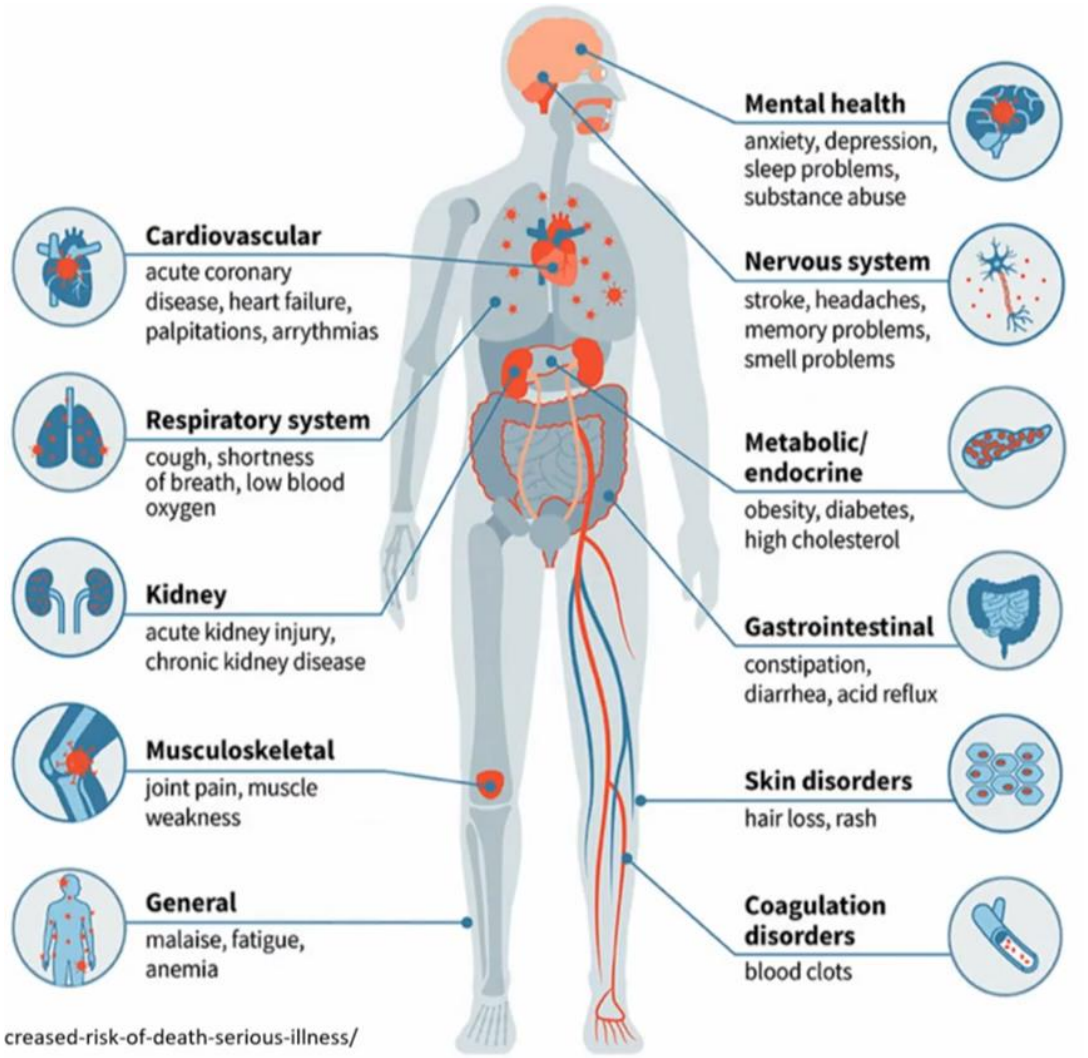
What other terms are used for Long COVID?

- Post COVID
- COVID Long-haulers
- Post-acute sequelae of SARS-CoV-2 (PASC)
- Post-acute COVID-19 syndrome
- Late sequelae of COVID-19
- Chronic COVID syndrome

What is Long COVID?

- Signs, symptoms, or conditions that develop after acute COVID-19
  - From mild to incapacitating
- Many definitions consider ≥4 weeks as the start of Long COVID
- May occur with no to only mild symptomatic initial infection

What are the symptoms of Long COVID?



Many symptoms are vague, making diagnosis & treatment more challenging

https://medicine.wustl.edu/news/among-covid-19-survivors-an-increased-risk-of-death-serious-illness/

Unique Features of Long COVID

Original Investigation

May 25, 2023

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD[1,2]; Sarah E. Jolley, MD, MS[3]; Elizabeth W. Karlson, MD, MS[4]; et al

Author Affiliations | Article Information

JAMA. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823

- Analysis of ~10,000 participants
- 37 unique symptoms had frequency of ≥2.5%
- Compared with no prior COVID infection, 12 symptoms identified as having probable PASC (Long COVID)
  - Loss of smell/taste, post-exertional malaise, cough, brain fog, thirst, palpitations, chest pain, fatigue, loss of sexual desire/capacity, dizziness, gastrointestinal, abnormal movements, hair loss

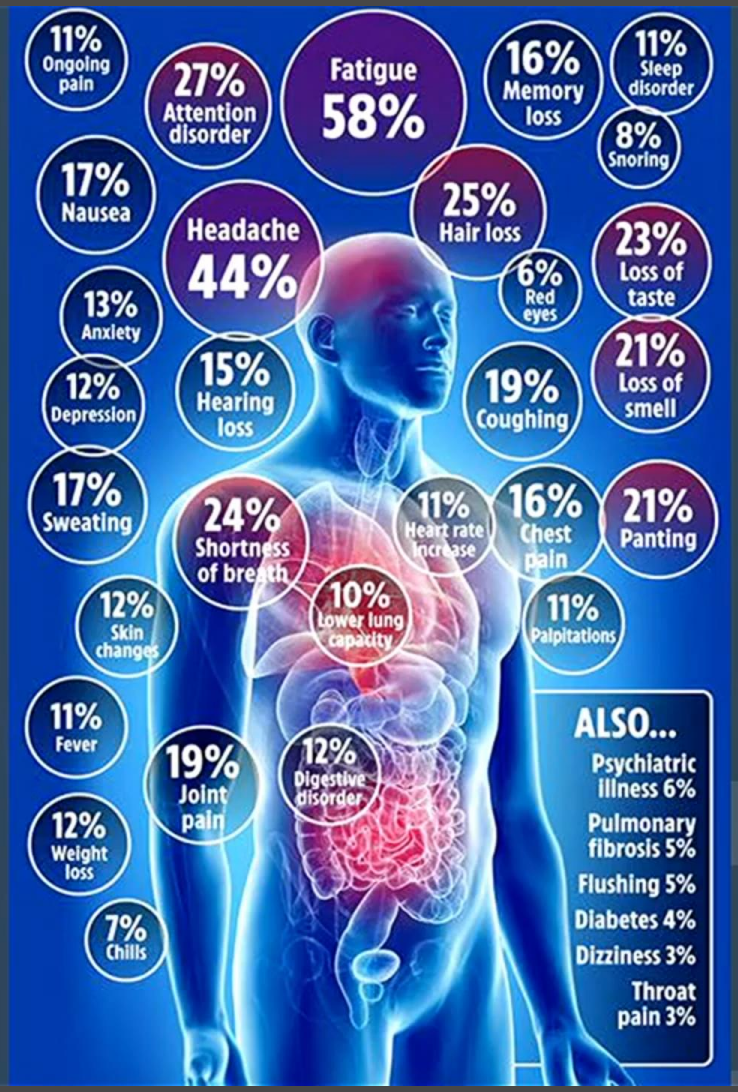
Unique Features of Long COVID

- Symptoms can wax and wane
- Symptoms in some similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
  - Profound fatigue/post-exertional malaise
  - Dysautonomia
- “Brain fog” and sleep disturbances
- Profound impact on quality of life associated with disability

Long COVID at a Glance

Symptoms – diverse affecting multiple systems respiratory, nervous system, cardiovascular, musculoskeletal

Most common- fatigue, shortness of breath, muscle pains, chest pain, brain fog, headache, depression

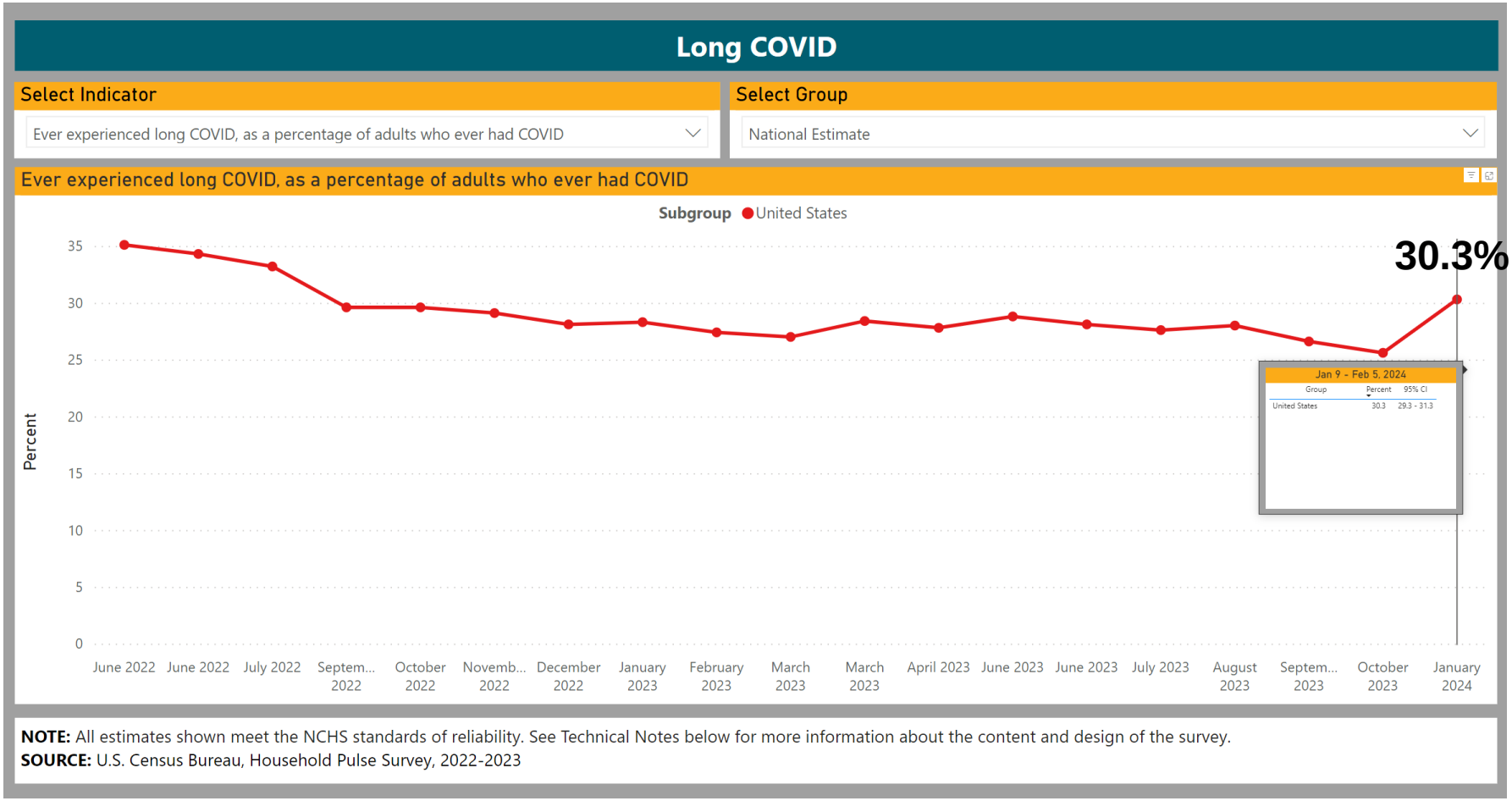


Leonard Calabrese. Cleveland Clinic. VuMEDI July 14, 2023.

What is the chance of developing Long COVID?

- Initial studies reported Long COVID in up to 80% of people with COVID-19
  - More recent estimates between 5-30%
- Accurate estimates difficult because of:
  - Underdiagnosis
  - Limited post-COVID care
  - Limited use of billing code (**U09.9**)
  - Many long COVID symptoms common

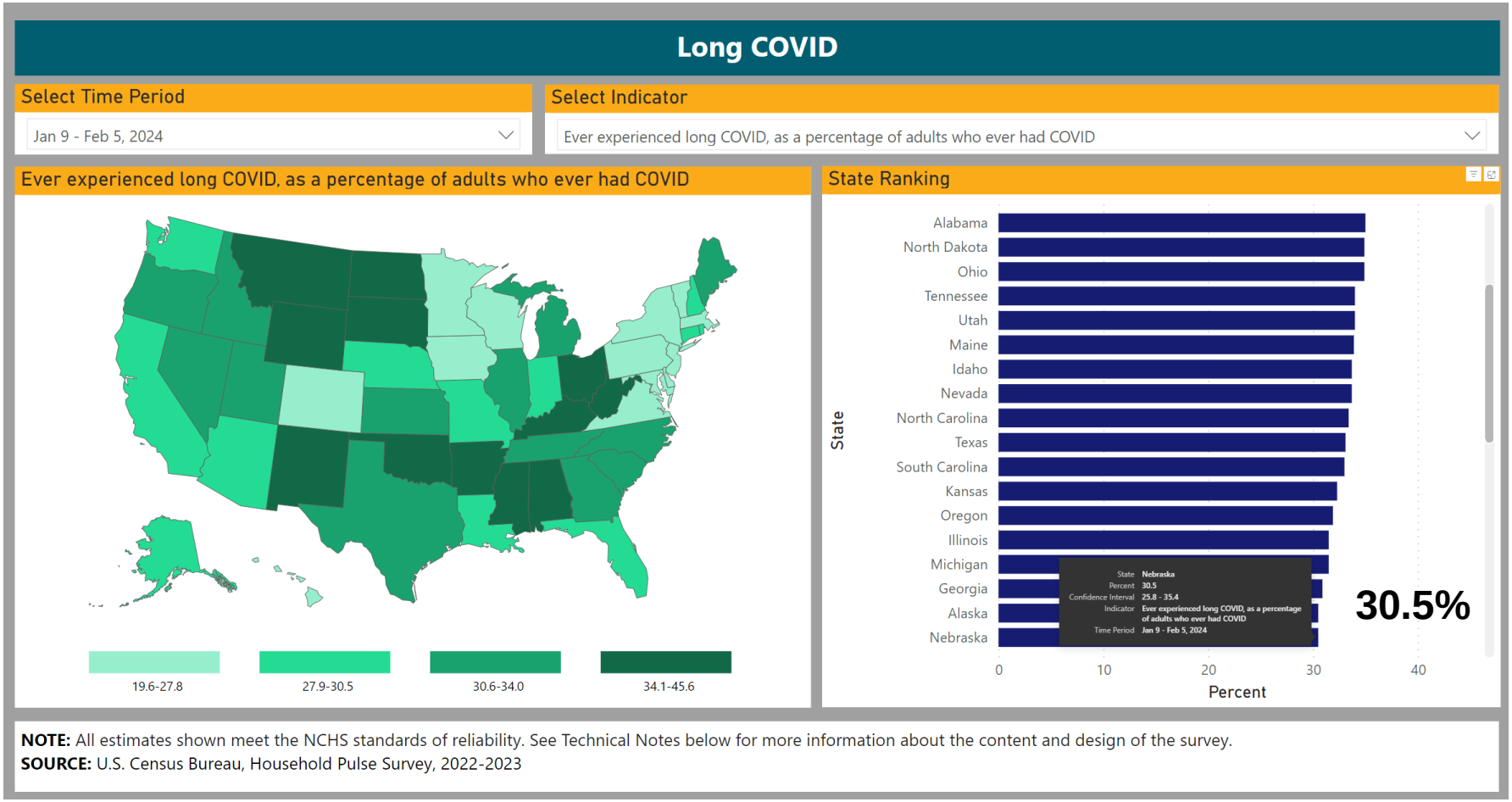
Ever Experienced Long COVID who had COVID-19



NOTE: All estimates shown meet the NCHS standards of reliability. See Technical Notes below for more information about the content and design of the survey.
SOURCE: U.S. Census Bureau, Household Pulse Survey, 2022-2023

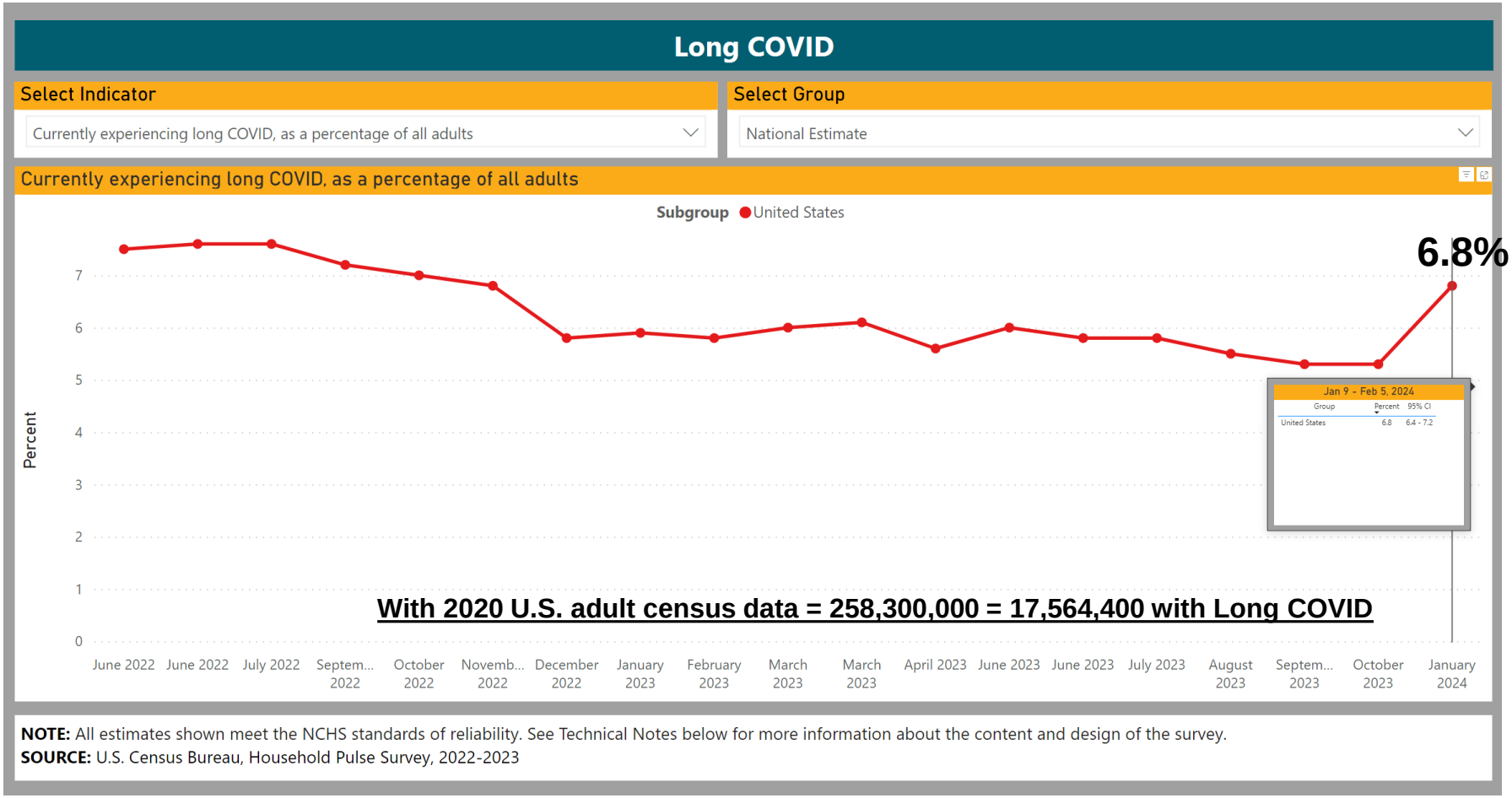
National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID.
Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

Ever Experienced Long COVID who had COVID-19



National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID.
Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

Currently Experiencing Long COVID of All Adults



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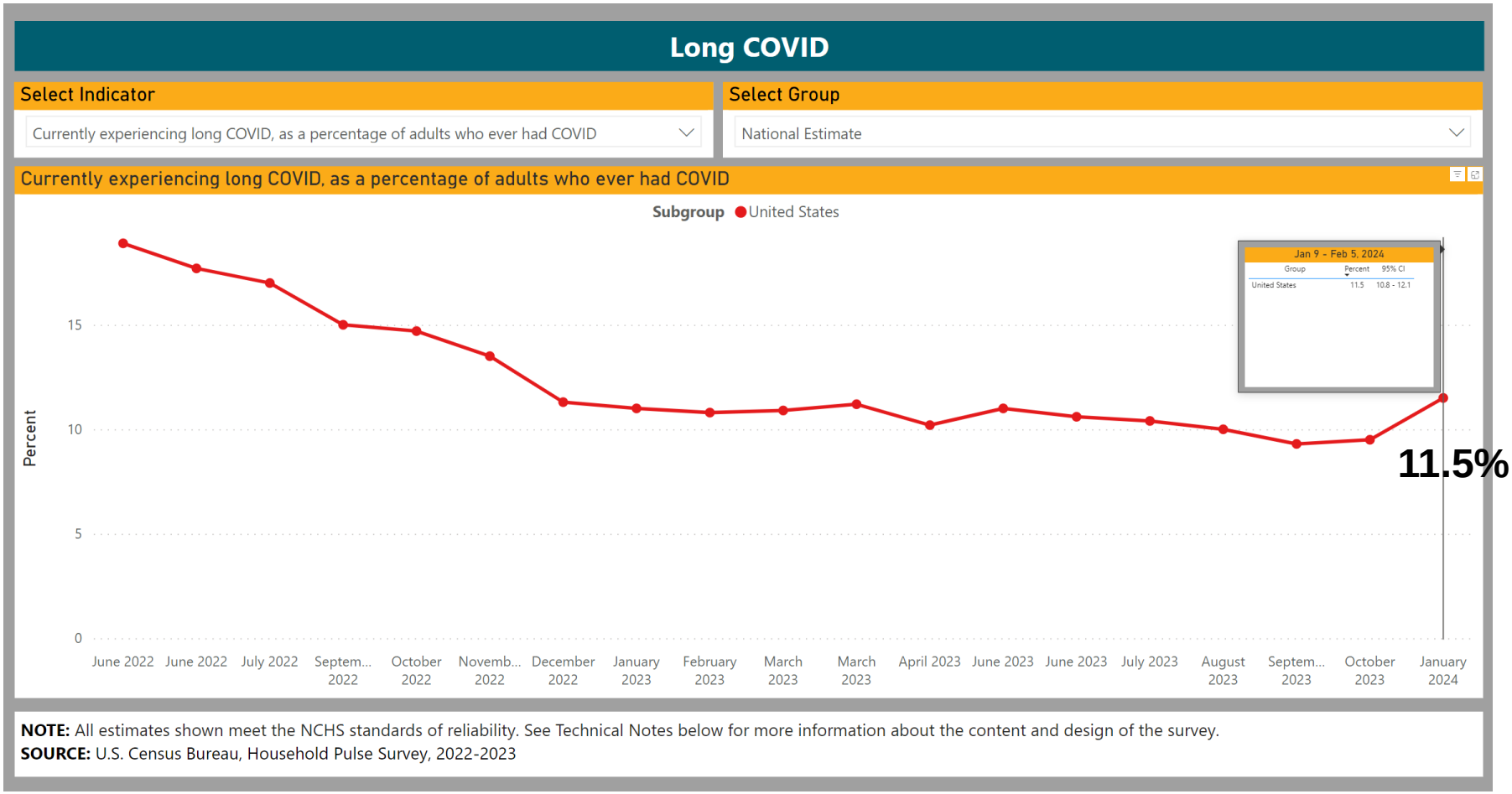
Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

Currently Experiencing Long COVID who had COVID-19



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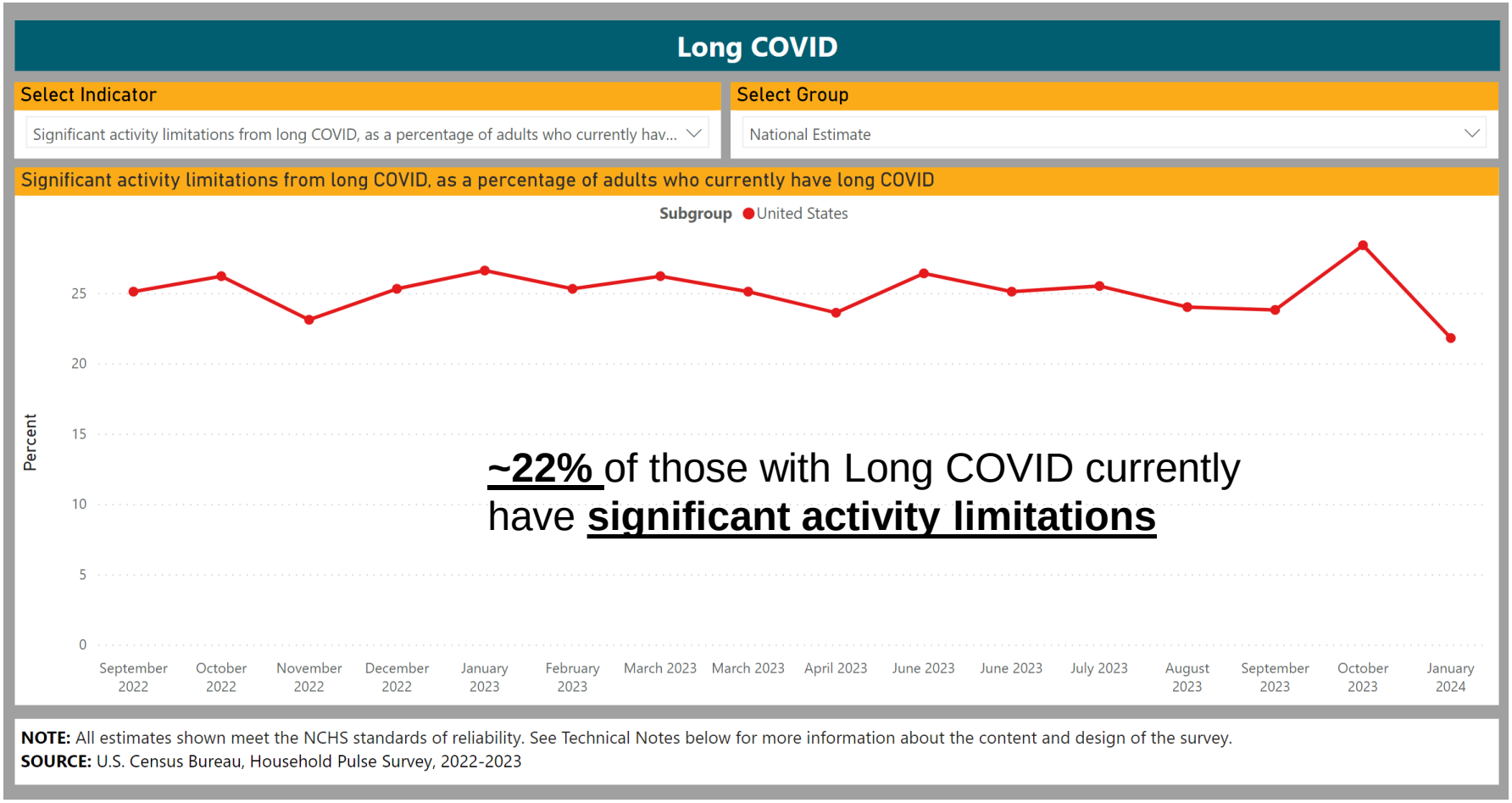
National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID.
Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

Significant Activity Limitations from Long COVID



National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID.
Generated interactively: from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

Who is Most Likely to Develop Long COVID?

- Greater comorbidity burden
  - Diabetes, obesity, anxiety/depression, HIV
- Female sex
- Race/ethnicity
- Socioeconomic status
- Tobacco use
- Recurrent COVID-19 infections

Khullar D, et al. J Gen Intern Med 2023
Klein, et al. Nature 2023
Pfaff, et al. BMC Med 2023
Tsampasian V, et al. JAMA IM 2023
Perlis et al. JAMA 2022
Global Burden of Disease Collaborators; JAMA 2022

Host and viral risk factors potentially associated with increased likelihood of long COVID after SARS-CoV-2 reinfection

	Factor Type	Risk Factor for Long COVID upon Reinfection
Host	Biological	Female sex
		Older age [1]
		Certain comorbidities (e.g., type 2 diabetes)
		Having had severe COVID-19 (particularly during the first few weeks of illness) [2]
	Lifestyle	Obesity
		Smoking
Viral	SARS-CoV-2 variant	Omicron [3]

[1] Older age seems to hold as a risk factor for long COVID after SARS-CoV-2 reinfection also in children (probably >2 years) and adolescents. [2] With a gradient/descending order of severity and likelihood of long COVID after SARS-CoV-2 reinfection as follows: Intensive Care Unit (ICU) vs. hospitalization vs. Symptomatic vs. Mild vs. Asymptomatic infection. [3] Reflecting the increased number of SARS-CoV-2 reinfections with subvariants of the Omicron family.

Boufidou F, Int J Mol Sci. 2023.

Summary of key findings on the associations of long COVID with reinfection, vaccination, and affected population

	Key Findings Regarding Long COVID
Reinfection	Reinfections increase the likelihood of long COVID (and additional complications, e.g., cardiac, pulmonary, neurological, in older subjects).
	The risk of developing long COVID symptoms is significantly lower after asymptomatic (compared to symptomatic) reinfection.
	Long COVID cases have been increasing upon reinfection with Omicron subvariants.
Vaccination	Vaccination against (severe) COVID-19 seems to also protect from long COVID (reduced risk by 15–41%).
	Two vaccine doses (of the primary scheme) are more effective than one dose.
	No difference in relation to the type of received vaccine.
Affected population	Children may also suffer from long COVID, but less frequently and less severely than adults.
	Chronic fatigue is one of the most common symptoms of long COVID present in up to 87% of children and adolescents with long COVID.
	Older age, comorbidities, and symptomatic infection are risk factors for long COVID in children.

Boufidou F, Int J Mol Sci. 2023.

Tired !

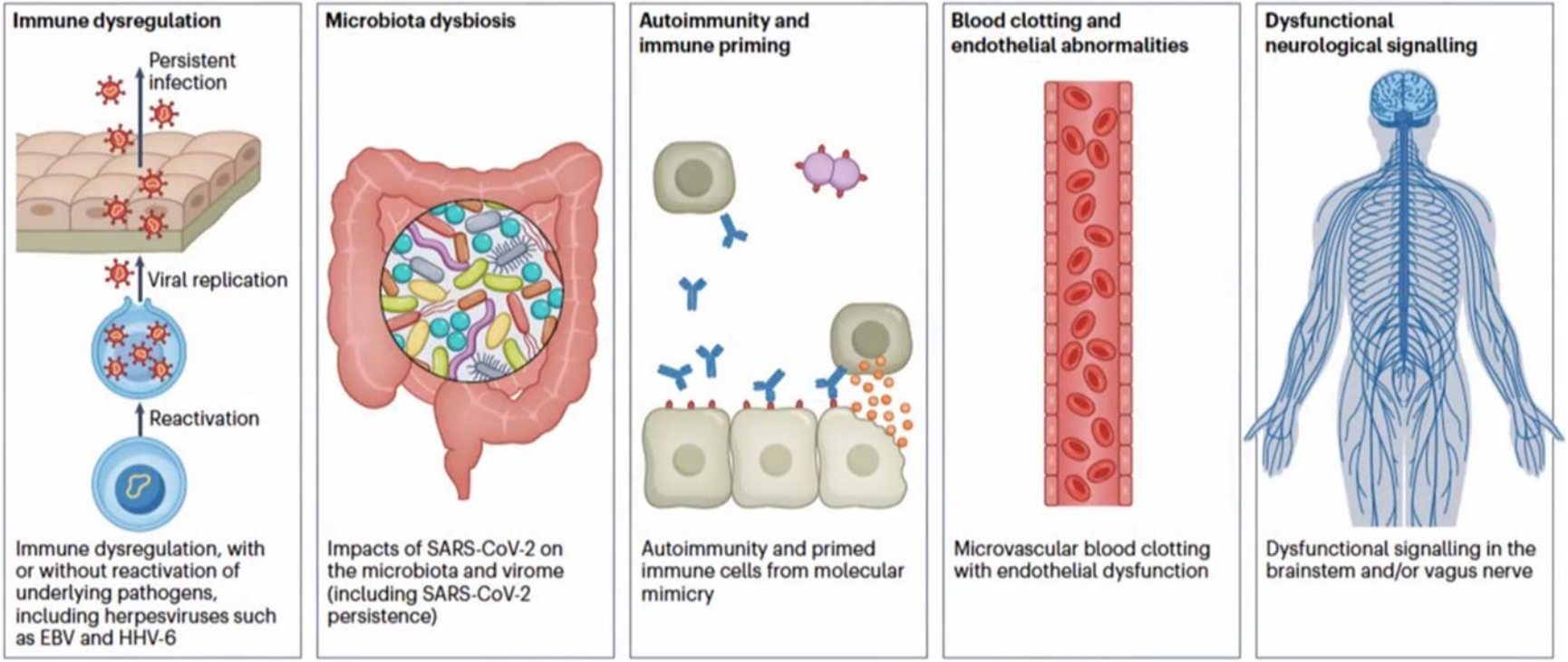
DESCRIBE THE CURRENT UNDERSTANDING OF THE IMMUNOPATHOGENESIS OF LONG COVID

What are the Underlying Causes of Long COVID?

- Phenotyping of 152 persons with long COVID, 40 unvaccinated controls, 39 vaccinated controls, 37 with COVID prior to vaccination
  - Immunologic differences between long COVID and controls
  - Higher antibodies to SARS-CoV-2, EBV, VZV
  - Differences in cytokines and hormones
- Machine learning approach suggested that findings were more consistent with persistent SARS-CoV-2 viral antigens, reactivation of latent herpes viruses and chronic inflammation

Klein J, et al. Nature 2023
Berentschot JC, et al. Front Immunol 2023
Wang K, et al. Cell Rep Med 2023

What are the Underlying Causes of Long COVID?



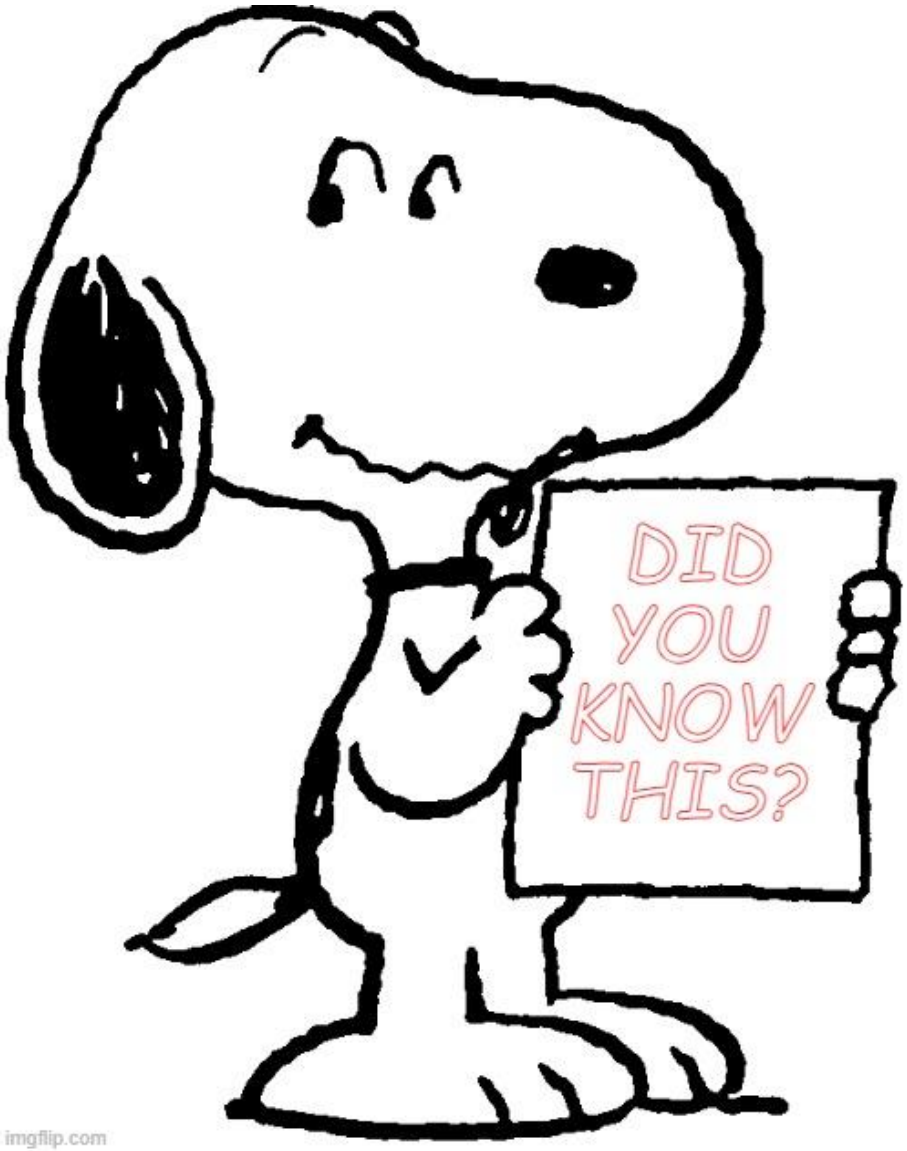
Davis HE, et al. Nat Rev Microbiol. 2023.

Can COVID-19 Vaccines Cause Long COVID?

- Every vaccination, including the COVID-19 vaccine, can cause side effects like fatigue and muscle pain
- Yet….there is emerging data to suggest a Post-COVID vaccination syndrome or

  "Long VAX"

Patterson BK, et al. Research Square. 2022.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POLISH ANNALS OF MEDICINE

Author *Michael Thoene*

Department of Medical Biology, School of Public Health, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland

REVIEW PAPER

Changing Views toward mRNA based Covid Vaccines in the Scientific Literature: 2020 - 2024

Michael Allen Thoene

DOI: https://doi.org/10.29089/paom/189961

Abstract Article (PDF)

Conclusions:

The early scientific literature was biased, so as not to report SAEs, due to social and political concerns and overwhelming corporate greed. Only in the last year have scientists been able to publish articles that acknowledge a high number of SAEs linked to mRNA based vaccines. This should act as a warning that science should be completely objective when evaluating health risks, but can often be influenced by social and economic considerations.

Thoene MA. Changing Views toward mRNA based Covid Vaccines in the Scientific Literature: 2020–2024. Pol Ann Med. 2024 [in press]. https://doi.org/10.29089/paom/189961

Molecular Neurobiology (2022) 59:1850–1861
https://doi.org/10.1007/s12035-021-02696-0

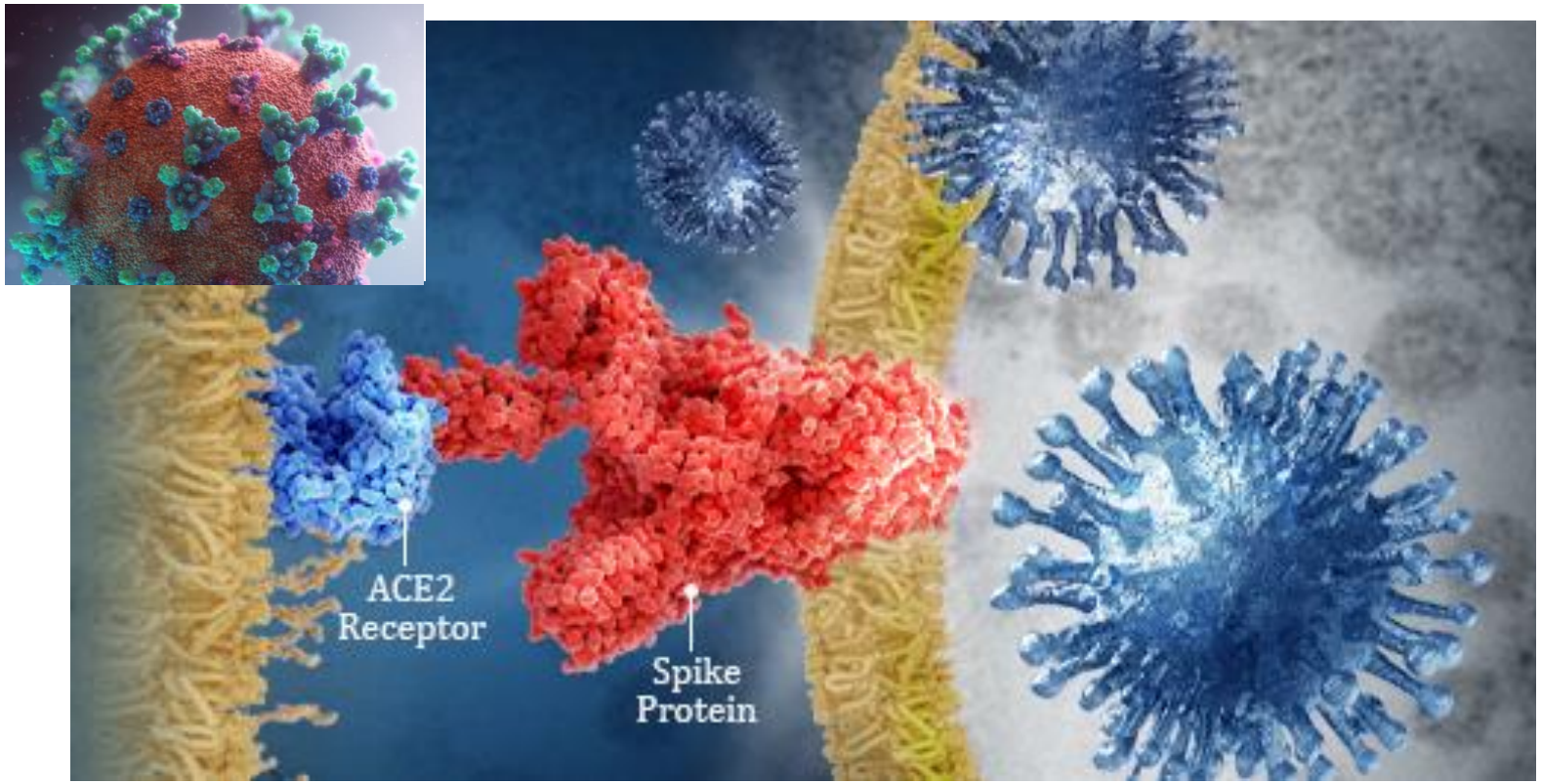
Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome?

Theoharis C. Theoharides[1,2,3,4]

Hypothesis/Theory

Some of the damaging effects of SARS-CoV-2, especially in the brain, may be due to direct action of the Spike protein, acting alone or in conjunction with other mediators such as inflammatory cytokines, on target cells.

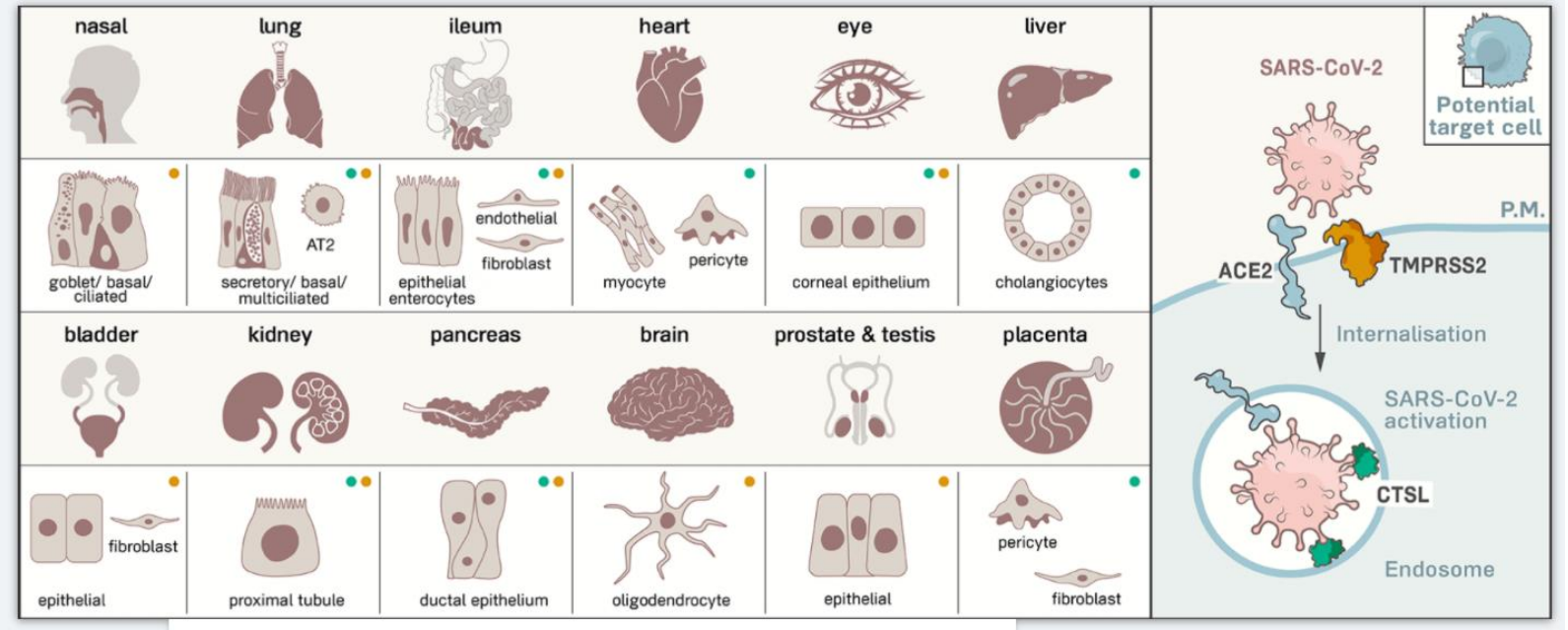
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8757925/pdf/12035_2021_Article_2696.pdf



- Spike (S) protein binds with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor
- ACE2 is expressed in type II alveolar cells and in most organs
- Protease activation is required for entry into the human host cell

https://www.genetex.com/Research/Overview/infectious_diseases/SARS-CoV-2

Receptors for SARS-CoV-2 Present in Wide Variety of Human Cells

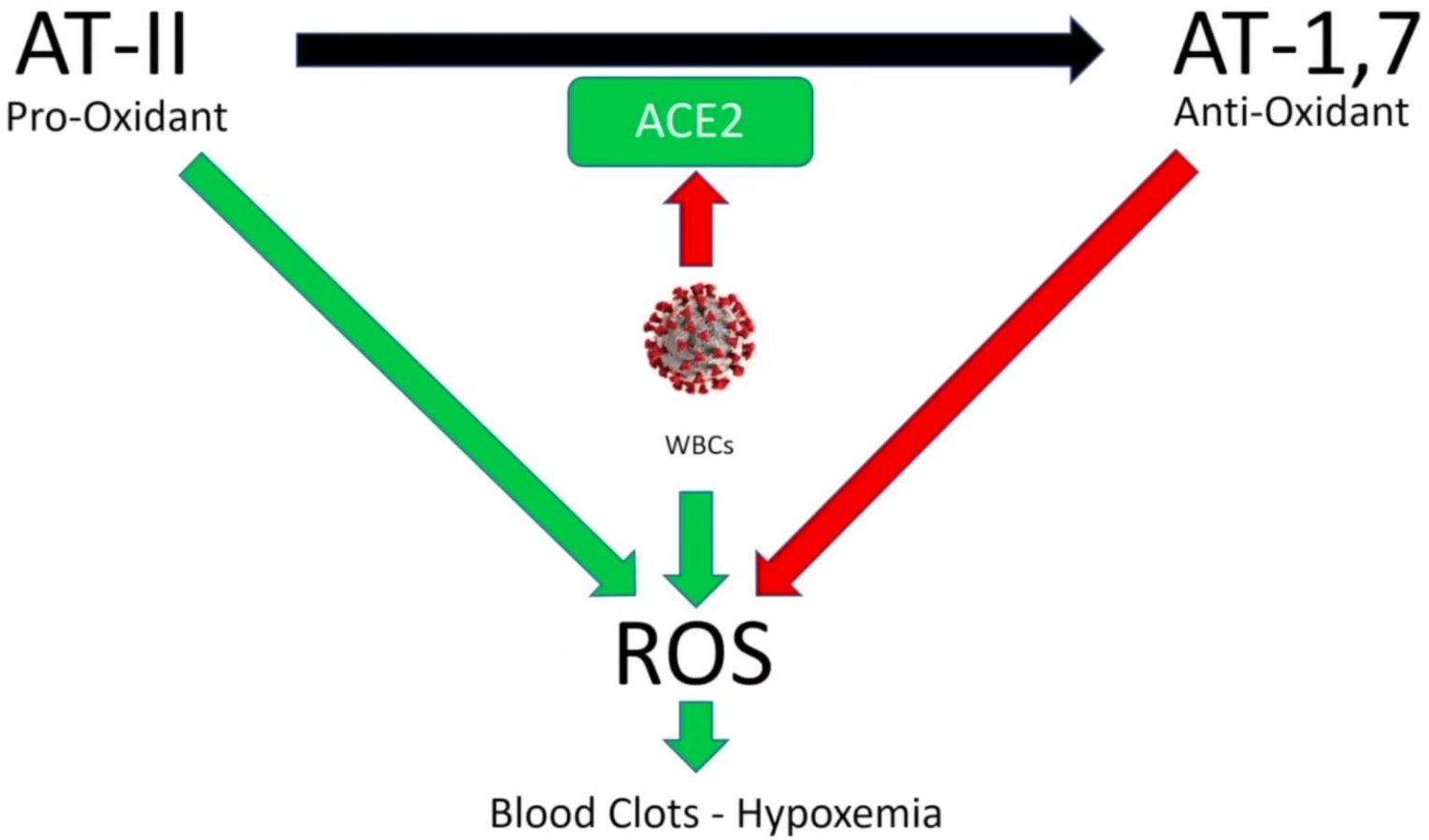


Human cell types within corresponding organs that express the genes for both ACE2 and CTSL (green dot) or both ACE2 and TMPRSS2 (orange dot).
ANNA HUPALOWSKA

Baraniuk C. TheScientist. April 29, 2020.

SARS-CoV-2 and ACE-2 Dysregulation

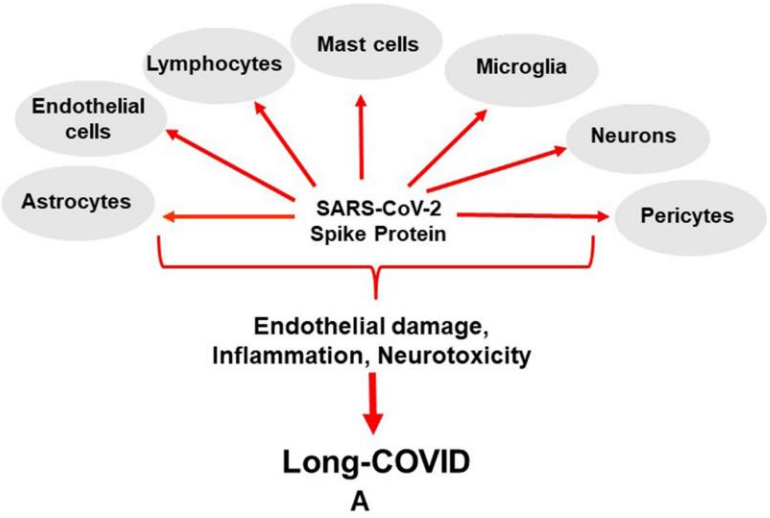
Renin-angiotensin System (RAS)



Seheult, Roger. YouTube. 2023.

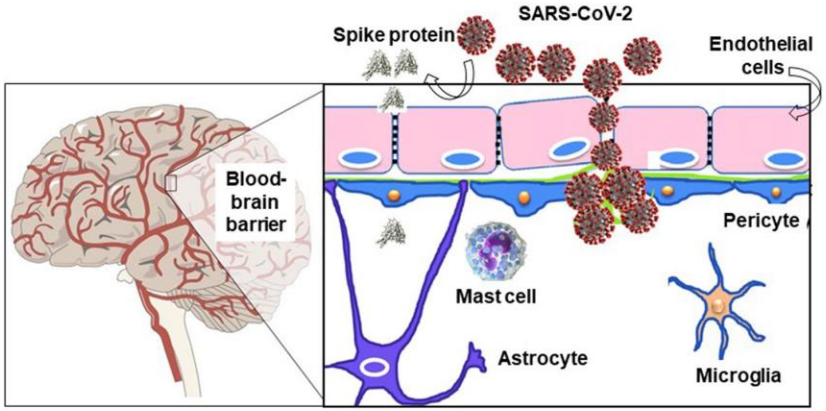
SARS-CoV-2 Spike Protein

A. SARS-CoV-2 spike protein:
-- stimulate different cell types
-- collectively contribute to the pathogenesis of long-COVID



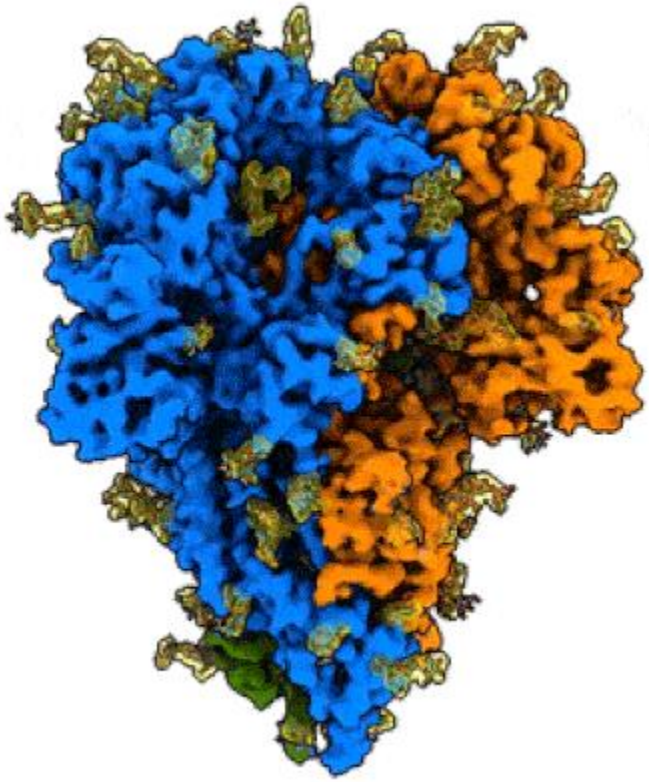
A

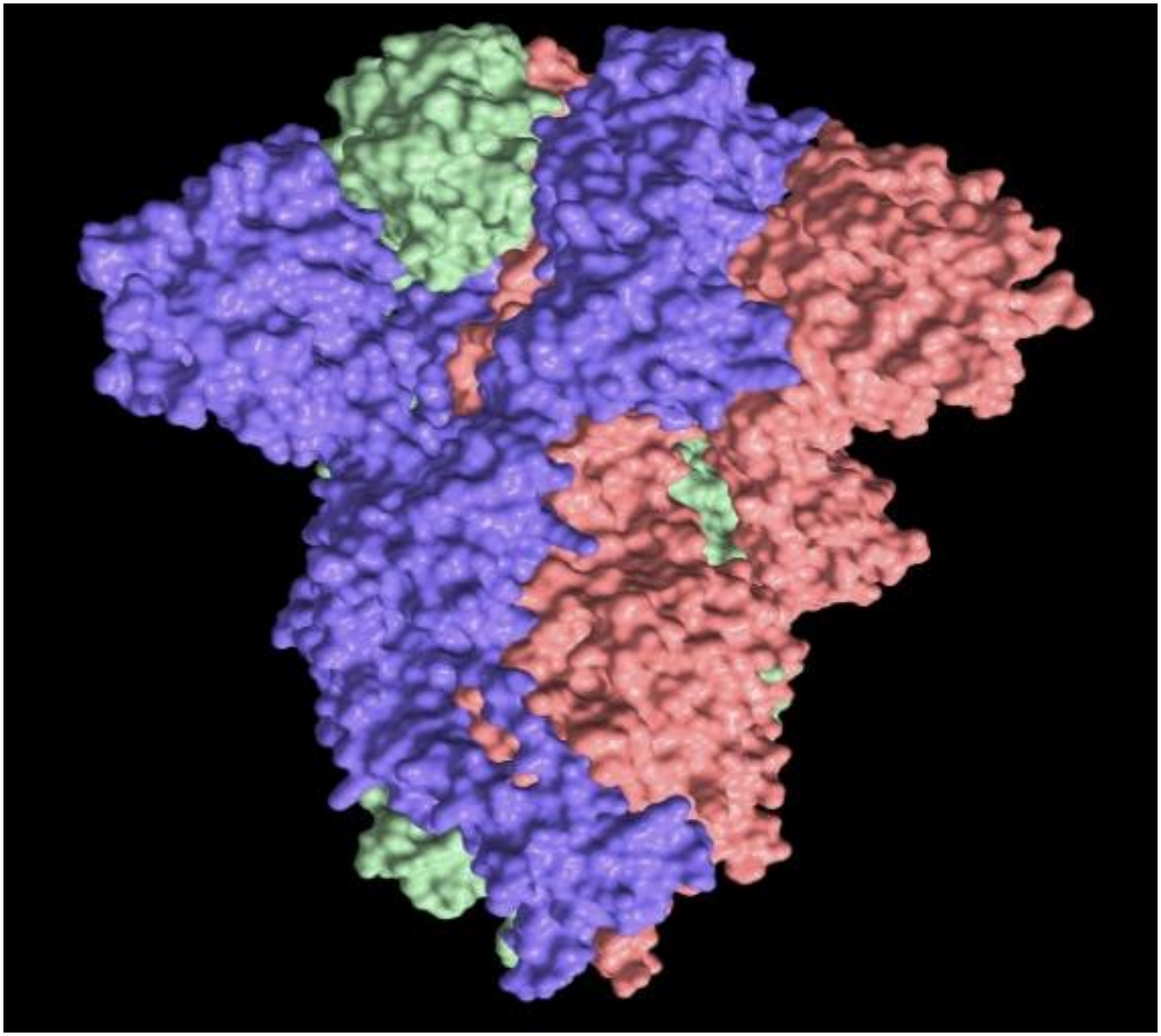
B. SARS-CoV-2
-- cross the blood-brain barrier (BBB) through endothelial cell gaps
-- free spike protein can damage the integrity of the BBB and enter the brain



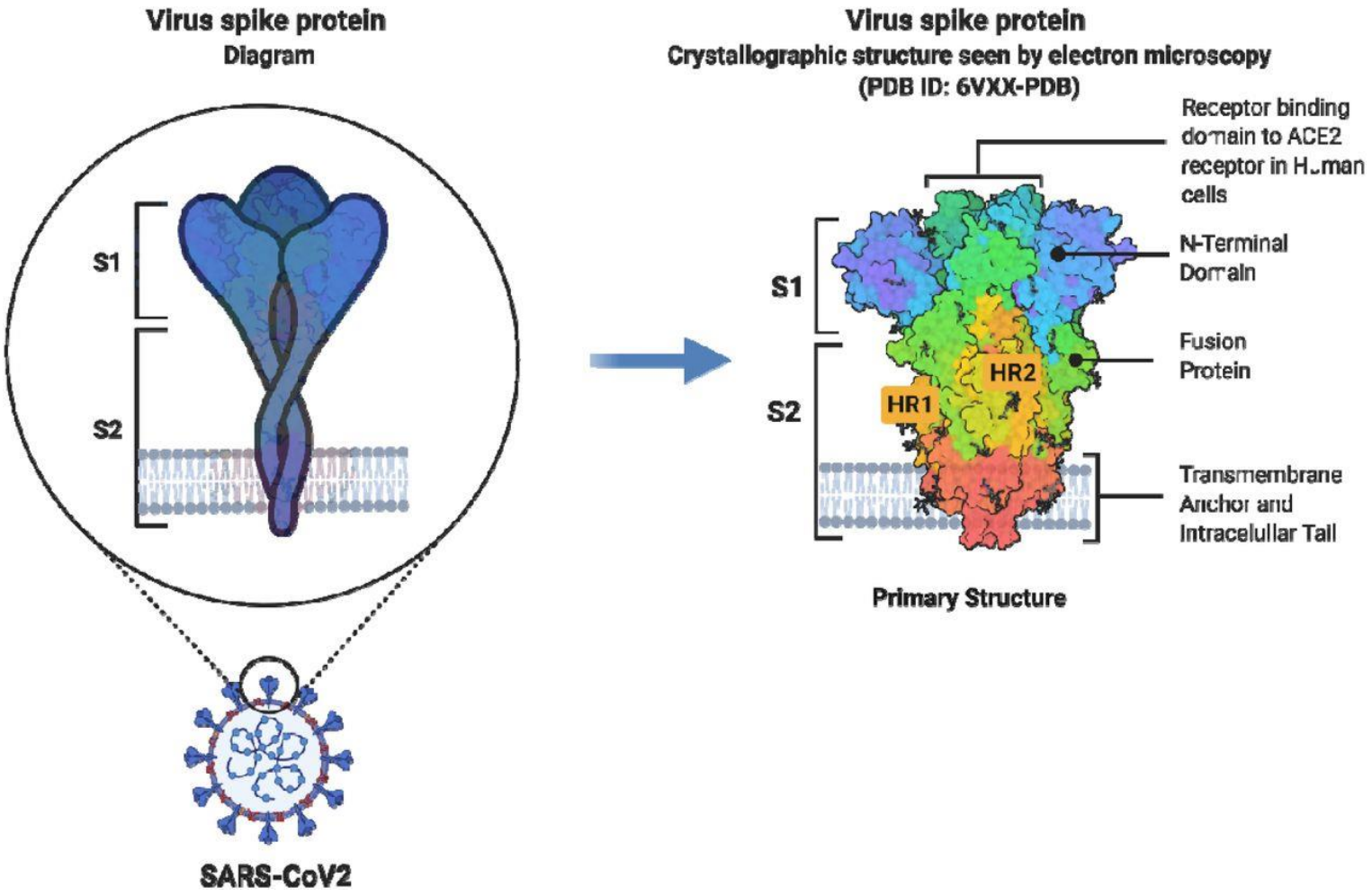
B

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8757925/pdf/12035_2021_Article_2696.pdf

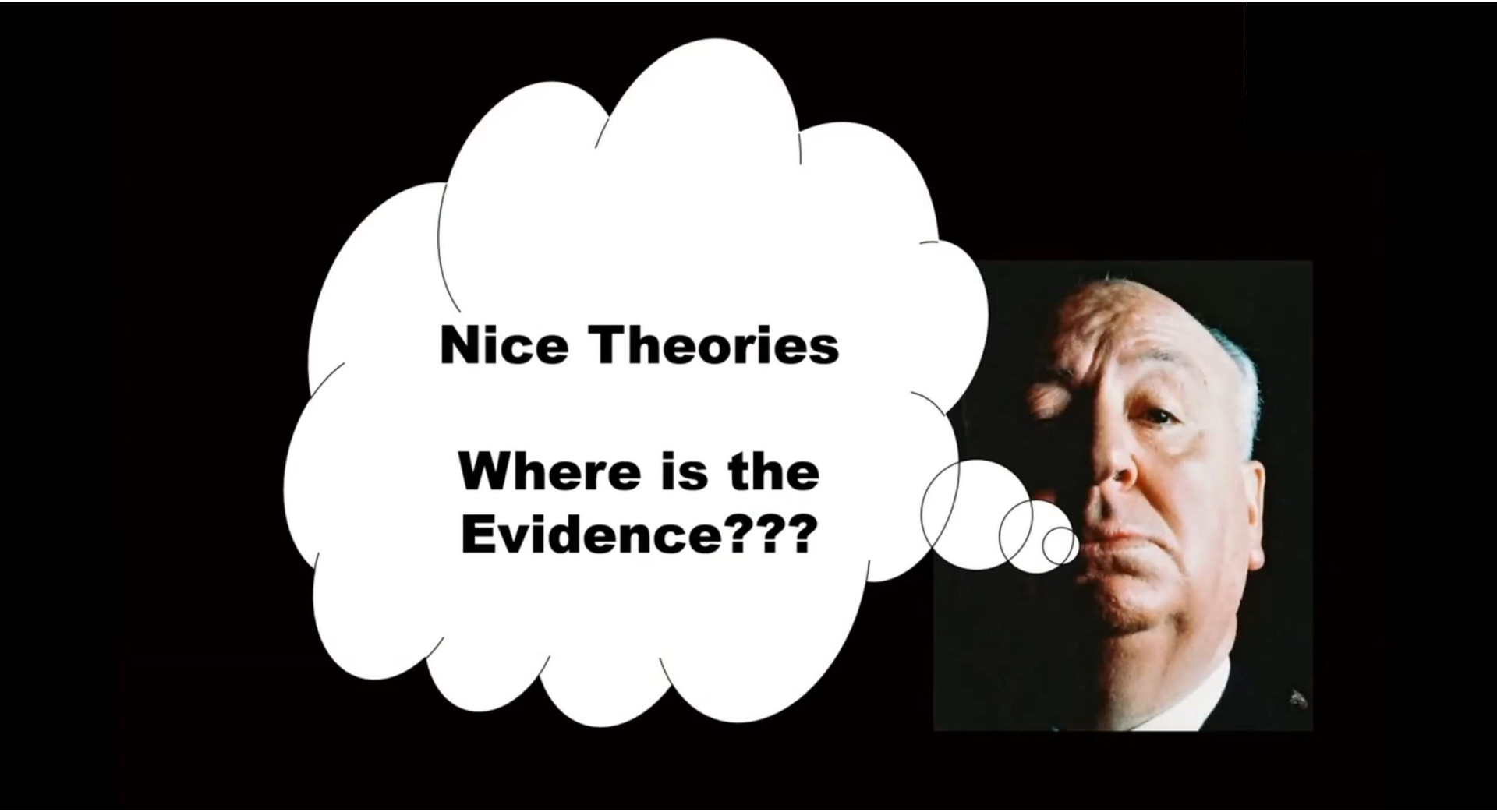




Schematic representation of SARS-CoV-2 Spike glycoprotein



Adapted from (Duan et al., 2020). Abbreviations: S1, subunit 1; S2, subunit 2; HR1, heptad repeat 1; HR2, heptad repeat 2. This image was created with BioRender (https://biorender.com/)


Nice Theories
Where is the Evidence???

biomedicines

MDPI

Review

'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA

Peter I. Parry [1,2,*], Astrid Lefringhausen [3], Conny Turni [4], Christopher J. Neil [5], Robyn Cosford [3], Nicholas J. Hudson [6] and Julian Gillespie [3]

Key problem areas:

(1) the toxicity of the spike protein—both from the virus and also when produced by gene codes in the novel COVID-19 mRNA and adenovectorDNA vaccines, hence the novel term 'spikeopathy'

(2) inflammatory properties of certain lipid-nanoparticles used to ferry mRNA

(3) N1-methylpseudouridine in the synthetic mRNA that causes long-lasting action

(4) widespread biodistribution of the mRNA and DNA codes via the lipid-nanoparticle and the viral-vector carrier matrices, respectively

(5) the problem of human cells producing a foreign protein in our ribosomes that can engender autoimmunity

Parry PI, et al. Biomedicines. 2023.

Biopsy and Autopsy Evidence of Spikeopathy

Cardiac Tissue

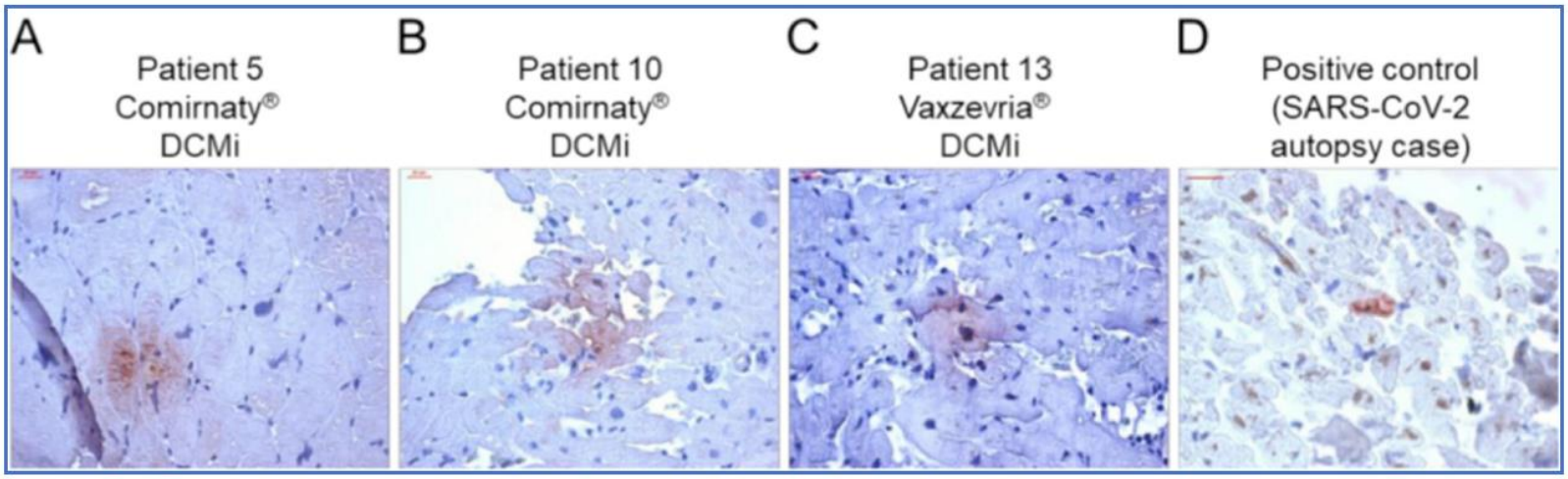


Figure 7. A. Evidence of SARS-CoV-2 spike protein in cardiac tissue after COVID-19 vaccination. (A–C) Representative immunohistochemical stainings of SARS-CoV-2 spike protein in EMBs from patients diagnosed with DCMi after receiving Comirnaty® (panel (A,B), patients 5 and 10) or Vaxzevria® (panel (C), patient 13). (D) SARS-CoV-2-positive cardiac tissue served as positive control. Magnification 400. Scale bars 20 m. Reprinted with permission from Baumeier C, et al. Int J Mol Sci. 2022. Copyright 2022 MDPI. From Parry PI, et al. Biomedicines. 2023.

Biopsy and Autopsy Evidence of Spikeopathy

Brain Tissue

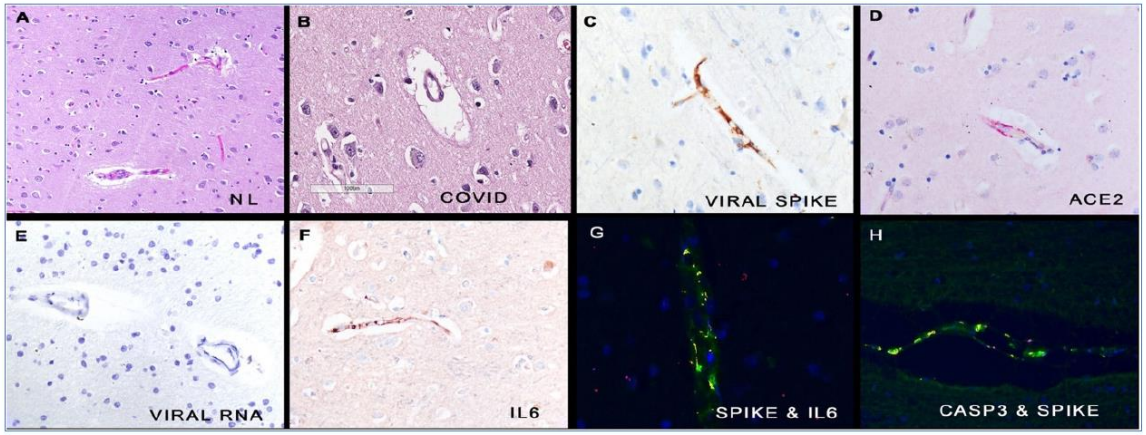


Figure 8. Histologic and molecular correlates of COVID-19 in human brains. Panel (A) shows the microvessels in normal brain. In comparison, many of the capillaries in COVID-19 brain tissues show marked perivascular oedema (panel (B)). Serial section analyses of the COVID-19 brain shows that the endothelial cells of the microvessels contained the spike glycoprotein (panel (C)), the ACE2 receptor (panel (D)) and IL 6 (panel (F)), but not viral RNA (panel (E)). The fluorescent yellow signal marks co-localisation of the spike protein with IL6 (panel (G)) and caspase 3 (panel (H)), respectively, in these endothelial cells. Each magnification is 800 with DAB (brown) signal (panels (C–F)) or Fast Red (red) (panel D). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). Reprinted from Annals of Diagnostic Pathology, Vol. 51, Nuovo GJ, Magro C, Shaffer T. et al., Endothelial cell damage is the central part of COVID-19 and a mouse model induced by injection of the S1 subunit of the spike protein. Figure 1, 151682, Reprinted with permission from Nuovo GJ, et al. Ann Diag Path. 2021. Copyright (2020) Elsevier. From Parry PI, et al. Biomedicines. 2023.

DRTROZZI

COVID Injections: Unveiling the Mechanisms of Harm

New pathology, a new wave of disease, and 44 common examples of injection-induced illnesses supported by over 930 scientific publications linking these diseases with the injections.

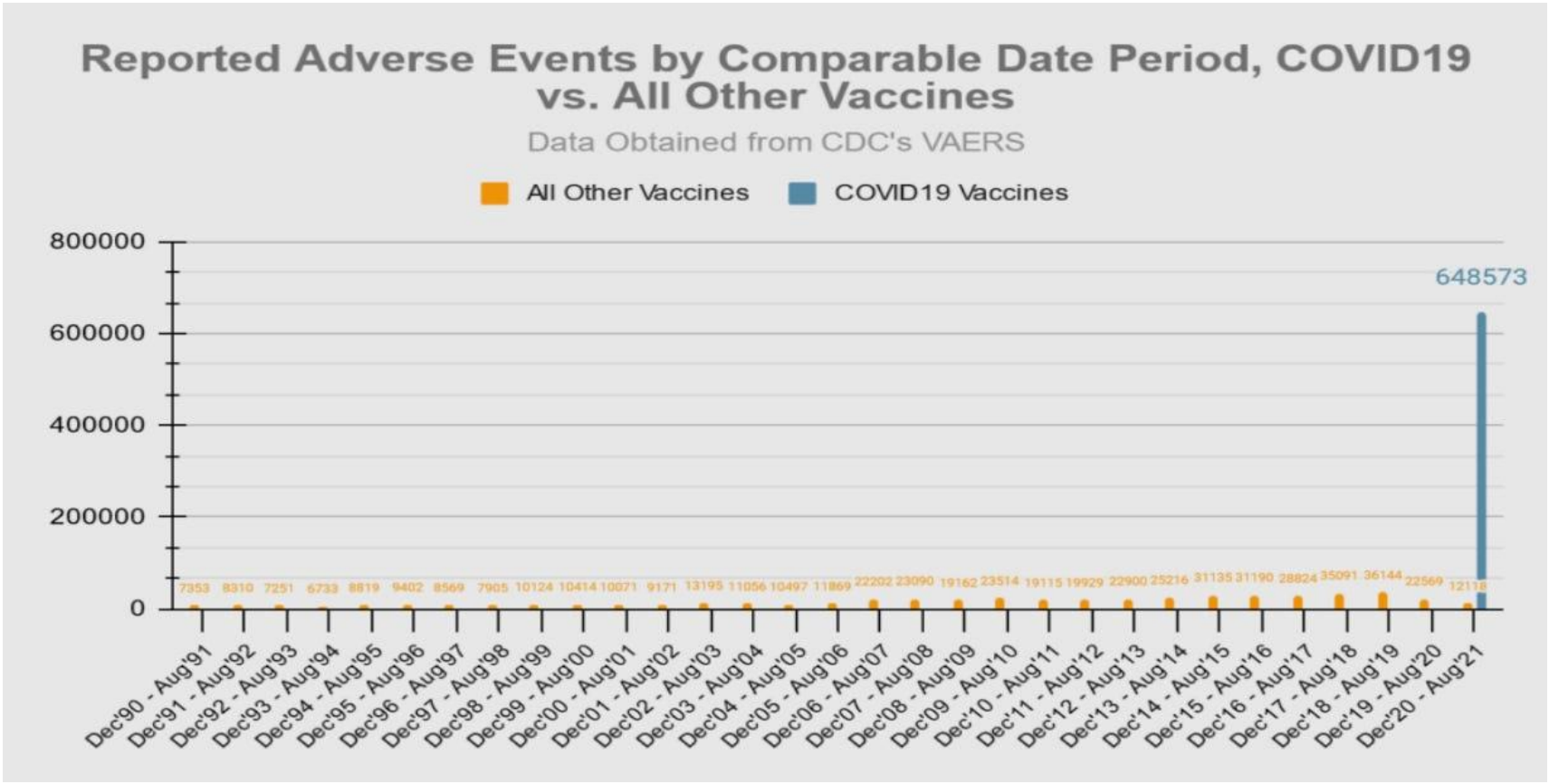
OCT 04, 2024

84 14 Share

Introduction

The list of traditional diagnoses arising as sequel from the COVID-19 genetic injections is extensive. Pfizer's own analysis alone lists over a thousand different diagnosed adverse reactions (Click Here, Page 30-38). The failure and dangers of these genetic experiments were predictable, based on pre-2020 scientific knowledge. Yet, despite diligent efforts to warn the public, elected officials, and bureaucrats, billions of people (many repeatedly) have been subjected to these injections in what can only be described as a radical and unethical medical experiment. In many countries, including Canada, doctors who voiced caution were unlawfully persecuted—our careers, incomes, and reputations tarnished.

https://www.drtrozzi.news/p/covid-injections-unveiling-the-mechanisms?r=2238xm&utm_medium=ios&triedRedirect=true


Reported Adverse Events by Comparable Date Period, COVID19 vs. All Other Vaccines
Data Obtained from CDC's VAERS
All Other Vaccines
COVID19 Vaccines
800000
600000
400000
200000
0
648573
7353 8310 7251 6733 8819 9402 8569 7905 10124 10414 10071 9171 13195 11056 10497 11869 22202 23090 19162 23514 19115 19929 22900 25216 31135 31190 28824 35091 36144 22569 12118
Dec'90 - Aug'91
Dec'91 - Aug'92
Dec'92 - Aug'93
Dec'93 - Aug'94
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Dec'14 - Aug'15
Dec'15 - Aug'16
Dec'16 - Aug'17
Dec'17 - Aug'18
Dec'18 - Aug'19
Dec'19 - Aug'20
Dec'20 - Aug'21

44 examples of COVID 'vaccine'-induced diseases, backed by 930+ scientific articles linking these conditions to the injections

- Acute Hyperactive Encephalopathy
- Acute Kidney Injury
- Acute Myelitis
- Allergic Reactions
- Alopecia Areata
- Anaphylaxis
- Axillary Adenopathy
- Bell's Palsy
- Bullous Drug Eruption
- Capillary Leak Syndrome
- Cardiac Complications
- Central Serous Retinopathy
- Cerebral Venous Thrombosis
- Cutaneous Adverse Effects
- Facial Nerve Palsy
- Guillain-Barré Syndrome
- Hemophagocytic Lymphohistiocytosis
- Henoch-Schonlein Purpura
- Immune-Mediated Disease Outbreaks
- Immune-Mediated Hepatitis
- Internal Bleeding
- Intracerebral Haemorrhage
- Lymphadenopathy
- Multiple Sclerosis
- Myocarditis
- Myopericarditis
- Nephrotic Syndrome
- Neurological Symptoms
- Oculomotor Paralysis
- Pericarditis
- Perimyocarditis
- Petechiae
- Prion Disease
- Psoriasis
- Pulmonary Embolism
- Purpura Annularis Telangiectodes
- Rhabdomyolysis
- Systemic Lupus Erythematosus
- Takotsubo Cardiomyopathy
- Thrombocytopenia
- Thrombosis
- Thrombotic Thrombocytopenic Purpura
- Vasculitis
- Vogt-Koyanagi-Harada Syndrome

https://www.drtrozzi.news/p/covid-injections-unveiling-the-mechanisms?r=2238xm&utm_medium=ios&triedRedirect=true

Correlation versus Causation?

Unusual rubbery clots found in arteries and veins

https://www.drtrozzi.news/p/covid-injections-unveiling-the-mechanisms?r=2238xm&utm_medium=ios&triedRedirect=true

What can we conclude about Spikeopathy?

- SARS-CoV-2 spike protein is pathogenic, whether from the virus or created from genetic code in mRNA and adenovector DNA vaccines.

Parry PI, et al. Biomedicines. 2023.

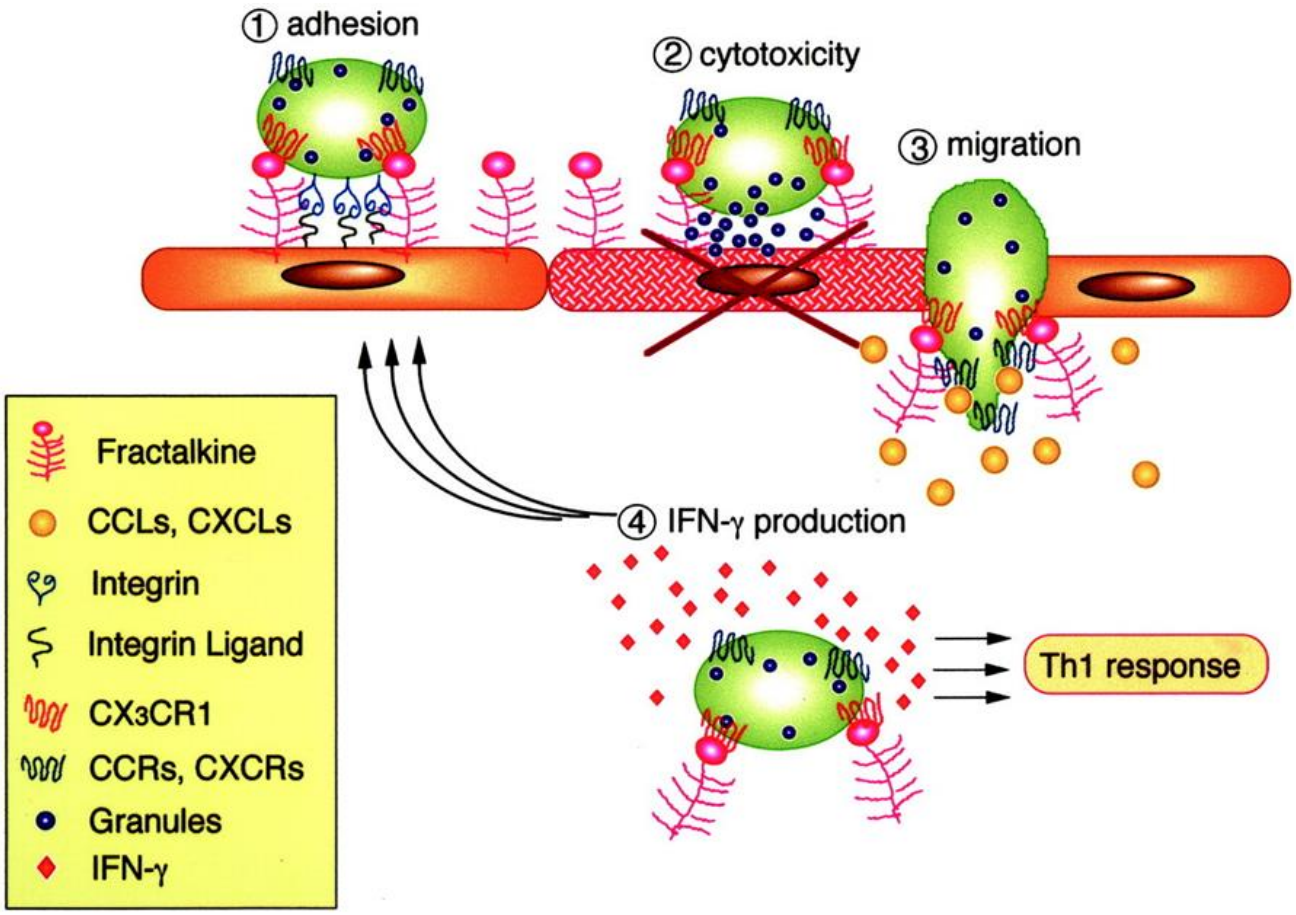
https://www.5oclockreflections.com/assets/ostrich-650x400.jpg

Pathogenesis of Long COVID

- Data from incellDx has shown that long COVID is vascular inflammation caused by persistence of the S1 protein in white blood cells months and now over a year post-infection

Patterson, Bruce. Incellkine Multiplex Assay Cytokine Test. YouTube video, 1:02:19. September 8, 2023.

Role of fractalkine (CX3CL1) in vascular inflammation



Umehara H, et al. Fractalkine in Vascular Biology. Arteriosclerosis, Thrombosis, and Vascular Biology. January 2004. Volume: 24, Issue: 1, Pages: 34-40, DOI: (10.1161/01.ATV.0000095360.62479.1F)

Circulation

ON MY MIND

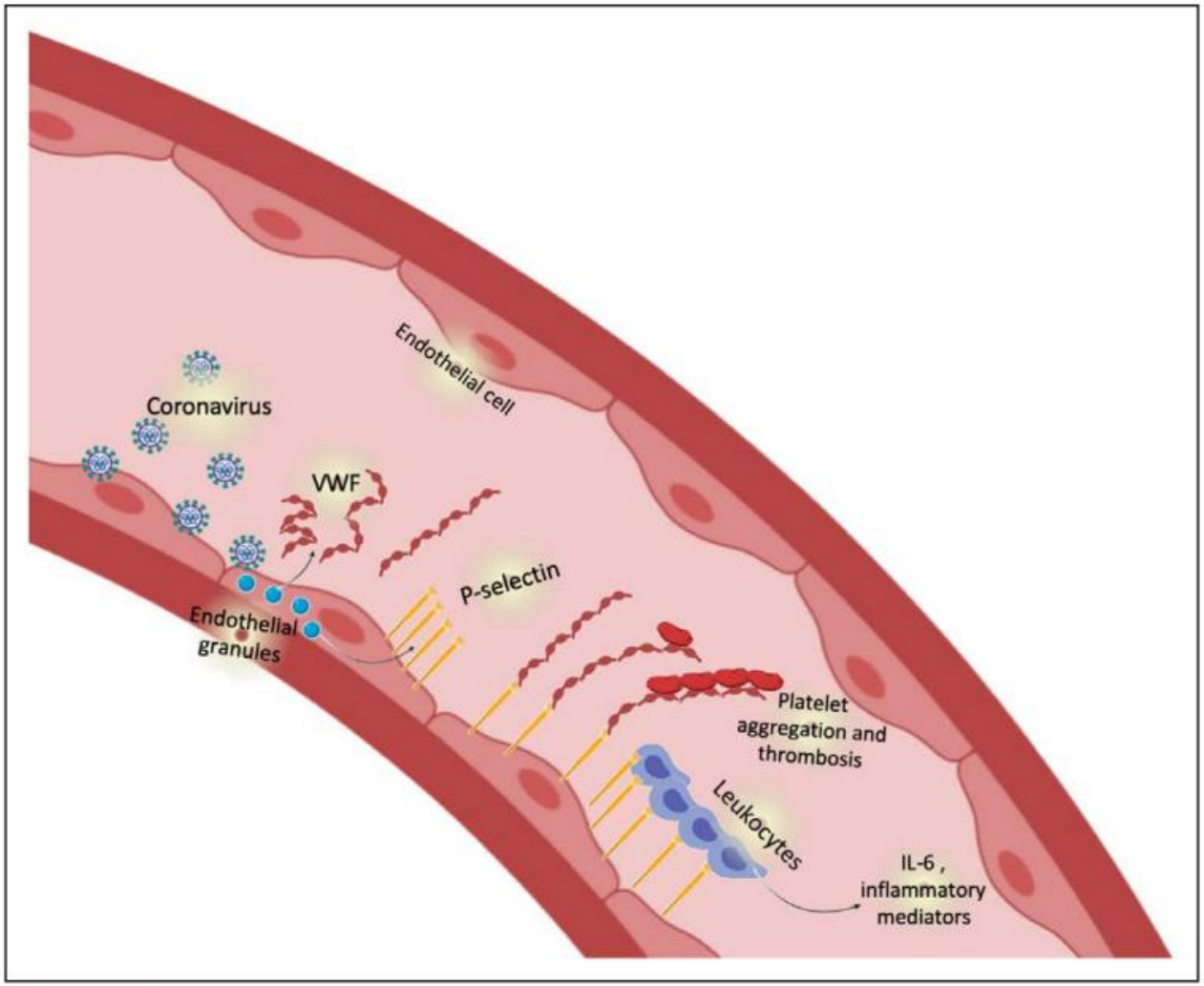
Severe COVID-19 Is a Microvascular Disease

Charles J. Lowenstein, MD, Scott D. Solomon, MD

- Clues to the pathogenesis of severe COVID-19 may lie in the systemic inflammation and thrombosis observed in infected patients
- Patients with severe COVID-19 often have laboratory findings consistent with a hypercoagulable state, suggesting widespread thrombosis and fibrinolysis, as well as elevated levels of D-dimer, von Willebrand factor (VWF), and factor VIII
- Endothelial injury is an underlying mechanism that might link inflammation and thrombosis in severe COVID-19
- We propose that severe COVID-19 is a microvascular disease in which coronavirus infection activates endothelial cells, triggering exocytosis, a rapid vascular response that drives microvascular inflammation and thrombosis

Circulation. 2020;142:1609–1611. DOI:10.1161/CIRCULATIONAHA.120.050354

Endothelial exocytosis in coronavirus disease 2019 (COVID-19)



Lowenstein CJ, et al. Circulation. 2020.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

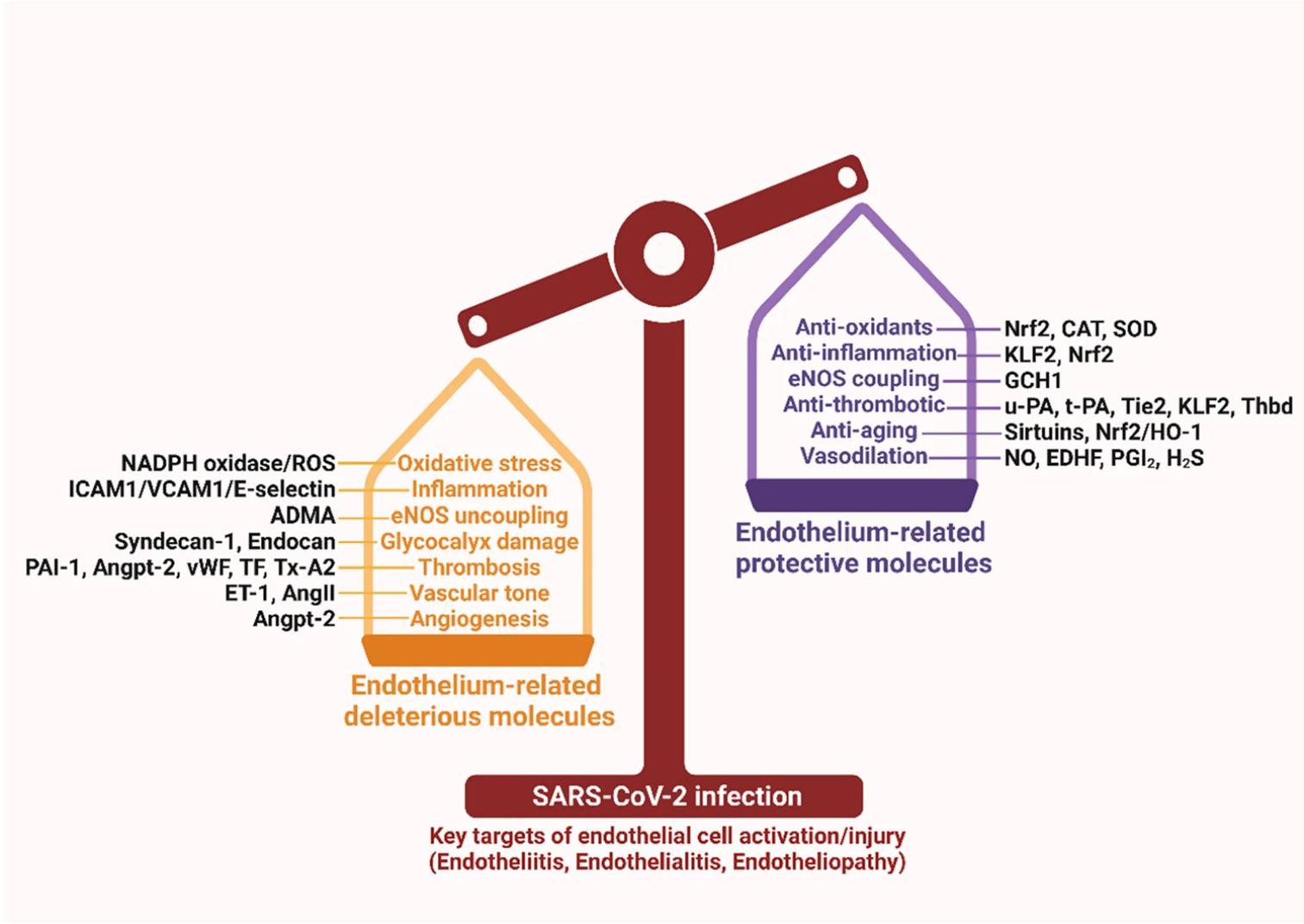
Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

ABSTRACT

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2015432

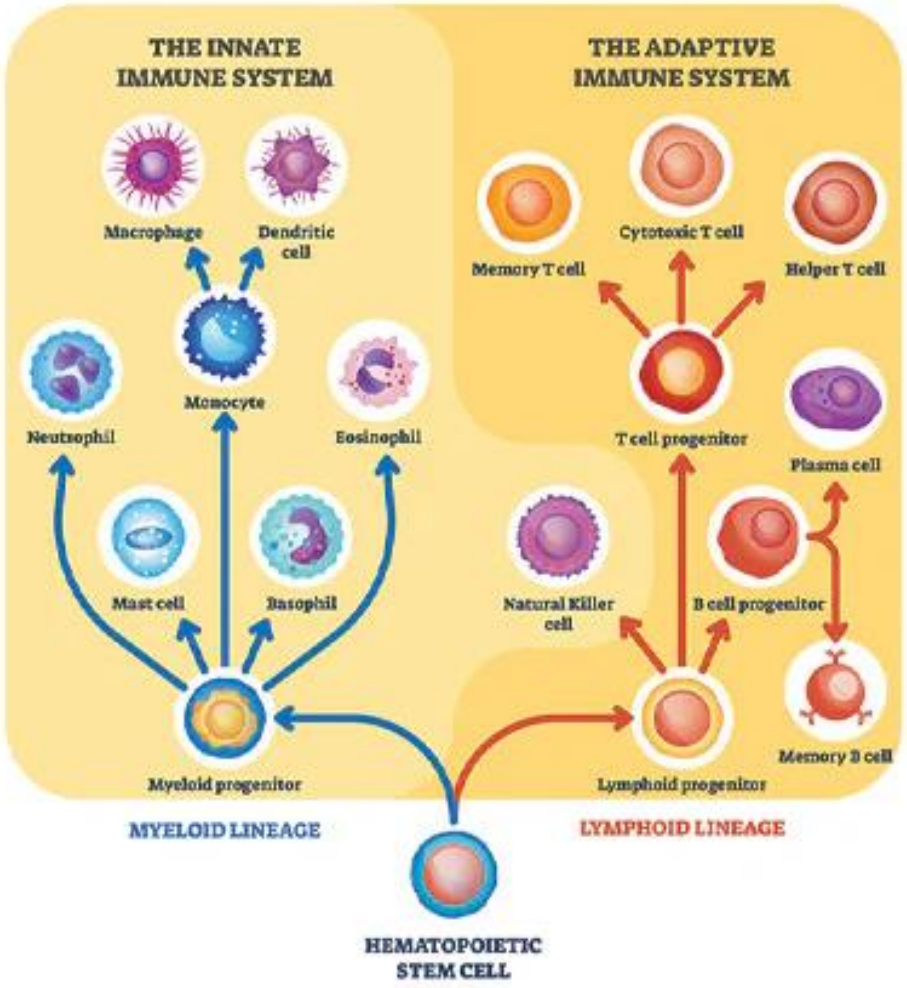
Ackermann M, et al. N Engl J Med. 2020.

SARS-CoV-2 induced endothelial dysfunction



Xu S, et al. Acta Pharmacol Sin. 2023

Cells of the Immune System



https://skinkraft.com/blogs/articles/difference-between-innate-and-adaptive-immunity

Naïve T cell Polarization

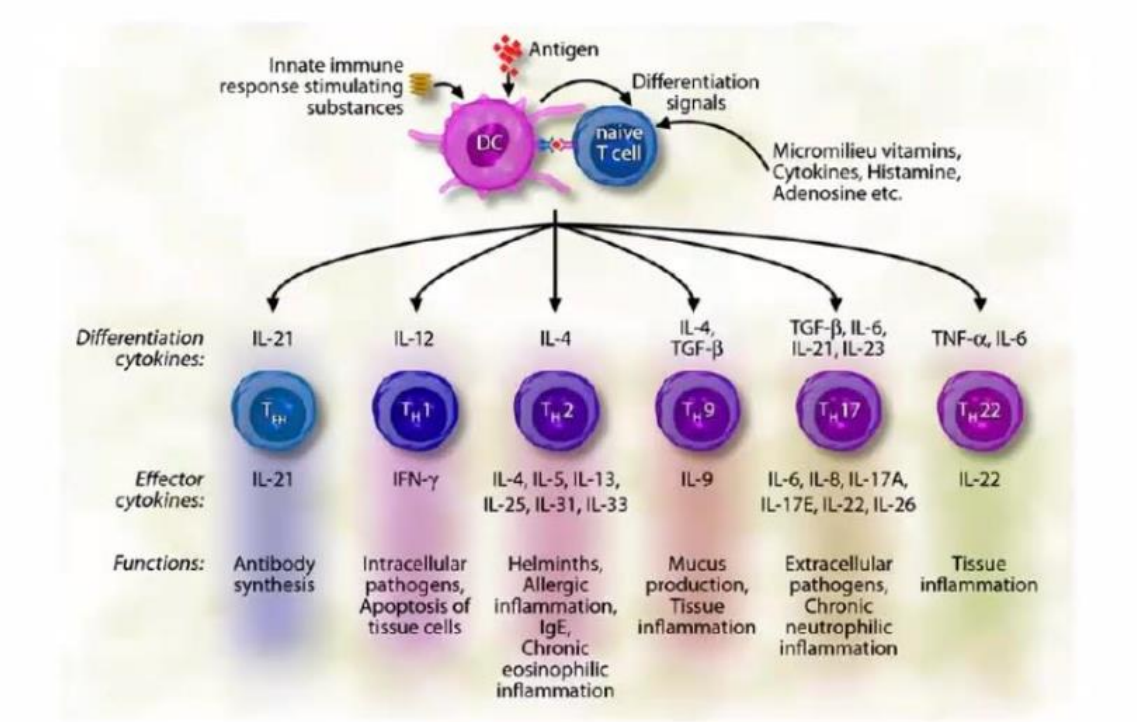


FIG 2. Antigen presentation by DCs to naive T cells and other factors (innate immune response substances, vitamins, cytokines in the environment) induces the T cells to produce ILs and differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, or follicular T_H (T_{FH}) cells. These T-cell subsets can promote different types of inflammatory responses on the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells.

Akdis M, et al. J Allergy Clin Immunol. 2011.

Monocyte Heterogeneity

- As early as 1989, with the use of monoclonal antibodies and two-color flow cytometry, three distinct human monocyte subsets could be identified based on the expression of CD14 and CD16 surface antigens:
  - Classical CD14++CD16−
  - Intermediate CD14++CD16+
  - Nonclassical CD14+CD16++

Subsets

Narasimhan PB, et al. Annu Rev Immunol. 2019

Phenotype and function of circulating monocyte subsets in humans

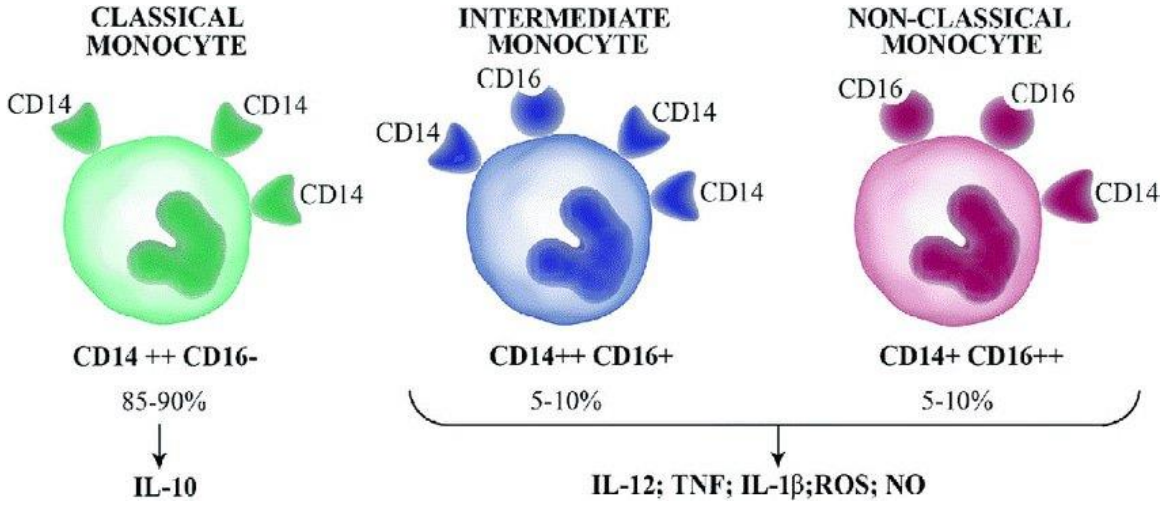
Subset	Surface markers	Chemokine receptors	% of total	Functions	Cytokine production
Classical	$CD14^{++}CD16^{-}$	$CXCR2^{+}CX3CR1^{-}$	80–95	Phagocytic, tissue repair	IL-1, IL-10, IL-12, TNF-α
Intermediate	$CD14^{++}CD16^{+}$	$CCR2^{-}CX3CR1^{+}$	2–11	Highly proinflammatory cells that produce high levels of ROS and inflammatory mediators	TNF-α, IL-1β, IL-6
Nonclassical	$CD14^{+}CD16^{++}$	$CCR2^{-}CX3CR1^{+}$	2–8	Patrolling, clearance of debris, cearance of apoptotic cells, anti-viral responses	TNF-α, IL-1β, IL-6

CX3CR1 = fractalkine

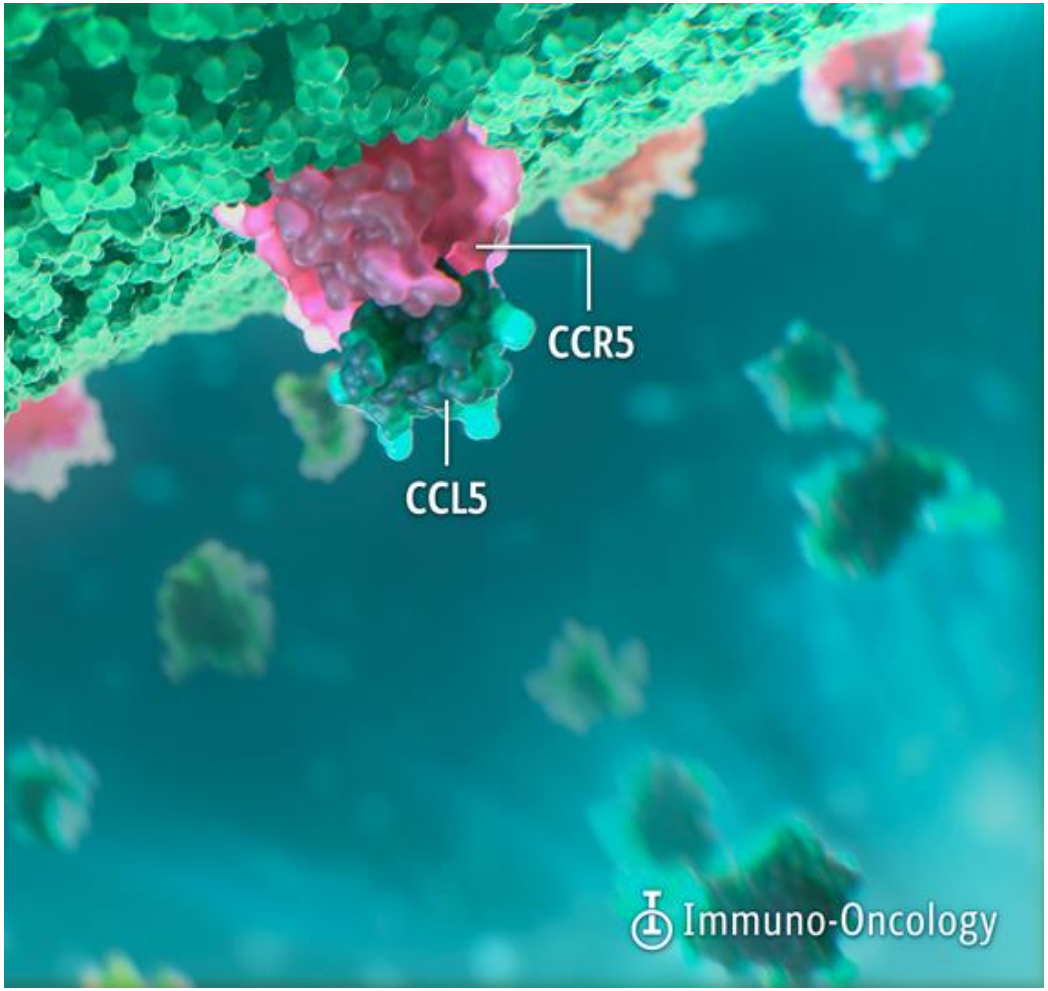
Han Z, et al. Front Cardiovasc Med. 2023.

S1 Protein-Immunosubset Assay

- Monocyte subpopulations are divided into 3 phenotypes
  - Classical monocytes: CD14++, CD16-
    - Express high levels of ACE-2 receptor
    - Express low levels of chemokine receptors CX3R1 and CCR5
  - Intermediate monocytes: CD14+, CD16+
    - Express very little ACE-2 receptor
    - Express high levels of CCR5
  - Non-classical monocytes: CD14lo, CD16+
    - Express very little ACE-2 receptor
    - Express high levels of CX3R1



CCL5 – CCR5 Interaction



frontiers in Immunology

ORIGINAL RESEARCH
published: 10 January 2022
doi: 10.3389/fimmu.2021.746021

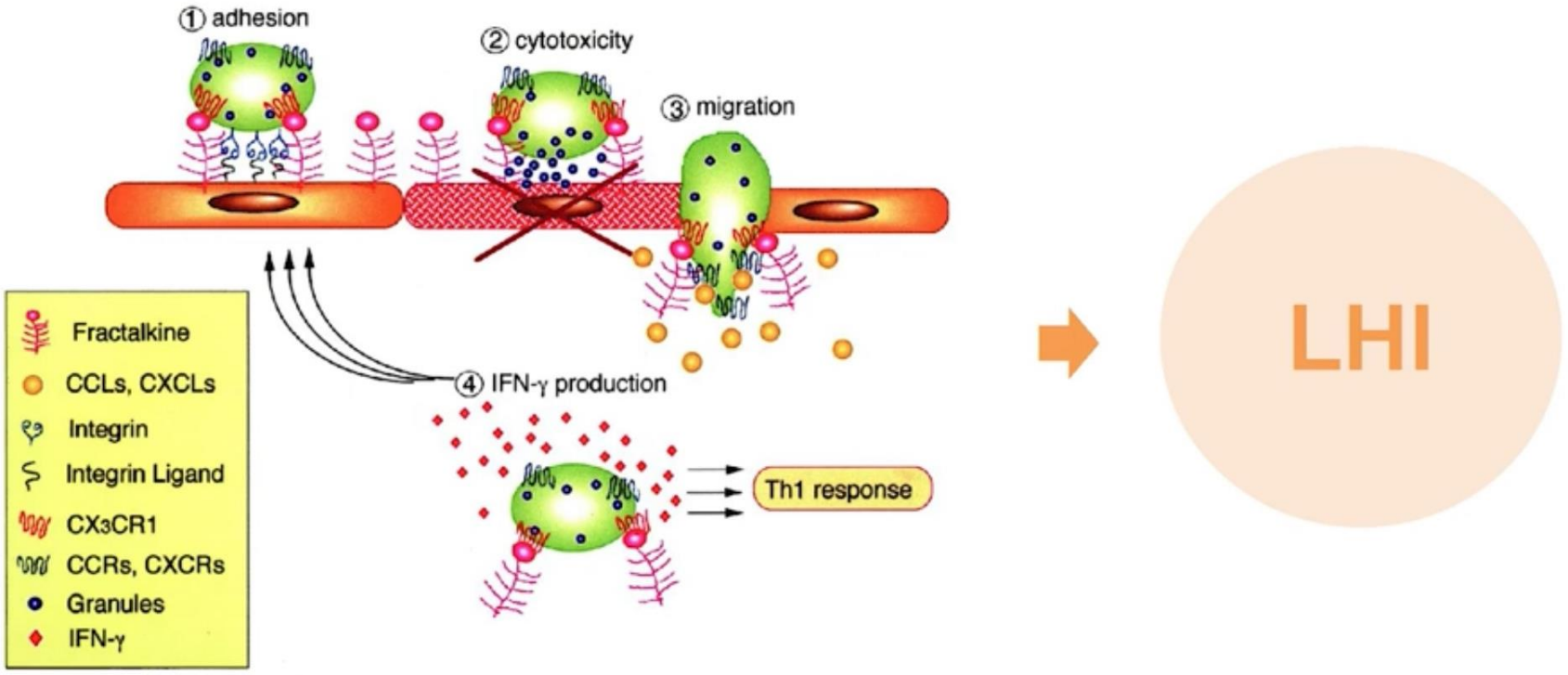
Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning

Bruce K. Patterson[1], Jose Guevara-Coto[2], Ram Yogendra[3], Edgar B. Francisco[1], Emily Long[1], Amruta Pise[1], Hallison Rodrigues[1], Purvi Parikh[4], Javier Mora[3] and Rodrigo A. Mora-Rodríguez[3]*

[1] IncellDx Inc, San Carlos, CA, United States, [2] Department of Computer Science and Informatics (ECCI), Universidad de Costa Rica, San Jose, Costa Rica, [3] Lab of Tumor Chemosensitivity, CIET/DC Lab, Faculty of Microbiology, Universidad de Costa Rica, San Jose, Costa Rica, [4] Department of Allergy and Immunology, NYU Langone Tisch Hospital, New York, NY, United States

Expression of CCR5 and its cognate ligands have been implicated in COVID-19 pathogenesis, consequently therapeutics directed against CCR5 are being investigated. Here, we explored the role of CCR5 and its ligands across the immunologic spectrum of COVID-19. We used a bioinformatics approach to predict and model the immunologic phases of COVID so that effective treatment strategies can be devised and monitored. We investigated 224 individuals including healthy controls and patients spanning the COVID-19 disease continuum. We assessed the plasma and isolated peripheral blood mononuclear cells (PBMCs) from 29 healthy controls, 26 Mild-Moderate COVID-19 individuals, 48 Severe COVID-19 individuals, and 121 individuals with post-acute sequelae of COVID-19 (PASC) symptoms. Immune subset profiling and a 14-plex cytokine panel were run on all patients from each group. B-cells were significantly elevated compared to healthy control individuals ($P<0.001$) as was the CD14+, CD16+, CCR5+ monocytic subset ($P<0.001$). CD4 and CD8 positive T-cells expressing PD-1 as well as T-regulatory cells were significantly lower than healthy controls ($P<0.001$ and $P=0.01$ respectively).

Non classical monocytes drive vascular inflammation and cytokine production through Fractalkine

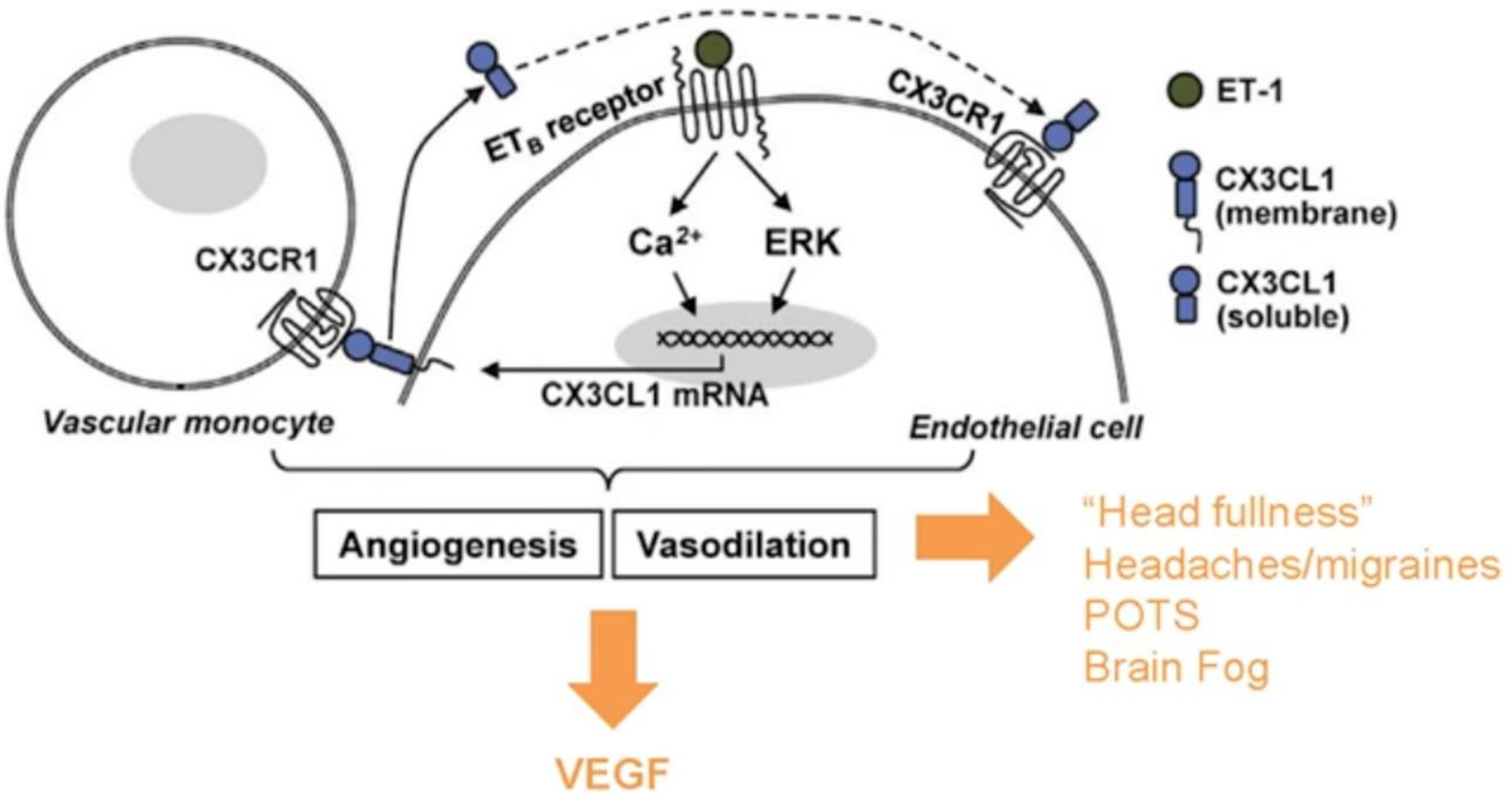


Umehara H,et al.. Arterioscler Thromb Vasc Biol. 2004

incellDx

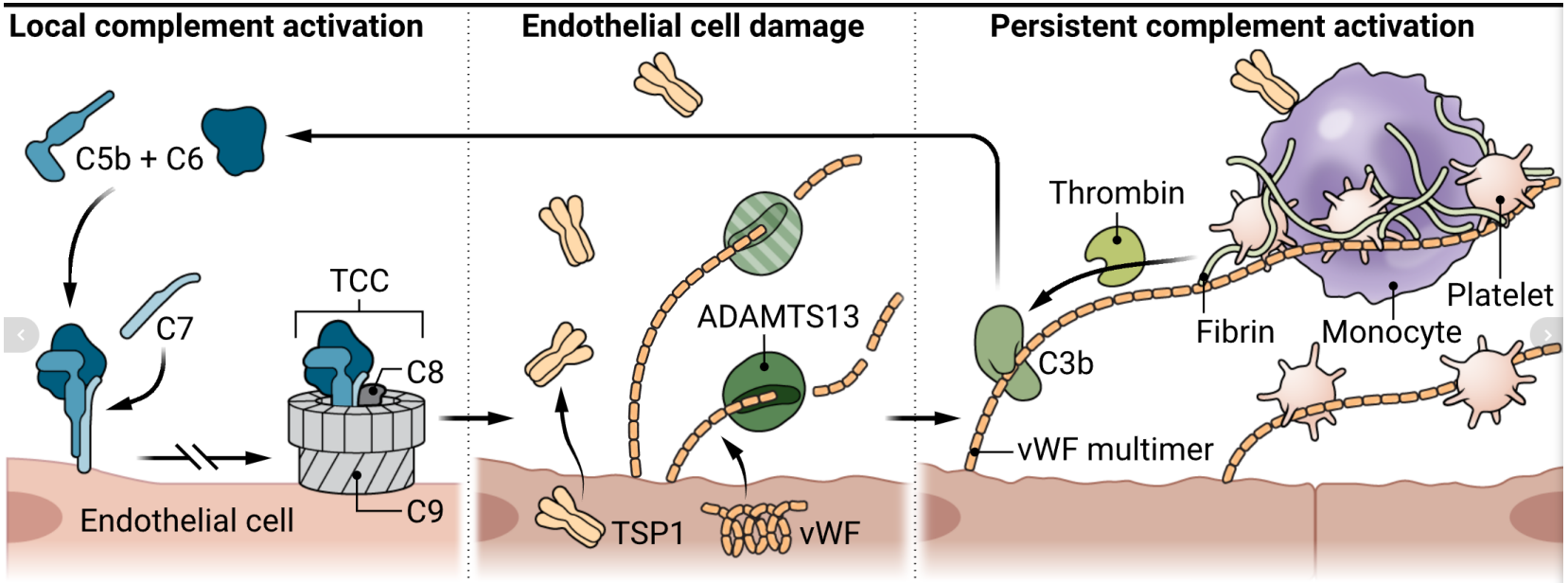
Patterson, Bruce. Incellkine Multiplex Assay Cytokine Test. YouTube video, 1:02:19. September 8, 2023.

Role of Fractalkine (CX3CL1) in Vascular Inflammation



Gawaz M, et al. J Clin Invest. 2005.
Patterson B. YouTube video. 2023.

Immune Damage in Long COVID - Complement-coagulation cross-talk at the endothelial interface



ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs 13; TCC, terminal complement complex; TSP1, thrombospondin 1; vWF, von Willebrand factor.

Cervia-Hasler C, et al., Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. Science. 2024 Jan 19;383(6680):eadg7942. doi: 10.1126/science.adg7942. Epub 2024 Jan 19. PMID: 38236961.

Pathogenesis of Long COVID

- Data from incellDx has shown that long COVID is vascular inflammation caused by persistence of the S1 protein in white blood cells months and now over a year post-infection

Patterson, Bruce. Incellkine Multiplex Assay Cytokine Test. YouTube video, 1:02:19. September 8, 2023.

Persistence of S1 Spike Protein in CD16+ Monocytes up to 245 Days in SARS-CoV-2 Negative Post COVID-19 Vaccination Individuals with Post-Acute Sequalae of COVID-19 (PASC)-Like Symptoms

Bruce K. Patterson[1], Ram Yogendra[2], Edgar B. Francisco[1], , Emily Long[1], Amruta Pise[1], Eric Osgood[3], John Bream[4], Mark Kreimer[5], Devon Jeffers[6], Christopher Beaty[1], Richard Vander Heide[7], Jose Guevara-Coto[8,9], Rodrigo A Mora-Rodríguez[8]

[1] IncellDx Inc, San Carlos, CA
[2] Lawrence General Hospital, Lawrence, MA
[3] Department of Medicine, St. Francis Medical Center, Trenton, NJ
[4] Department of Emergency Medicine, Novant Health Kernersville Medical Center, Kernersville, NC
[5] Department of Emergency Medicine, New York Presbyterian Hospital, Brooklyn, NY
[6] Department of Anesthesiology, Stamford Hospital, CT
[7] Department of Pathology, Marshfield Medical Center, Marshfield, Wi
[8] Lab of Tumor Chemosensitivity, CIET / DC Lab, Faculty of Microbiology, Universidad de Costa Rica

Summary: SARS CoV-2 S1 Protein in CD16+ Monocytes Post-Vaccination

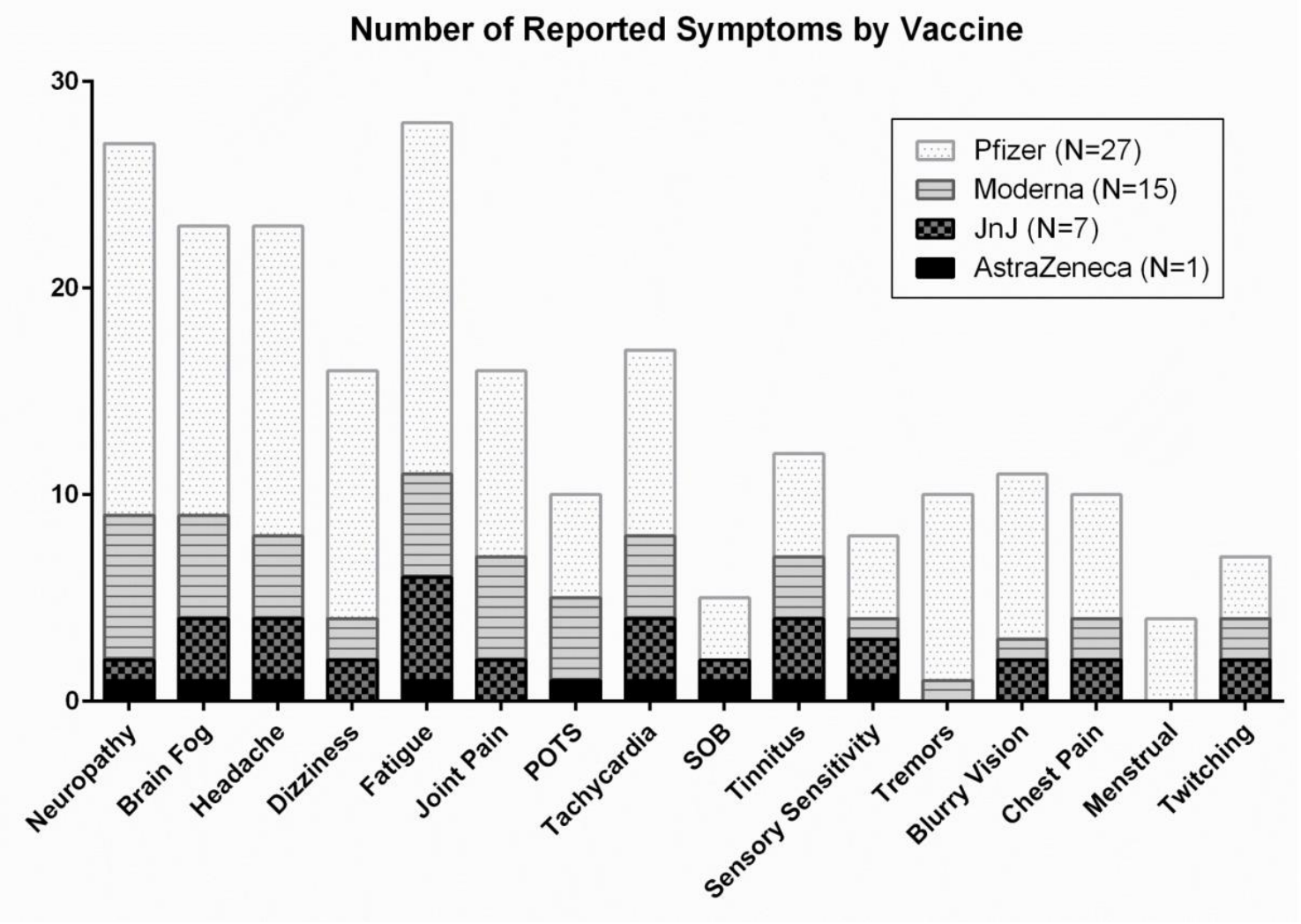
Corresponding Author:
Ram Yogendra M.D.

Key words:

COVID-19, PASC, SARS CoV-2 S1 protein, non-classical monocytes, CCR5, fractalkine

Abbreviations:
PASC, post-acute sequelae of COVID-19; POVIP, post-vaccination individuals with PASC-like symptoms; NCM, non-classical monocytes; IM, intermediate monocytes; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; IL, interleukin; RANTES, regulation on activation, healthy control T-expressed and secreted; CCR, chemokine receptor; IFN, interferon; TNF, tumor necrosis factor; MIP, macrophage inflammatory protein; PBMCs, peripheral blood mononuclear cells; VEGF, vascular endothelial growth factor; LH, long hauler or PASC.

Post-Vaccination with PASC Symptoms



How is Long COVID Diagnosed?

- No universally accepted blood work or diagnostic test
- Diagnosis is made based on health history, exam, and excluding other conditions
  - IncellKINE test supports the clinical diagnosis
    - CE-IVD marking in Europe
  - Immune subtype panel
    - Identifies monocyte subtype and S1 protein

https://www.covidlonghaulers.com/

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IncellKINE Test - incellDX

- COVID Long Hauler Panel
- A panel that collectively evaluates cytokines known to be involved in chronic COVID-19 and was developed using an algorithm established on a large, long-hauler patient population
- 14 cytokines
- Based on flow cytometry methodology

IncellKINE Test

- Is there a distinctive immunologic pattern that identifies long COVID?
- Preliminary study of 64 individuals with long COVID
  - Plasma levels of 14 cytokines measured
  - Analyzed using neural networking and machine learning
  - “Long hauler score” developed
    - Sensitivity of 97%
    - Specificity of 100%

IncellKINE Test

- Is there a distinctive immunologic pattern that identifies long COVID?
- Preliminary study of 64 individuals with long COVID
  - Significant elevation: IL-2, IL-4, CCL3, IL-6, IL-10, INF-gamma, and VEGF
  - Significantly lower: GM-CSF, CCL4
  - IL-6 = oxidative stress, inflammation, endothelial dysfunction, and thrombogenesis
  - VEGF = vascular involvement
  - sCD40L = platelet activation, activation of coagulation cascade

IncellKINE Test Performance

Label | Metric	Sensitivity	Specificity	PPV	NPV
Not Perturbed	0.9091	0.9689	0.9098	0.9757
Severe	0.7200	0.9692	0.7667	0.9695
PASC	0.9322	0.9842	0.9583	0.9797
Long-Vax	0.9048	0.9857	0.9467	0.9816
ME-CFS	0.9400	0.9800	0.9381	0.9861
Lyme	1.0000	1.0000	1.0000	1.0000

Patterson, Bruce. YouTube video. September 8, 2023.

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https://www.covidlonghaulers.com/

REVIEW CURRENT TREATMENT AND PREVENTION STRATEGIES FOR LONG COVID

Case Presentation – Jane

August 2020

- 38-year old female with multiple medically unexplained symptoms – “MUS”
  - Fatigue
  - Dyspnea on exertion
  - Paroxysmal tachycardia
  - Palpitations
  - Insomnia
  - Brain fog
  - Anxiety

Modifiable Lifestyle Habits

The ACTION PLAN (12 Ss)

- Strike out adverse environmental factors
- Select a healthy nutrient dense nutrition plan
- Supplement to restore deficiencies
- Strengthen through exercise, yet PACE
- Sleep that is adequate and restorative
- Socially Interact to bring joy/meaning/purpose
- Develop strategies for Stress management
- Enjoy Sunshine and Shinrin yoku
- Practice Utilize Sauna and red light therapy
- Stay well hydrated
- Ground with the Soil
- Nourish and enrich your Spirit

If you're afraid to go into the ocean because of sharks, you might want to avoid hotel hallways and break rooms, because vending machines are twice as likely to kill you.

Paul J.richards / AFP via Getty Images

Mahajan, S. Freakanomics. September 8, 2011.

Case Presentation – Jane's MUS Rx

August 2020→June 2023

- Chronic EBV reactivation
  - Kerr JR. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. J Clin Pathol. 2019 Oct;72(10):651-658. doi: 10.1136/jclinpath-2019-205822. Epub 2019 Jul 17. PMID: 31315893.
- Mast cell activation syndrome
  - Afrin LB, et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". Diagnosis (Berl). 2020 Apr 22;8(2):137-152. doi: 10.1515/dx-2020-0005. PMID: 32324159.
- Mycotoxin associated "CIRS"
  - Valtonen V. Clinical Diagnosis of the Dampness and Mold Hypersensitivity Syndrome: Review of the Literature and Suggested Diagnostic Criteria. Front Immunol. 2017 Aug 10;8:951. doi: 10.3389/fimmu.2017.00951. PMID: 28848553; PMCID: PMC5554125.
- Th17 dominance with high Th17 and low normal Treg; Low CD8; +ANA
  - Cyrex Lymphocyte Map Test
- Micronutrient deficiencies
  - Johnson CR, Thacher TD. Vitamin D: immune function, inflammation, infections and auto-immunity. Paediatr Int Child Health. 2023 Nov;43(4):29-39. doi: 10.1080/20469047.2023.2171759. Epub 2023 Mar 1. PMID: 36857810.
- Dysautonomia
  - Peltier AC. Autonomic Dysfunction from Diagnosis to Treatment. Prim Care. 2024 Jun;51(2):359-373. doi: 10.1016/j.pop.2024.02.006. Epub 2024 Mar 20. PMID: 38692780.

Case Presentation – Jane

June 2023

- Ongoing weakness, fatigue, tinnitus, palpitations, constipation, bloating, rash with acne and intermittent chest rash, headache, anxiety, susceptible to getting anxious, vibrations feeling with "fight/flight" feelings, and poor memory
- Acute COVID-19 March 2020, January 2022, and no symptoms when husband and three children ill with COVID-19 August 2022
- Three Pfizer mRNA COVID-19 vaccines with the booster on 10/13/2021
- Diagnostic test

IncellKINE Test – Jane – 7/12/2023

Test	Result	Flag	Unit	Range/Comments
COVID LONG HAULER PANEL				
LH CYTOKINE 14 PANEL				
IL-2	12.9	HIGH	pg/mL	1.6 - 7.0
IL-4	25.8	HIGH	pg/mL	2.3 - 6.2
IL-6	5.0	HIGH	pg/mL	1.4 - 3.0
IL-8	59.5	HIGH	pg/mL	5.4 - 21.0
IL-10	1.3	HIGH	pg/mL	0.7 - 1.2
IL-13	4.6	NORMAL	pg/mL	1.5 - 6.1
GM-CSF	3.6	LOW	pg/mL	5.8 - 77.0
SCD40L	101280.6	HIGH	pg/mL	35.0 - 9236.0
CCL3 (MIP-1 ALPHA)	2.4	LOW	pg/mL	3.5 - 33.0
CCL4 (MIP-1 BETA)	1.2	LOW	pg/mL	1.5 - 93.0
CCL5 (RANTES)	12685.8	HIGH	pg/mL	7.2 - 11800.0
TNF-ALPHA	19.6	HIGH	pg/mL	3.7 - 11.0
IFN-GAMMA	10.6	HIGH	pg/mL	1.8 - 3.5
VEGF	324.1	HIGH	pg/mL	2.0 - 12.3
LONG HAULER INDEX	19.56	HIGH	INDEX	< 0.70

IncellKINE Test -- Jane – 7/12/2023

Abnormal Results Summary				
IL-2	12.9	HIGH	pg/mL	1.6 - 7.0
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*Proinflammatory Cytokines

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*Activation of platelets and the coagulation cascade

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Treatment of Long COVID for Jane

1. Comprehensive history with timeline, antecedents, triggers, and mediators and physical exam
   - Develop a problem list
2. Create a personalized action plan
   - Shared decision making
3. Rule out other causes and contributing factors
4. Acknowledge symptoms are real and treatment course is uncertain
5. Set expectations, reassess frequently
6. Consider multidisciplinary care
7. Series of treatment cycles

Treatment and Mitigation of Long COVID

- Initial Comprehensive Consultation
  1. Baseline laboratory testing – CBC w/diff, CMP, GTT, vitamin D 25 hydroxy, TSH/Free T4/Free T3/Reverse T3, homocysteine, fasting insulin, HgA1c, Lipid Panel, Tryptase, EBV antibody panel
  2. Consider thrombo-inflammation testing
  3. Review and optimize modifiable lifestyle habits
  4. Consider referral – Cardiology, Pulmonary, Neurology, Behavioral health (Psychiatry, Psychology), Rehab (PT, OT), Social services
  5. IncellKINE testing
     - +/- Immune Subtype Panel

Thrombo-Inflammation Testing

- Evaluate clotting characteristics
  - Von Willebrand Factor Ag/Activity
  - Thrombotic Marker Panel (Quest Diagnostics)
    - D-Dimer, Quantitative
    - Fibrin Monomer
    - Prothrombin Fragment 1.2
    - Thrombin- Antithrombin (TAT) Complex

Thrombo-Inflammation Testing

- Evaluate inflammatory status
  - hsCRP, ESR, GlycA, ferritin, uric acid, Galectin-3, Omega 3 RBC index (OmegaQuant, Omegacheck)
- Evaluate the oxidative stress/fibrosis activation system
  - oxLDL, F2-isoprostane, glutathione, TGFβ

Treatment and Mitigation of Long COVID

- Goal: address the causes of Long Covid
  - Alleviate symptoms
  - Focusing on immunologic mechanism of inflammation is key to improved patient results
- Rule out non-PASC causes
- Process of resolving endothelial dysfunction/endotheliopathy/endotheliitis, enhancing ACE 2 activity, and rescuing mitochondrial function
- Personalized
- Step by step
- Series of cycled interventions

Treatment of Long COVID

- Data from incellDx has shown that long COVID is vascular inflammation caused by persistence of the S1 protein in white blood cells months and now over a year post-infection
- In over 20,000 patients, disruption of these mechanisms with CCR5 antagonists and statins have resulted in profound improvement in >80% of patients treated
- As similar pathology may exist in patients with Post-Vaccination Injury, Fibromyalgia, and ME-CFS

Patterson, Bruce. Incellkine Multiplex Assay Cytokine Test. YouTube video, 1:02:19. September 8, 2023.

frontiers | Frontiers in Medicine

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Case series: Maraviroc and pravastatin as a therapeutic option to treat long COVID/Post-acute sequelae of COVID (PASC)

Bruce K. Patterson[1], Ram Yogendra[2]*, Jose Guevara-Coto[3], Rodrigo A. Mora-Rodriguez[4], Eric Osgood[5], John Bream[6], Purvi Parikh[7], Mark Kreimer[8], Devon Jeffers[9], Cedric Rutland[10], Gary Kaplan[11]† and Michael Zgoda[12]†

Post-acute sequelae of COVID (PASC), or long COVID, is a multisystem complication of SARS-CoV-2 infection that continues to debilitate millions worldwide thus highlighting the public health importance of identifying effective therapeutics to alleviate this illness. One explanation behind PASC may be attributed to the recent discovery of persistent S1 protein subunit of SARS-CoV-2 in CD16+ monocytes up to 15 months after infection. CD16+ monocytes, which express both CCR5 and fractalkine receptors (CX3CR1), play a role in vascular homeostasis and endothelial immune surveillance. We propose targeting these receptors using the CCR5 antagonist, maraviroc, along with pravastatin, a fractalkine inhibitor, could disrupt the monocytic-endothelial-platelet axis that may be central to the etiology of PASC.

Manage Immune Dysregulation and endothelial dysfunction/endotheliopathy/endotheliitis

- Maraviroc
- Statin – atorvastatin, pravastatin, rosuvastatin

Case Presentation – Jane's Rx

July 2023

- Maraviroc
- Atorvastatin

Jane -- 8/22/2023

Test	Result	Flag	Unit	Range/Comments
COVID LONG HAULER PANEL				
COVID 19 S1 PROTEIN IMMUNE SUBSET PANEL				
CD3 T MATURE CELLS	72.14	NORMAL	%	57.00 - 85.00
CD3 T MATURE CELLS #	0.99	NORMAL	x10³/µL	0.84 - 3.06
CD4 + T CELLS	44.61	NORMAL	%	30.00 - 61.00
CD4 + T CELLS #	0.61	NORMAL	x10³/µL	0.49 - 2.57
CD8 T CELLS	32.18	NORMAL	%	12.00 - 42.00
CD8 T CELLS #	0.32	NORMAL	x10³/µL	0.18 - 1.17
CD4/CD8 RATIO	1.4	NORMAL	%	0.9 - 5.0
LH [CD14LO,CD16+] NONCLASSICAL MONOCYTES	0.58	**LOW**	%	25.50 - 40.00
LH [CD14LO,CD16+]+S1 S1+NONCLASSICAL MONOCYTES	1.71	**HIGH**	%	0.00 - 0.00
LH [CD14+,CD16+] INTERMEDIATE MONOCYTES	40.86	**HIGH**	%	4.60 - 13.40
LH [CD14+,CD16+]+S1 S1+INTERMEDIATE MONOCYTES	0.0	NORMAL	%	0.00 - 0.00
LH [CD14++,CD16-] CLASSICAL MONOCYTES	2.14	**LOW**	%	34.40 - 51.20
LH [CD14++,CD16-]+S1 S1+CLASSICAL MONOCYTES	0.0	NORMAL	%	0.00 - 0.00

COVID-19 S1 Protein Immune Subset Panel 8/22/2023

Test	Result	Flag	Unit	Range/Comments
Abnormal Results Summary				
LH [CD14LO,CD16+]	0.58	**LOW**	%	25.50 - 40.00
LH [CD14LO,CD16+]+S1	1.71	**HIGH**	%	0.00 - 0.00
LH [CD14+,CD16+]	40.86	**HIGH**	%	4.60 - 13.40
LH [CD14++,CD16-]	2.14	**LOW**	%	34.40 - 51.20

Case Presentation – Jane's Rx

August 2023

- Maraviroc
- Atorvastatin

IncellKINE Test – Jane -- 11/8/2023

Test	Result	Flag	Unit	Range/Comments
COVID LONG HAULER PANEL				
LH CYTOKINE 14 PANEL				
IL-2	4.0	NORMAL	pg/mL	1.6 - 7.0
IL-4	46.8	**HIGH**	pg/mL	2.3 - 6.2
IL-6	2.7	NORMAL	pg/mL	1.4 - 3.0
IL-8	7.2	NORMAL	pg/mL	5.4 - 21.0
IL-10	6.7	**HIGH**	pg/mL	0.7 - 1.2
IL-13	1.2	**LOW**	pg/mL	1.5 - 6.1
GM-CSF	4.6	**LOW**	pg/mL	5.8 - 77.0
SCD40L	18208.1	**HIGH**	pg/mL	35.0 - 9236.0
CCL3 (MIP-1 ALPHA)	74.6	**HIGH**	pg/mL	3.5 - 33.0
CCL4 (MIP-1 BETA)	34.2	NORMAL	pg/mL	1.5 - 93.0
CCL5 (RANTES)	10698.3	NORMAL	pg/mL	7.2 - 11800.0
TNF-ALPHA	10.4	NORMAL	pg/mL	3.7 - 11.0
IFN-GAMMA	11.5	**HIGH**	pg/mL	1.8 - 3.5
VEGF	77.6	**HIGH**	pg/mL	2.0 - 12.3
LONG HAULER INDEX	0.45	NORMAL	INDEX	< 0.70

Abnormal Results Summary

IL-4	46.8	**HIGH**	pg/mL	2.3 - 6.2
IL-10	6.7	**HIGH**	pg/mL	0.7 - 1.2
IL-13	1.2	**LOW**	pg/mL	1.5 - 6.1
GM-CSF	4.6	**LOW**	pg/mL	5.8 - 77.0
SCD40L	18208.1	**HIGH**	pg/mL	35.0 - 9236.0
CCL3 (MIP-1 ALPHA)	74.6	**HIGH**	pg/mL	3.5 - 33.0
IFN-GAMMA	11.5	**HIGH**	pg/mL	1.8 - 3.5
VEGF	77.6	**HIGH**	pg/mL	2.0 - 12.3

Case Presentation – Jane's Rx

- Maraviroc 300 mg by mouth twice a day ~8/2023-->ongoing-->taper to daily starting 12/27/2023 x 7 days then DC
- Atorvastatin 20 mg by mouth qhs along with ubiquinol ~8/2023-->ongoing-->taper to qod for two weeks then DC
- September 2024 she overall is dong much better with getting back to baseline with body handling stress with some ongoing memory and cognitive issues with the goal to get off anxiety medication

Summary of Candidate Treatments and Supporting Evidence

Symptoms and/or biological mechanism	Treatments	Supporting evidence	Comments
Postexertional malaise	Pacing	ME/CFS literature	Exercise, cognitive behavioural therapy and graded exercise therapy are contraindicated
POTS	Pharmacological: β-blockers, pyridostigmine, fludrocortisone, midodrine	POTS and ME/CFS literature	Options can be prioritized on the basis of a specific constellation of symptoms
	Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings	POTS and ME/CFS literature	–
Immune dysfunction	Intravenous immunoglobulin	ME/CFS literature	Consider consulting an immunologist on implementation
Cognitive dysfunction	Cognitive pacing	ME/CFS literature	Consider implementation alongside pacing physical exertion
Cognitive dysfunction	Postconcussion syndrome protocols	ME/CFS and postconcussion syndrome literature	–
Fatigue	Coenzyme Q_{10}, D-ribose	ME/CFS literature	–
Pain, fatigue, neurological symptoms	Low-dose naltrexone	ME/CFS and other literature	Substantial anecdotal reports of success within the patient community
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole	ME/CFS literature	–
Autoimmunity	BC007	Long COVID case report	Neutralizes G protein-coupled receptor autoantibodies
Abnormal clotting	Anticoagulants	Long COVID pilot study	Additional trials in progress
Abnormal clotting	Apheresis	ME/CFS literature, long COVID pilot study	–
Viral persistence and antivirals (COVID-19)	Paxlovid	Long COVID case reports	No active trials, despite strong evidence for viral persistence
Viral persistence and antivirals (reactivations such as of EBV, HCMV and VZV)	Valaciclovir, famciclovir, valganciclovir and other antivirals	ME/CFS literature	–
Endothelial dysfunction	Sulodexide	Long COVID pilot study	–
Gastrointestinal symptoms	Probiotics	Long COVID pilot study	Resolved gastrointestinal and other symptoms
Dysautonomia	Stellate ganglion block	Long COVID case report	Effects may wane over time and require repeated procedures
Endothelial function, microcirculation, inflammatory markers and oxidative stress	Pycnogenol	COVID-19 pilot study	–
MCAS	H_1 and H_2 antihistamines, particularly famotidine	Long COVID case reports, MCAS literature	Expected to treat symptoms, not underlying mechanism
Autonomic dysfunction	Transcutaneous vagal stimulation	Long COVID pilot study	–

EBV, Epstein–Barr virus; HCMV, human cytomegalovirus; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome; VZV, varicella zoster virus.

Li J, et al. Sig Transduct Target Ther. 2023.

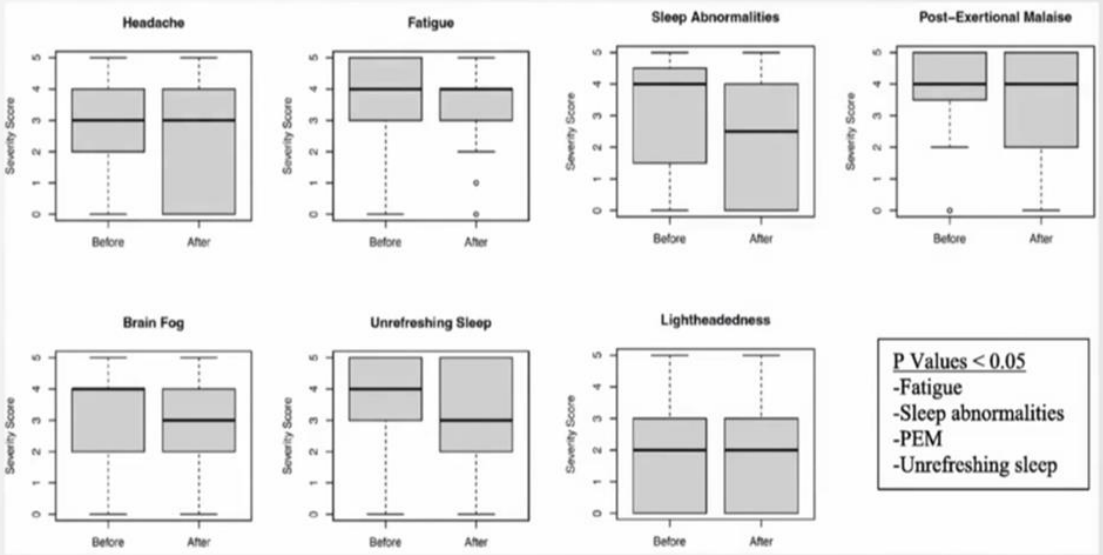
What is the Research for Long COVID?

- Current FDA-approved therapies for Long COVID = 0
- Interventional studies listed on ClinicalTrials.gov = 274
  - Autologous stem cells
  - Sauna, hyperbaric oxygen
  - Lithium
  - Metformin
  - Cannabidiol
  - Probiotics/prebiotics
  - Chinese medicine
  - Water therapy, paced exercise, inspiratory muscle training, cognitive training, yoga

Naltrexone for Long COVID?

- Observational study of 59 patients receiving low-dose naltrexone* (0.5-6mg) in Long COVID clinic

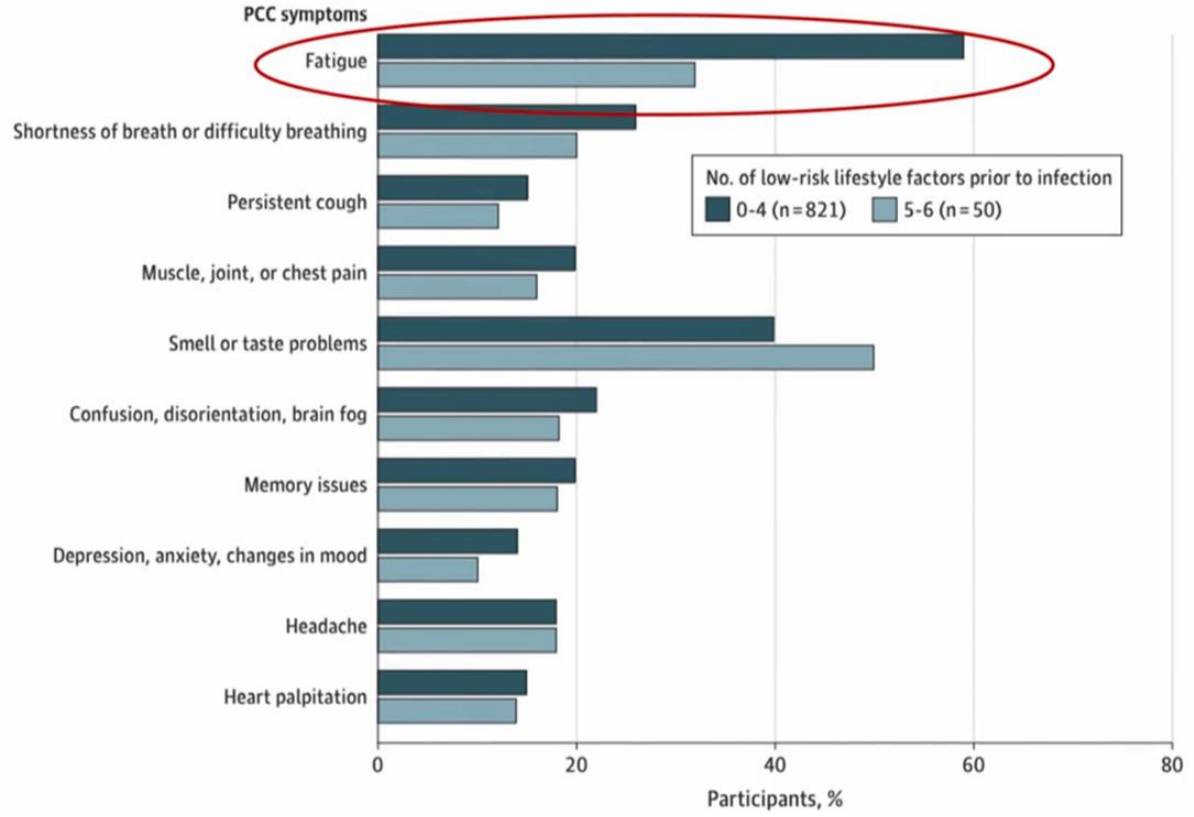
- Improvement across multiple systems
- Other observational studies with similar findings



Bonilla H, et al. Int Immunopharmacology Nov 2023
O'Kelly B, et al. Brain Behav Immun Health 2022
Eisenstein TK, Front Immunol 2019
Skolnick P, et al. Trends Pharmacol Sci 2014

Healthy Lifestyle* is Protective for Some Long COVID Symptoms

Figure 2. Post–COVID-19 Condition (PCC) Symptoms According to Number of Healthy Lifestyle Factors Prior to the Pandemic Among Persons Who Developed PCC, the Nurses' Health Study II, 2015-2021



*Normal BMI, never smoker, 150 min physical activity/week, High quality diet, moderate (or less) alcohol, adequate sleep

Wang et al. JAMA IM. 2023.

POST-COVID REHABILITATION CLINIC

Madonna offers a specialty clinic to support individuals who are experiencing long-lasting symptoms following a COVID-19 infection. Our interdisciplinary, comprehensive services paired with decades of specialized rehabilitation experience makes us uniquely equipped in assisting patients in achieving their recovery goals. A physician's referral is required to become a patient of this program.

Some people may be experiencing symptoms that are causing distress or impacting their daily lives. These symptoms may be connected to lingering effects of COVID-19. Take our assessment to help determine if your symptoms may be related to post-COVID.
If you think you are a candidate for the program, consult your physician for a referral. If you don't have a primary care provider, contact our clinic at **402.413.3930** for help determining next steps.

The most common symptoms of post-COVID-19 include fatigue, notably during the daytime; tiring easily, especially with activity; and difficulty with mental processing or "brain fog". However, there are many symptoms that can impact a person's physical, mental and emotional health and their ability to function. Individuals may experience symptoms in one or more of the following categories:
Physical Mental Emotional Functional

RECOVERY PROTOCOLS

I-RECOVER: Post-Vaccine Treatment

TAKE ME TO:

- Prevention
- Treatment
- Recovery
- More Treatment Guidelines
- Back to All Protocols

SUPPORTING DOCUMENTS

- Efficacy of Ivermectin
- Nutritional Therapeutics and COVID-19
- Vitamins and Nutraceuticals During Pregnancy
- Nutrient Guide
- Traducciones de Nuestros Protocolos en Español
- Frequently Asked Questions

I-RECOVER

LONG COVID TREATMENT

Download I-RECOVER Long COVID Summary

Download I-RECOVER Long COVID Protocol

An Approach to Treating Long COVID

Long COVID, a prolonged illness after COVID-19, may persist for months after the acute infection and affects at least 65 million individuals worldwide. A puzzling feature of long COVID is that initial disease severity is not an accurate predictor; long COVID frequently occurs in people who had mild-to-moderate COVID cases as well as in younger adults who did not require respiratory support or intensive care. Patients with long COVID should be managed by clinicians who have experience treating this troublesome disorder. Early treatment is essential; the response to treatment will likely be attenuated when treatment is delayed.

What is Long COVID?

Many patients experience prolonged illness after COVID-19. This is commonly known as 'long COVID', though it also referred to as 'Long Haul COVID Syndrome (LHCS)' or 'Post-acute sequelae of COVID-19 (PASC)'.

Long COVID may persist for months after the acute infection and almost half of patients report reduced quality of life. At least 65 million individuals worldwide are estimated to have long COVID.

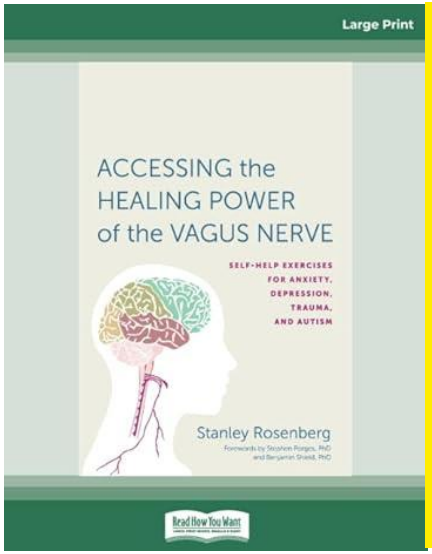
A puzzling feature of long COVID is that initial disease severity is not an accurate predictor; long COVID frequently occurs in people who had mild-to-moderate COVID cases as well as in younger adults who did not require respiratory support or intensive care.

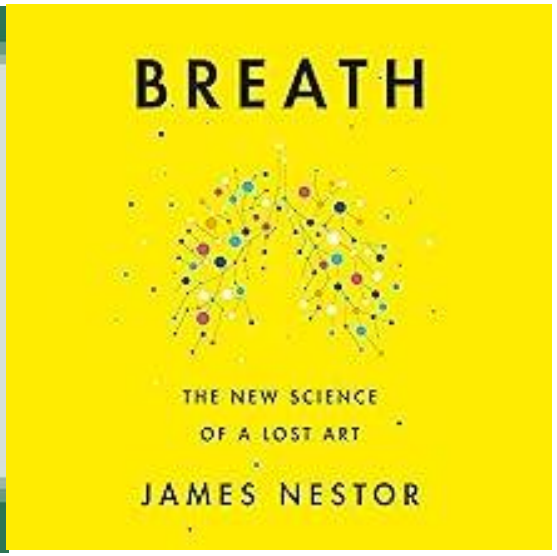
What are the Symptoms of Long COVID?

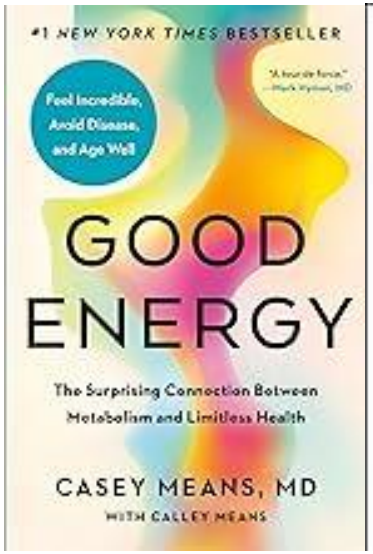
REACT 19

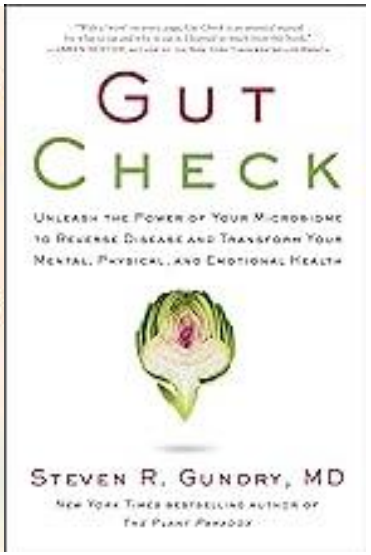
FOR PATIENTS FOR PROVIDERS Search MENU

Recommended Books









Recommended Podcasts

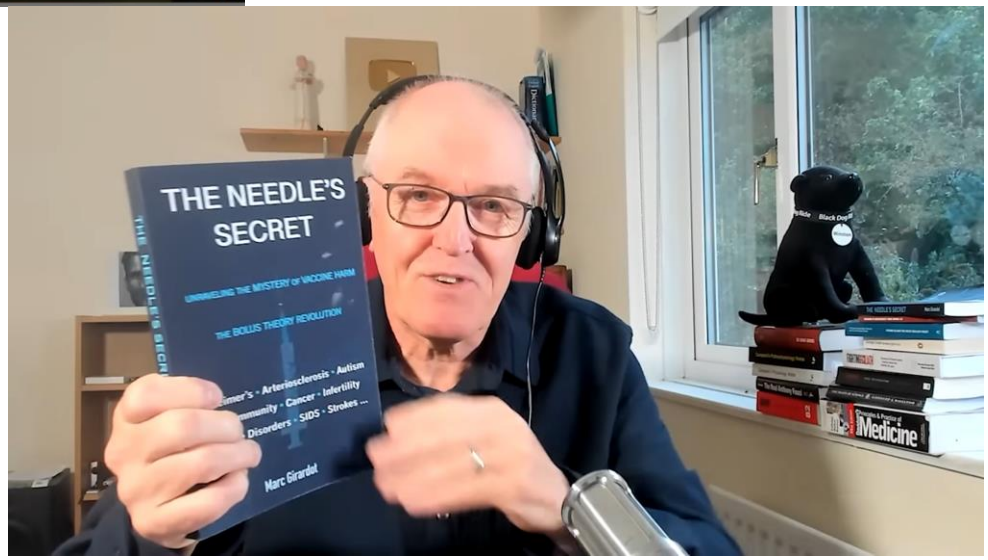
Imbalances

- Immune dysregulation
- Impaired vagus nerve activation
- Hypervigilant limbic system

YouTube Recommendations

MedCram - Medical Lectures Explained CLEARLY

Dr. John Campbell
3.13M subscribers
Sept 25, 2024. 91K views 5 days ago,
Are we playing a game of chance when we give intramuscular injections? Great talk with Marc Girardot, get a copy of his new book from the links below…



Summary

- Long COVID is a **clinical syndrome** with signs, symptoms, or conditions that develop after acute COVID-19
- It is estimated that **11.5%** of people who had COVID-19 are now currently experiencing Long COVID
- **~22%** of those with Long COVID currently have significant activity limitations

Summary

- Long COVID is associated with **multiple symptoms**, and many are vague, making diagnosis & treatment more challenging
- **12 symptoms** identified as having probable PASC (Long COVID)
  - Fatigue, brain fog, loss of smell/taste, post-exertional malaise, cough, thirst, palpitations, chest pain, loss of sexual desire/capacity, dizziness, gastrointestinal, abnormal movements, hair loss

Summary

- Long COVID is an immune mediated inflammatory disease associated with
  - Immune dysregulation - Monocyte polarization, mast cell activation, T-cell impairment, and autoantibodies
  - Blood clotting and endothelial abnormalities - endotheliitis, microthrombosis
  - Dysfunctional neurological signaling
  - Microbiome and virome dysbiosis
- SARS-CoV-2 **spike protein is pathogenic**, whether from the virus or created from genetic code in mRNA and adenovector DNA vaccines

Summary

- Data from incellDx has shown that long COVID is **vascular inflammation** caused by persistence of the S1 protein in monocytes months and now over a year post-infection
- In over 20,000 patients, disruption of these mechanisms with **CCR5 antagonists and statins** have resulted in profound improvement in >80% of patients treated

Summary

- Long COVID management should be **comprehensive**, many times a multidisciplinary team, coordinating with restorative medicine
- **Healthy lifestyle** [normal BMI, never smoker,150 min physical activity/week, high quality diet, moderate (or less) alcohol, adequate sleep] **is protective**

References (cont.)

- Leung JSM. Interaction between gut microbiota and COVID-19 and its vaccines. World J Gastroenterol. 2022 Oct 28;28(40):5801-5806. doi: 10.3748/wjg.v28.i40.5801. PMID: 36353201; PMCID: PMC9639653. Leung JSM. Interaction between gut microbiota and COVID-19 and its vaccines. World J Gastroenterol. 2022 Oct 28;28(40):5801-5806. doi: 10.3748/wjg.v28.i40.5801. PMID: 36353201; PMCID: PMC9639653.
- Appelman, B., Charlton, B.T., Goulding, R.P. et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. Nat Commun 15, 17 (2024). https://doi.org/10.1038/s41467-023-44432-3
- Ozonoff, A., Jayavelu, N.D., Liu, S. et al. Features of acute COVID-19 associated with post-acute sequelae of SARS-CoV-2 phenotypes: results from the IMPACC study. Nat Commun 15, 216 (2024). https://doi.org/10.1038/s41467-023-44090-5
- COVID-19 rapid guideline: managing the long-term effects of COVID-19. https://www.nice.org.uk/guidance/ng188. (2022).
- Rafałowicz B, Wagner L, Rafałowicz J. Long COVID Oral Cavity Symptoms Based on Selected Clinical Cases. Eur J Dent. 2022 May;16(2):458-463. doi: 10.1055/s-0041-1739445. Epub 2021 Dec 17. PMID: 34921381; PMCID: PMC9339924.
- Ma, Y., Zhang, L., Wei, R. et al. Risks of digestive diseases in long COVID: evidence from a population-based cohort study. BMC Med 22, 14 (2024). https://doi.org/10.1186/s12916-023-03236-4
- Carlo Cervia-Hasler *et al.* Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. *Science* **383**,eadg7942(2024). DOI:10.1126/science.adg794
- Zaki A SherifChristian R GomezThomas J ConnorsTimothy J HenrichWilliam Brian ReevesRECOVER Mechanistic Pathway Task Force (2023) Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC) eLife 12:e86002. https://doi.org/10.7554/eLife.86002
- Wong AC, Devason AS, Umana IC, et al. Serotonin reduction in post-acute sequelae of viral infection. Cell. 2023 Oct 26;186(22):4851-4867.e20. doi: 10.1016/j.cell.2023.09.013. Epub 2023 Oct 16. PMID: 37848036.
- Thoene MA. Changing Views toward mRNA based Covid Vaccines in the Scienti□c Literature: 2020–2024. Pol Ann Med. 2024 [in press]. https://doi.org/10.29089/paom/189961
- Akdis M, Burgler S, Crameri R, et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2011 Mar;127(3):701-21.e1-70. doi: 10.1016/j.jaci.2010.11.050. Erratum in: J Allergy Clin Immunol. 2011 Oct;128(4):739. Quaked, Nadia [corrected to Ouaked, Nadia]. PMID: 21377040.

References

- Harris E. Long COVID in Nursing Home Residents Manifests as Functional Decline. JAMA. 2024;331(1):15. doi:10.1001/jama.2023.24682
- Clark SE, Bautista L, Neeb K, Montoya A, Gibson KE, Mantey J, Kabeto M, Min L, Mody L. Post-acute sequelae of SARS-CoV-2 (PASC) in nursing home residents: A retrospective cohort study. J Am Geriatr Soc. 2023 Nov 10. doi: 10.1111/jgs.18678. Epub ahead of print. PMID: 37950496.
- https://www.england.nhs.uk/wp-content/uploads/2022/07/C1669_Long-Covid-Toolkit_Advice-and-resources-for-healthcare-professionals-in-primary-care_July-2022-1.pdf
- https://www.england.nhs.uk/long-read/commissioning-guidance-for-post-covid-services-for-adults-children-and-young-people/
- Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2
- Li, J., Zhou, Y., Ma, J. et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. Sig Transduct Target Ther 8, 416 (2023). https://doi.org/10.1038/s41392-023-01640-z
- Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, Li S, Hong S, Zhang R, Xie J, Kornilov SA, Scherler K, Pavlovitch-Bedzyk AJ, Dong S, Lausted C, Lee I, Fallen S, Dai CL, Baloni P, Smith B, Duvvuri VR, Anderson KG, Li J, Yang F, Duncombe CJ, McCulloch DJ, Rostomily C, Troisch P, Zhou J, Mackay S, DeGottardi Q, May DH, Taniguchi R, Gittelman RM, Klinger M, Snyder TM, Roper R, Wojciechowska G, Murray K, Edmark R, Evans S, Jones L, Zhou Y, Rowen L, Liu R, Chour W, Algren HA, Berrington WR, Wallick JA, Cochran RA, Micikas ME; ISB-Swedish COVID-19 Biobanking Unit; Wrin T, Petropoulos CJ, Cole HR, Fischer TD, Wei W, Hoon DSB, Price ND, Subramanian N, Hill JA, Hadlock J, Magis AT, Ribas A, Lanier LL, Boyd SD, Bluestone JA, Chu H, Hood L, Gottardo R, Greenberg PD, Davis MM, Goldman JD, Heath JR. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022 Mar 3;185(5):881-895.e20. doi: 10.1016/j.cell.2022.01.014. Epub 2022 Jan 25. PMID: 35216672; PMCID: PMC8786632.
- Mohandas S, Jagannathan P, Henrich TJ, Sherif ZA, Bime C, Quinlan E, Portman MA, Gennaro M, Rehman J; RECOVER Mechanistic Pathways Task Force. Immune mechanisms underlying COVID-19 pathology and post-acute sequelae of SARS-CoV-2 infection (PASC). Elife. 2023 May 26;12:e86014. doi: 10.7554/eLife.86014. PMID: 37233729; PMCID: PMC10219649.
- Boufidou F, Medić S, Lampropoulou V, Siafakas N, Tsakris A, Anastassopoulou C. SARS-CoV-2 Reinfections and Long COVID in the Post-Omicron Phase of the Pandemic. Int J Mol Sci. 2023 Aug 19;24(16):12962. doi: 10.3390/ijms241612962. PMID: 37629143; PMCID: PMC10454552.

References (Cont.)

- Weinstock LB, Pace LA, Rezaie A, Afrin LB, Molderings GJ. Mast Cell Activation Syndrome: A Primer for the Gastroenterologist. Dig Dis Sci. 2021 Apr;66(4):965-982. doi: 10.1007/s10620-020-06264-9. Epub 2020 Apr 23. PMID: 32328892.
- Klinker MW, Lundy SK. Multiple mechanisms of immune suppression by B lymphocytes. Mol Med. 2012 Feb 10;18(1):123-37. doi: 10.2119/molmed.2011.00333. PMID: 22033729; PMCID: PMC3276396.
- Patterson BK, Yogendra R, Francisco EB, Long E, Pise A, Osgood E, Bream J, Kreimer M, Jeffers D, Beaty C, Vander Heide R, Guevara-Coto J, Mora-Rodríguez RA. Persistence of S1 Spike Protein in CD16+ Monocytes up to 245 Days in SARS-CoV-2 Negative Post COVID-19 Vaccination Individuals with Post-Acute Sequalae of COVID-19 (PASC)-Like Symptoms. medRxiv 2024.03.24.24304286; doi: https://doi.org/10.1101/2024.03.24.24304286
- Schett G, McInnes IB, Neurath MF. Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs. N Engl J Med. 2021 Aug 12;385(7):628-639. doi: 10.1056/NEJMra1909094. PMID: 34379924.
- Naidu AS, Wang CK, Rao P, Mancini F, Clemens RA, Wirakartakusumah A, Chiu HF, Yen CH, Porretta S, Mathai I, Naidu SAG. Precision nutrition to reset virus-induced human metabolic reprogramming and dysregulation (HMRD) in long-COVID. NPJ Sci Food. 2024 Mar 30;8(1):19. doi: 10.1038/s41538-024-00261-2. PMID: 38555403; PMCID: PMC10981760.
- Theoharides TC, Kempuraj D. Role of SARS-CoV-2 Spike-Protein-Induced Activation of Microglia and Mast Cells in the Pathogenesis of Neuro-COVID. Cells. 2023 Feb 22;12(5):688. doi: 10.3390/cells12050688. PMID: 36899824; PMCID: PMC10001285.
- Patterson BK, Yogendra R, Guevara-Coto J, Mora-Rodriguez RA, Osgood E, Bream J, Parikh P, Kreimer M, Jeffers D, Rutland C, Kaplan G, Zgoda M. Case series: Maraviroc and pravastatin as a therapeutic option to treat long COVID/Post-acute sequelae of COVID (PASC). Front Med (Lausanne). 2023 Feb 8;10:1122529. doi: 10.3389/fmed.2023.1122529. PMID: 36844201; PMCID: PMC9944830.
- Patterson BK, Francisco EB, Yogendra R, et al. SARS-CoV-2 S1 Protein Persistence in SARS-CoV-2 Negative Post-Vaccination Individuals with Long COVID/ PASC-Like Symptoms. Research Square; 2022. DOI: 10.21203/rs.3.rs-1844677/v1.
- Thaweethai T, et al; RECOVER Consortium. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023 Jun 13;329(22):1934-1946. doi: 10.1001/jama.2023.8823. Erratum in: JAMA. 2024 Apr 10;: PMID: 37278994; PMCID: PMC10214179.

References (Cont.)

- Umehara H, Bloom ET, Okazaki T, Nagano Y, Yoshie O, Imai T. Fractalkine in vascular biology: from basic research to clinical disease. Arterioscler Thromb Vasc Biol. 2004 Jan;24(1):34-40. doi: 10.1161/01.ATV.0000095360.62479.1F. Epub 2003 Sep 11. PMID: 12969992.
- Xu, Sw., Ilyas, I. & Weng, Jp. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin 44, 695–709 (2023). https://doi.org/10.1038/s41401-022-00998-0
- Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. Circulation. 2020 Oct 27;142(17):1609-1611. doi: 10.1161/CIRCULATIONAHA.120.050354. Epub 2020 Sep 2. PMID: 32877231; PMCID: PMC7580651.
- Narasimhan PB, Marcovecchio P, Hamers AAJ, Hedrick CC. Nonclassical Monocytes in Health and Disease. Annu Rev Immunol. 2019 Apr 26;37:439-456. doi: 10.1146/annurev-immunol-042617-053119. PMID: 31026415.
- Parry PI, Lefringhausen A, Turni C, Neil CJ, Cosford R, Hudson NJ, Gillespie J. 'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA. Biomedicines. 2023 Aug 17;11(8):2287. doi: 10.3390/biomedicines11082287. PMID: 37626783; PMCID: PMC10452662.
- Cuffari, B. What are Spike Proteins? News-Medical.Net. 2021. Available online: https://www.news-medical.net/health/Whatare-Spike-Proteins.aspx (accessed on 26 April 2023).
- Baumeier, C.; Aleshcheva, G.; Harms, D.; Gross, U.; Hamm, C.; Assmus, B.;Westenfeld, R.; Kelm, M.; Rammos, S.;Wenzel, P.; et al. Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series. Int. J. Mol. Sci. 2022, 23, 6940.
- Nuovo, G.J.; Magro, C.; Shaffer, T.; Awad, H.; Suster, D.; Mikhail, S.; He, B.; Michaille, J.J.; Liechty, B.; Tili, E. Endothelial cell damage is the central part of COVID-19 and a mouse model induced by injection of the S1 subunit of the spike protein. Ann. Diagn. Pathol. 2021, 51, 151682.
- Bauer, Kristina. “Chronic Inflammation and its treatment with Dr. Bruce Patterson 5/21/23.” YouTube video, 27:53. May 21, 2023. https://www.youtube.com/watch?v=CdGJUtVOlv0&t=1006s
- Lyons JJ. Hereditary alpha-tryptasemia. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 20, 2024.)
- Gibo M, Kojima S, Fujisawa A, et al. (April 08, 2024) Increased Age-Adjusted Cancer Mortality After the Third mRNA-Lipid Nanoparticle Vaccine Dose During the COVID-19 Pandemic in Japan. Cureus 16(4): e57860. doi:10.7759/cureus.57860

References (Cont.)

- Calabrese L, Colloca L. Long COVID-19 and the Role of the Patient–Clinician Interaction in Symptom Management. Journal of Patient Experience. 2022;9. doi:10.1177/23743735221077514
- Erlandson, Kristine. "Post COVID Syndrome: Where are we Now? VuMEDi video, 26.58. February 9, 2024.
- Baraniuk C. Receptors for SARS-CoV-2 Present in Wide Variety of Human Cells. TheScientist. April 29, 2020.
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120-128. doi: 10.1056/NEJMoa2015432. Epub 2020 May 21. PMID: 32437596; PMCID: PMC7412750.
- Afrin, Lawrence B., et al. "Diagnosis of mast cell activation syndrome: a global "consensus-2"" Diagnosis, vol. 8, no. 2, 2021, pp. 137-152. https://doi.org/10.1515/dx-2020-0005
- Sabato V, Van De Vijver E, Hagendorens M, Vrelust I, Reyniers E, Fransen E, et al. Familial hypertryptasemia with associated mast cell activation syndrome. J Allergy Clin Immunol 2014;134: 1448–50.e3.10.1016/j.jaci.2014.06.007
- Smatti MK, Al-Sadeq DW, Ali NH, Pintus G, Abou-Saleh H, Nasrallah GK. Epstein-Barr Virus Epidemiology, Serology, and Genetic Variability of LMP-1 Oncogene Among Healthy Population: An Update. Front Oncol. 2018 Jun 13;8:211. doi: 10.3389/fonc.2018.00211. PMID: 29951372; PMCID: PMC6008310.
- El-Arif G, Farhat A, Khazaal S, Annweiler C, Kovacic H, Wu Y, Cao Z, Fajloun Z, Khattar ZA, Sabatier JM. The Renin-Angiotensin System: A Key Role in SARS-CoV-2-Induced COVID-19. Molecules. 2021 Nov 17;26(22):6945. doi: 10.3390/molecules26226945. PMID: 34834033; PMCID: PMC8622307.
- Han Z, Liu Q, Li H, Zhang M, You L, Lin Y, Wang K, Gou Q, Wang Z, Zhou S, Cai Y, Yuan L, Chen H. The role of monocytes in thrombotic diseases: a review. Front Cardiovasc Med. 2023 Jun 2;10:1113827. doi: 10.3389/fcvm.2023.1113827. PMID: 37332592; PMCID: PMC10272466.
- Pereira PC, de Lima CJ, Fernandes AB, Zângaro RA, Villaverde AB. Cardiopulmonary and hematological effects of infrared LED photobiomodulation in the treatment of SARS-COV2. J Photochem Photobiol B. 2023 Jan;238:112619. doi: 10.1016/j.jphotobiol.2022.112619. Epub 2022 Dec 5. PMID: 36495670; PMCID: PMC9721157.
- Seheult, Roger. "Near Infrared Light (940nm) Improves COVID Outcomes: Exciting Randomized Control Trial." YouTube video, 42.39. January 2, 2023. https://www.youtube.com/watch?v=ZdiUnmpOgqE

References

- Patterson BK, et al. CCR5 Inhibition in CriticalCOVID-19 Patients Decreases Inflammatory Cytokines, Increases CDS T- Cells, and Decreases SARS-CoV2 RNA in Plasma by Day 14. IntiJ Infect Dis 2020 doi: 10.1016/j.ijid.2020.10.101
- Patterson Bruce K., Guevara-Coto Jose, Yogendra Ram, Francisco Edgar B., Long Emily, Pise Amruta, Rodrigues Hallison, Parikh Purvi, Mora Javier, Mora-Rodríguez Rodrigo A.Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning Frontiers in Immunology, 12, 2021;2520
- Patterson BK, et al. CCR5 Inhibition in Critical COVID-19 Patients Decreases Inflammatory Cytokines, Increases CDS T- Cells, and Decreases SARS-CoV2 RNA in Plasma by Day 14. Inti J Infect Dis 2020 doi: 10.1016/j.ijid.2020.10.101
- Patterson BK, et al. Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning. BioRxiv 2020 doi: https://doi.org/10. 1101/2020.12. 16.4231 22
- Zhang, JM, An J. Cytokines, Inflammation and Pain. lnt Anesthesia! Clin 2007;45(2):27-37.
- Sokol, CL, Luster AD. The Chemokine System in Innate Immunity. Cold Spring Harb Perspect Biol2015;7: a016303.
- Zhou YQ, et al. lnterleukn-6: an emerging regulator of pathological pain. Journal of Neuroinflammation 206; 13:141.
- Kany, S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. lnt J MolSci 2019, 2608; doi:10.3390/ijms20236008
- Monastero RN, Pentyala S. Cytokines as Biomarkers and Their Respective Clinical Cutoff Levels.Review Article. lnt J lnflamm 2017
- Rider P, Carmi Y, Cohen I. Biologics for Targeting Inflammatory Cytokines Clinical Uses, and Limitations. Inti J Cell Biology 2016
- Turner MD., et al. Cytokines and chemokines: At the crossroads of cell signaling and inflammatory disease. Biochimci a et Biophysica Acta 2014; 1843:2563-2582.
- RaeI EL, Lockey RF. lnterleukin-13 signaling and its role in asthma. The World Allergy Organization Journal 2011;4(3):54- 64.

References (cont.)

- Gulati K., et al. Cytokines and their Role in Health and Disease: A Brief Overview. MOJ Immunology 2016, 4(2):00121.
- Mukaida N, SasakiSl, SabaT. CCL4 Signaling in the Tumor Microenvironment. Adv Exp Med Biol 1231:23-32.
- Lui JY, et al. CTL-vs Treg lymphocyte-attracting chemokines. CCL4 and CCL20 are strong reciprocal predictive markers for survival of patients with oesphagealsquamous cell carcinoma. Br J Cancer 113:747-755.
- Rojas JM et al. IL-10: A Multifunctional Cytokine in Viral infections. J lmmunol Res 2017, 6104054
- Muhl H. Pro-Inflammatory Signaling by IL-10 and IL-22: Bd Habits Sirred Up by Interferons? Front lmmunol4;18
- Sharif MN, et al. IFN-alpha priming results in a gain of proinflammatory function by IL-10: implications for systemic lupus erythematosus pathogenesis. J lmmunol172:6476-6481
- Hou T., et al. Roles of IL-6-gp130 Signaling in Vascular Inflammation. Curr Cardiel Rev 4:179-192.
- Lee J, et al. Interaction of IL-6 and TNF-alpha contributes to endothelial dysfunction in type 2 diabetic mouse hearts. PLoS One 12: e0187189
- Roldan V, et al. lnterluekin-6, endothelial activation and thrombogenesis in chronic atrial fibrillation. Eur Heart J 24:1373- 1380.
- Wassmann S, et al. lnterleukin-6 induces oxidative stress and endothelial dysfunction by overexpress of the angiotensin II type 1 receptor. Cir Res 94:534-541.
- Nobile-Orazio E, et al. Neurology 2009;72:1024-1026
- Patterson, Bruce. Incellkine Multiplex Assay Cytokine Test. YouTube video, 1:02:19. September 8, 2023.
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120-128. doi: 10.1056/NEJMoa2015432. Epub 2020 May 21. PMID: 32437596; PMCID: PMC7412750.
- Lippi G, et al. Do genetic polymorphisms in angiotensin converting enzyme 2 (ACE2) gene play a role in coronavirus disease 2019 (COVID-19)? CCLM. June 29, 2020. https://doi.org/10.1515/cclm-2020-0727

References (cont.)

- Patterson et al,. Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection, Frontiers in Immunology.12, 2022.
- Kapellos T et al.,.Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases Frontiers in Immunology; 10, 2019
- Patterson BK, et al. CCR5 Inhibition in CriticalCOVID-19 Patients Decreases Inflammatory Cytokines, Increases CDS T- Cells, and Decreases SARS-CoV2 RNA in Plasma by Day 14. IntiJ Infect Dis 2020
- Patterson Bruce K., Guevara-Coto Jose, Yogendra Ram, Francisco Edgar B., Long Emily, Pise Amruta, Rodrigues Hallison, Parikh Purvi, Mora Javier, Mora-Rodríguez Rodrigo A.Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning Frontiers in Immunology, 12, 2021;2520
- Patterson BK, et al. CCR5 Inhibition in Critical COVID-19 Patients Decreases Inflammatory Cytokines, Increases CDS T- Cells, and Decreases SARS-CoV2 RNA in Plasma by Day 14. Inti J Infect Dis 2020
- Patterson BK, et al. Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning. BioRxiv 2020 doi: https://doi.org/10. 1101/2020.12. 16.4231 22
- Zhang, JM, An J. Cytokines, Inflammation and Pain. lnt Anesthesia! Clin 2007;45(2):27-37.
- Sokol, CL, Luster AD. The Chemokine System in Innate Immunity. Cold Spring Harb Perspect Biol2015;7: a016303.
- CD4+T, CD8+T counts and severe COVID-19: A meta-analysis. Zhang H, Wu T. J Infect. 2020 Sep;81(3): e82-e84.
- Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. Liu Z et al., J Infect. 2020 Aug;81(2):318-356.
- T-Cell Subset Counts in Peripheral Blood Can Be Used as Discriminatory Biomarkers for Diagnosis and Severity Prediction of Coronavirus Disease 2019. Jiang M, Guo et al., J Infect Dis. 2020 Jun 29;222(2):198-202
- Patterson, B.K., Guevara-Coto, J., Mora, J. *et al.* Long COVID diagnostic with differentiation from chronic lyme disease using machine learning and cytokine hubs. *Sci Rep* **14**, 19743 (2024). https://doi.org/10.1038/s41598-024-70929-y

10 Common Logical Fallacies Everyone Should Know

1 Ad Hominem

It occurs when someone attacks directly the person making an argument rather than criticizing the argument itself.

2 Straw Man

When someone attacks a distorted version of the original argument that they themselves created (i.e "the straw man").

3 Appeal to Authority

Asserting that something **must** be true because it is backed up by someone who is (allegedly) an authority on the subject.

4 Slippery Slope

Taking an argument from the first, sensible premise to an undesirable or extreme conclusion via a number of hastily connected steps.

5 Bandwagon

The bandwagon fallacy occurs when something is said to be true or good simply because it is popular.

6 Appeal to Ignorance

When it is said that an argument must be true if it cannot be proven false, or false if it cannot be proven true.

7 False Dilemma

This occurs when two choices are presented as the only possible options when, in fact, other alternatives exist.

8 Hasty Generalization

This logical fallacy happens when a general conclusion is drawn based on a sample size that is too small.

9 Red Herring

This occurs when someone deliberately attempts to move the issue under discussion to a new, irrelevant topic.

10 Appeal to Tradition

When one claims that something must be good or true because it has been practiced for a long time (that is, traditionally).

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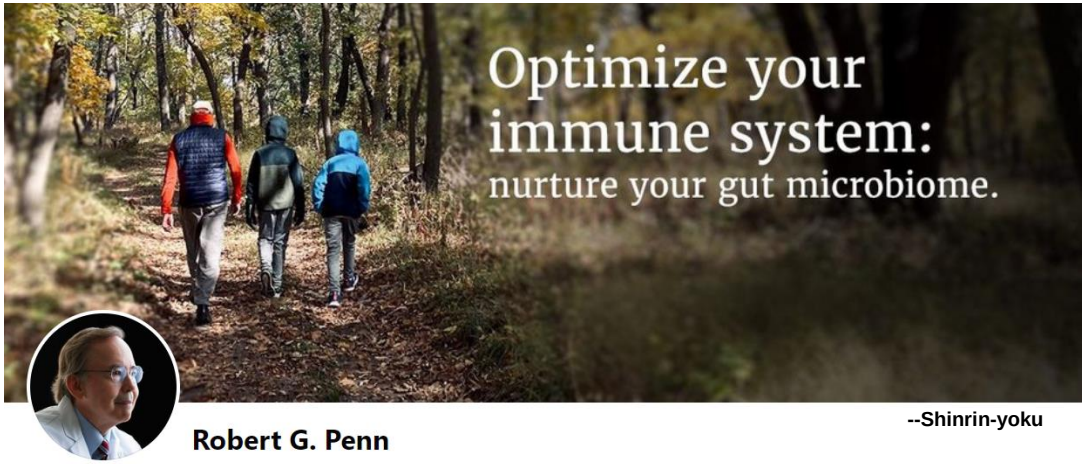
CHOCOLATE
is the answer
Who cares what the
question is



--Shinrin-yoku

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Questions or Comments?