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Viral Persistence, Viral Reactivation & Spike Protein Damage to Heme in Long Covid

WEBINAR FOUR

Presented by Antony Haynes, Nutritional Therapist
BA(Hons), Dip ION, mCNHC, mBANT

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1. Monday 23rd September 12 noon
Introduction to Long Covid, review of symptoms, example case history. Review of Nutritional Therapy solutions.

2. Friday 27th September 12 noon
Functional Medicine model of Long Covid from Dr Leo Galland, including blood clotting, viral persistence, and mitochondrial disruption. Nutritional Therapy solutions.

3. Monday 30th September 12 noon
Exploration into Mast Cell Activation Syndrome (MCAS) and its involvement in Long Covid symptomology. Nutritional Therapy solutions.

4. Friday 4th October 12 noon
Viral persistence and viral reactivation as causes of Long Covid and Spike Protein Damage to Heme. Nutritional Therapy solutions.

5. Monday 7th October 12 noon
Neurotransmitter imbalances as an explanation for multiple Long Covid symptoms. Nutritional Therapy solutions.

6. Monday 14th October 12 noon
Spike protein pathogenesis. Nutritional Therapy solutions. Review and summary and presentation of Model of Long Covid including lab tests and potential therapeutic interventions.

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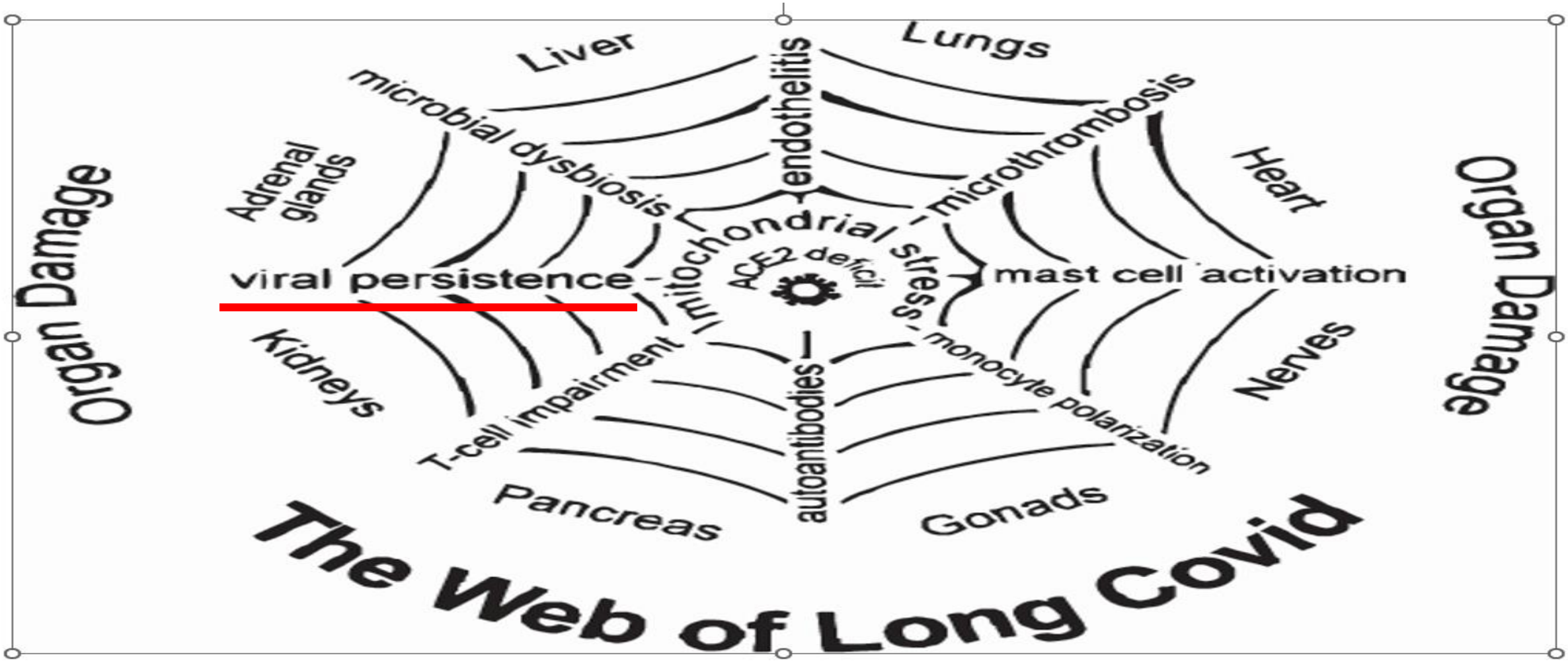
4. Friday 4th October 12 noon

Viral persistence and viral reactivation as causes of Long Covid
and Spike Protein Damage to Heme.
Nutritional Therapy solutions.

Viral Persistence – One Strand of The Web of Long Covid



What is Viral Persistence?

What is Viral Persistence?

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- In the context of long COVID, "viral persistence" refers to the continued presence of SARS-CoV-2 virus or its components in the body after the initial infection has resolved (Turner et al., 2022).
- This means that despite apparent recovery from the acute phase of COVID-19, the virus or its remnants continue to linger in certain tissues or organs, potentially leading to ongoing inflammation, immune activation, and symptoms characteristic of long COVID (El-Baky et al., 2024).

- Turner S, Naidoo CA, et al. Increased levels of inflammatory molecules in blood of Long COVID patients point to thrombotic endotheliitis. medRxiv 2022.10.13.22281055. Full Paper
- El-Baky NA, Amara AA, Uversky VN, Redwan EM. Intrinsic factors behind long COVID: III. Persistence of SARS-CoV-2 and its components. J Cell Biochem. 2024 Jan;125(1):22-44. View Abstract

What is Viral Persistence?

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- Thousands of research articles have described various post-COVID-19 conditions. Yet, the evidence around these ongoing health problems, the reasons behind them, and their molecular underpinnings are scarce. These persistent symptoms are also known as long COVID-19. The persistence of SARS-CoV-2 and/or its components in host tissues can lead to long COVID.
- For example, the presence of viral nucleocapsid protein and RNA was detected in the skin, appendix, and breast tissues of some long COVID patients.
- The persistence of viral RNA was reported in multiple anatomic sites, including non-respiratory tissues such as the adrenal gland, ocular tissue, small intestine, lymph nodes, myocardium, and sciatic nerve. (El-Baky et al., 2024; Goh et al., 2022)

- El-Baky NA, Amara AA, Uversky VN, Redwan EM. Intrinsic factors behind long COVID: III. Persistence of SARS-CoV-2 and its components. J Cell Biochem. 2024 Jan;125(1):22-44. View Abstract
- Goh D, Lim JCT, Fernaíndez SB, Joseph CR, Edwards SG, Neo ZW, Lee JN, Caballero SG, Lau MC, Yeong JPS. Case report: Persistence of residual antigen and RNA of the SARS-CoV-2 virus in tissues of two patients with long COVID. Front Immunol. 2022 Sep 5;13:939989. Full Paper

What is Viral Persistence?

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- Distinctive viral spike sequence variants were also found in non-respiratory tissues.
- Interestingly, prolonged detection of viral subgenomic RNA was observed across all tissues, sometimes in multiple tissues of the same patient, which likely reflects recent but defective viral replication.
- Moreover, the persistence of SARS-CoV-2 RNA was noticed throughout the brain at autopsy, as late as 230 days following symptom onset among unvaccinated patients who died of severe infection.

- El-Baky NA, Amara AA, Uversky VN, Redwan EM. Intrinsic factors behind long COVID: III. Persistence of SARS-CoV-2 and its components. J Cell Biochem. 2024 Jan;125(1):22-44. View Abstract

What is Viral Persistence?

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- This persistence is thought to contribute to the development of long COVID symptoms, which can affect multiple organ systems and manifest as fatigue, cognitive impairment, and other debilitating conditions (Xu et al., 2024).
- It is essential to note that viral persistence does not necessarily imply active viral replication, as some studies suggest that the lingering virus may be non-replicative (Ghafari et al., 2023).
- Nonetheless, the presence of viral components can trigger an immune response, leading to chronic inflammation and tissue damage, which are hallmarks of long COVID (Lee et al., 2024).

- Xu Z, Xu J t al. Dynamic Modeling of Antibody Repertoire Reshaping in Response to Viral Infections. bioRxiv 2024.05.28.596342. View Abstract
- Ghafari M, Hall M et al., 2023. High number of SARS-CoV-2 persistent infections uncovered through genetic analysis of samples from a large community-based surveillance study. medRxiv 2023.01.29.23285160. View Abstract
- Lee JD, Woodruff TM. Complement(ing) long-COVID thromboinflammation and pathogenesis. Trends Immunol. 2024 Jun;45(6):397-399. View Abstract

What is Viral Persistence?

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- The aetiologic mechanisms of post-acute medical morbidities and unexplained symptoms (Long COVID) following SARS-CoV-2 infection are incompletely understood. There is growing evidence that viral persistence and immune dysregulation may play a major role.
- Peluso et al 2023, identified cellular SARS-CoV-2 RNA in rectosigmoid lamina propria tissue in all participants with long COVID symptoms, ranging from 158 to 676 days following initial COVID-19 illness, suggesting that tissue viral persistence could be associated with long-term immunological perturbations.
- Patterson et al 2022 stated that it is important to note that the S1 protein detected in patients appears to be retained from prior infection or phagocytosis of infected cells undergoing apoptosis and is not the result of persistent viral replication.

- Peluso MJ, Ryder D et al. Multimodal Molecular Imaging Reveals Tissue-Based T Cell Activation and Viral RNA Persistence for Up to 2 Years Following COVID-19. medRxiv 2023.07.27.23293177. View Abstract
- Patterson BK, Francisco EB 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. Front Immunol. 2022 Jan 10;12:746021. Full Paper

Do the mRNA vaccines influence Viral Persistence?

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- Kayukawa et al 2021 demonstrated the expected finding. Antibodies go up with infection but because this is a natural process where the body fights SARS-CoV-2 on mucosal surfaces, the serological rise is low. However, vaccination after infection gives a huge rise in anti-spike antibodies implying the body is super-loaded with Spike.
- Moody et al 2022 demonstrated the Spike antigen is strongly correlated with anti-Spike antibodies. The higher the Spike antibody concentration, the greater the degree of autoimmunity induced in the human body.
- “No wonder those with high Spike antibody levels feel sick”. (Dr Peter McCullough)
- Dobrynin et al 2022 have implied that the Spike protein within us is durable, sticks to surfaces and is not easily broken down.

Do the mRNA vaccines influence Viral Persistence?

- Rubio et al. 2024 have demonstrated that anti-Spike antibodies remain elevated for at least two years after injection and this may be amplified by subsequent SARS-CoV-2 infection.

Key takeaways include:

- High levels of spike protein antibodies are associated with increased autoimmune reactions. (See WEBINAR SIX)
- Vaccination after infection results in a significant boost in anti-spike antibodies.
- Spike protein is relatively stable and resistant to degradation, potentially contributing to its durability within the body.
- Further investigation is necessary to confirm the existence and implications of viral persistence in relation to spike protein and antibodies.

References i

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- Chen T, Song J, Liu H, Zheng H, Chen C. Positive Epstein-Barr virus detection in coronavirus disease 2019 (COVID-19) patients. Sci Rep. 2021 May 25;11(1):10902. Full Paper
- Dobrynin D, Polishchuk I, Portal L, Zlotver I, Sosnik A, Pokroy B. Adsorption of SARS CoV-2 spike proteins on various functionalized surfaces correlates with the high transmissibility of Delta and Omicron variants. Mater Today Bio. 2022 Mar;14:100265. Full Paper
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- Gyöngyösi M, Lukovic D, et al. Effect of monovalent COVID-19 vaccines on viral interference between SARS-CoV-2 and several DNA viruses in patients with long-COVID syndrome. NPJ Vaccines. 2023 Sep 29;8(1):145. Full Paper
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- Kayukawa S, Nanya K, Morita M, Ina K, Ota Y, Hasegawa S. Spike Antibody Titers Evaluation after a 2-Dose Regimen of BNT162b2 Vaccination in Healthcare Workers Previously Infected with SARS-CoV-2. Microbiol Spectr. 2021 Dec 22;9(3):e0103621. Full Paper
- Lehner GF, Klein SJ, Zoller H, Peer A, Bellmann R, Joannidis M. Correlation of interleukin-6 with Epstein-Barr virus levels in COVID-19. Crit Care. 2020 Nov 23;24(1):657. Full Paper

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Nutritional Solutions

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- “While human enzymes can “activate” the protein to lock into receptors and enable the virus, no such endogenous enzymes have been found that completely degrade the protein outside of orally administered nattokinase, bromelain, and possibly serrapeptase.” (Dr Peter McCullough).

- Nattokinase 2000 FU b.i.d. away from food
- Bromelain 500mg qd away from food
- Curcumin 500mg b.i.d.
- Augmented NAC b.i.d.

Nutritional Solutions vs Spike Protein

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- Nattokinase 50mg (AR) – 2 caps twice daily on empty stomach (8+ hours apart)
- Nattokinase NSK-SD 50mg x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

- Bromelain Plus (BR) – 5 tabs on empty stomach once a day
- Bromelain Plus x 100 Tablets | Nutri-Link.co.uk (nutrilink.co.uk)

- CurcuWIN 500 (AR) – 1 with breakfast & 1 with dinner
- CurcuWIN 500 x 60 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

- Augmented NAC – 1 before breakfast & dinner by 20-15 mins
- NAC Augmented (N-Acetylcysteine) 90's: The Natural Dispensary

What is Viral Reactivation?

What is Viral Reactivation?

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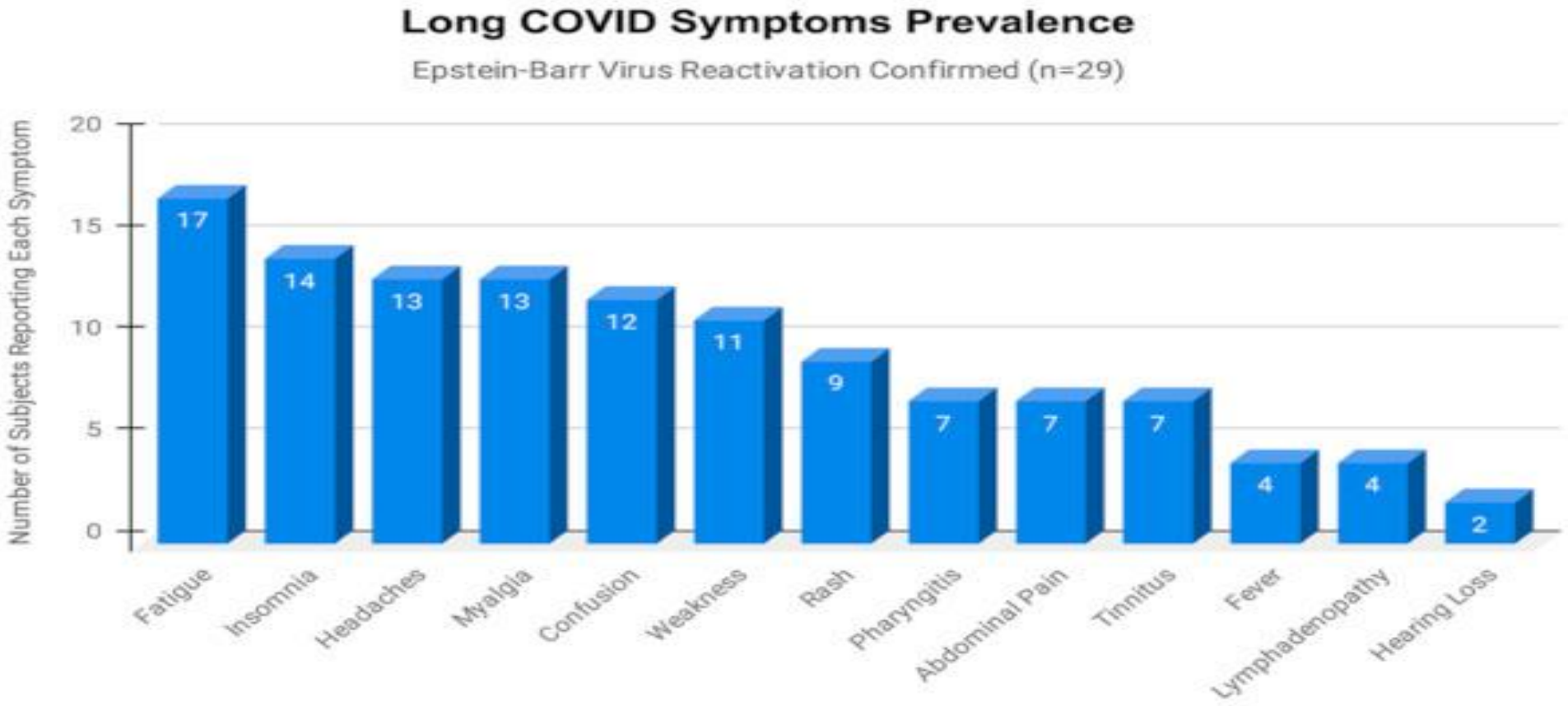
- Viral reactivation refers to the process by which a previously latent or dormant virus becomes active again, leading to the production of new viral particles and potentially causing symptoms or disease (Peluso et al., 2022, Chen et al., 2023, Bernal et al., 2023, Gold et al., 2021).
- In the context of Long Covid, viral reactivation seems to refer to the idea that certain viruses, such as Epstein-Barr Virus (EBV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), and Parvovirus B19, may reactivate due to the inflammation and immune system changes triggered by SARS-CoV-2 infection (Peluso et al., 2022, Chen et al., 2023, Bernal et al., 2023, Gold et al., 2021, Gyöngyösi et al., 2023).
- This reactivation might contribute to the development of Long Covid symptoms, although the exact mechanisms are not fully understood (Peluso et al., 2022, Chen et al., 2023, Bernal et al., 2023, Gold et al., 2021, Gyöngyösi et al., 2023).

Symptoms of Long Covid: Prevalence

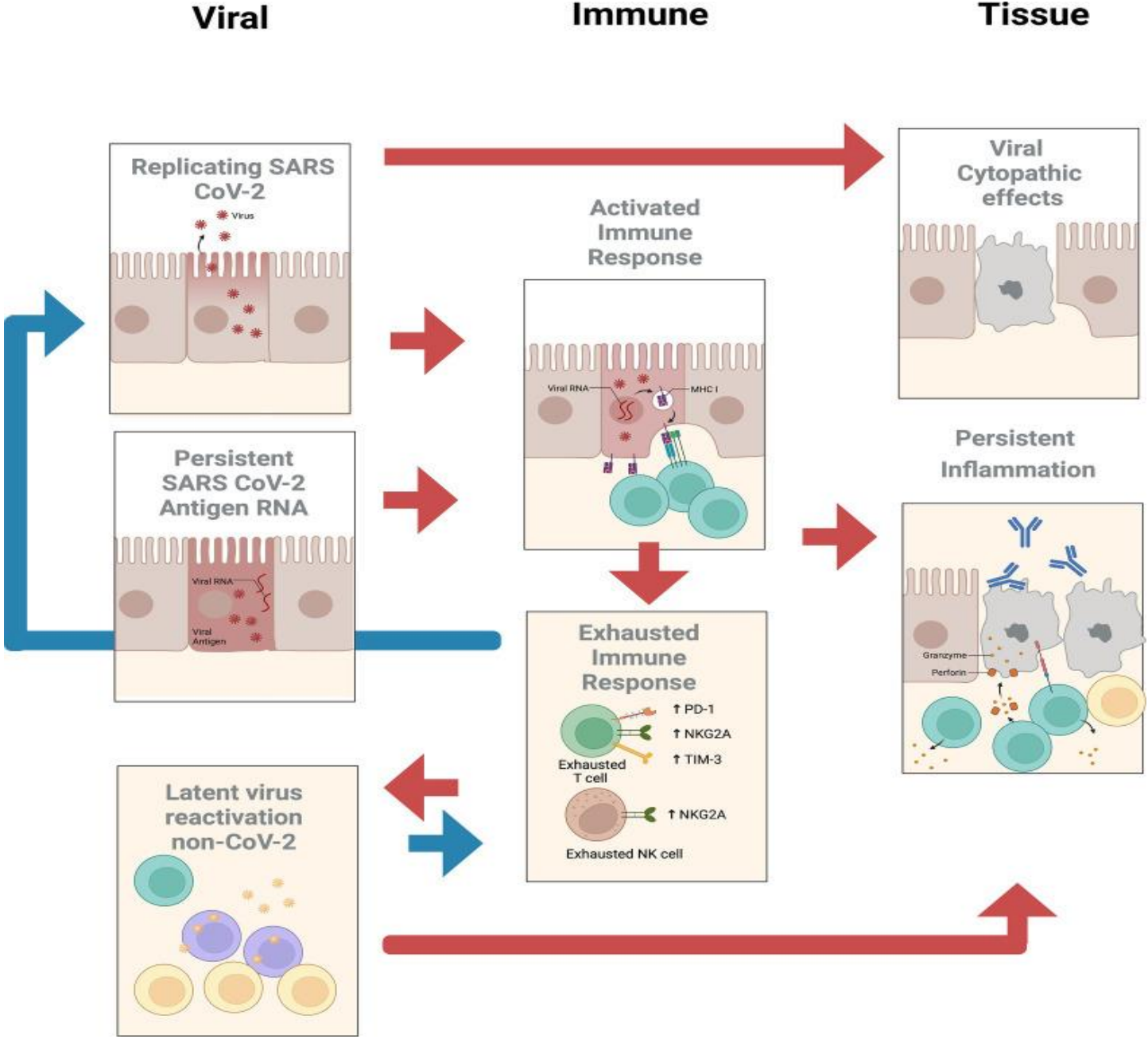


Fatigue, Insomnia, Headaches, Myalgia, Confusion, Weakness, Rash, Pharyngitis, Abdominal Pain, Tinnitus, Fever, Lymphadenopathy, Hearing Loss

Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. Pathogens. 2021 Jun 17;10(6):763. Full Paper

Post-acute sequelae of SARS-CoV-2 infection (PASC)

- Summary of potential viral, immune, and tissue roles in post-acute sequelae of SARS CoV-2 infection (PASC).



- Chen B, Julg B, Mohandas S, Bradfute SB; RECOVER Mechanistic Pathways Task Force. Viral persistence, reactivation, and mechanisms of long COVID. Elife. 2023 May 4;12:e86015. Full Paper

Viral Reactivation

- An intriguing aspect of Post-acute sequelae of SARS-CoV-2 infection (PASC) is the discovery of reactivation of latent viruses after SARS-CoV-2 infection.
- It has been shown that EBV, a herpesvirus that infects a majority of individuals and is typically in a latent state, can be reactivated after SARS-CoV-2 infection (Chen et al., 2021; Lehner et al., 2020).
- Some studies have demonstrated a correlation between EBV reactivation and development of PASC (Hao et al., 2021; Su et al., 2022).
- There has been evidence of reactivation of other herpesviruses, including cytomegalovirus, herpes simplex virus 1, human herpesvirus 6, and human herpesvirus 7, in acute SARS-CoV-2 infection (Drago et al., 2021; Lehner et al., 2020; Su et al., 2022; Xu et al., 2020), although the association with these viruses and development of PASC has not been ascertained (Proal and VanElzakker, 2021).

Viral Reactivation

- Furthermore, some human endogenous retroviruses (HERVs) have been associated with more severe acute SARS-CoV-2 infection (Simula et al., 2022; Temerozo et al., 2022).
- Therefore, while a few herpesviruses are known to be reactivated in PASC and other viruses have been found to be upregulated in acute disease, identification of the full range of viral species or nonviral pathogens that can be reactivated or triggered has not been characterised.
- Performing antibody tests combined with Elispot testing, if available, in people with PASC should answer the question of which latent pathogens are reactivated in PASC versus non-PASC convalescent individuals.
- Specifically, what spectrum of viruses is reactivated in PASC? Also of interest is whether the timing of latent virus reactivation relative to symptomatic onset of PASC is relevant.

Viral Reactivation

- The aim of this study was to conduct a literature review to compare the patient characteristics and outcomes of reactivations and co-infections of different viruses.
- In total, 53 articles were included in this review.
- We identified 40 reactivation studies, 8 coinfection studies, and 5 studies where concomitant infection in COVID-19 patients was not distinguished as either reactivation or coinfection.
- Data were extracted for 12 viruses including IAV, IBV, EBV, CMV, VZV, HHV-1, HHV-2, HHV-6, HHV-7, HHV-8, HBV, and Parvovirus B19. EBV, HHV-1, and CMV were most frequently observed within the reactivation cohort, whereas IAV and EBV were within the coinfection cohort.

- Kim, J.Y.H., Ragusa, M., Tortosa, F. et al. Viral reactivations and co-infections in COVID-19 patients: a systematic review. BMC Infect Dis 23, 259 (2023). Full Paper

Viral Reactivation

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- IAV (Influenza A Virus)
- IBV (Infectious bronchitis virus)
- **EBV (Epstein Barr Virus) (HHV-4)**
- **CMV (Cytomegalovirus) (HHV-5)**
- VZV (Varicella Zoster Virus)
- **HHV-1 (Human Herpes Virus-1)**
- HHV-2 (Human Herpes Virus-2)
- HHV-6 (Human Herpes Virus-6)
- HHV-7 (Human Herpes Virus-7)
- HHV-8 (Human Herpes Virus-8)
- HBV (Hepatitis B Virus)
- Parvovirus B19

Viral Reactivation

- In both reactivation and coinfection groups, patients reported cardiovascular disease, diabetes, and immunosuppression as comorbidities, acute kidney injury as complication, and lymphopenia and elevated D-dimer and CRP levels from blood tests.
- Common pharmaceutical interventions in two groups included steroids and antivirals.

- Kim, J.Y.H., Ragusa, M., Tortosa, F. et al. Viral reactivations and co-infections in COVID-19 patients: a systematic review. BMC Infect Dis 23, 259 (2023). Full Paper

Tests for Viruses

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	TEST NO.	TEST NAME	MATERIAL	PRICE
		BACTERIA		
☐	1	Borrelia Elispot	CPDA	£174
☐	1a	Borrelia iSpot	CPDA	£268
☐	2	CD5-/CD57+/CD56+/CD45+ Cells	Hep & EDTA	£127
☐	3	Borrelia IgG/IgM ELISA	Serum	£60
☐	4a	Borrelia IgG/IgM Seraspot	Serum	£138
☐	4b	Borrelia IgG/IgM Immunoblot	Serum	£138
☐	56	Borrelia miyamotoi Elispot	CPDA	£83
☐	5	Borrelia miyamotoi iSpot	CPDA	£135
☐	57	C6 ELISA (Borrelia)	Serum	£44
☐	6	Ehrlichia & Anaplasma Elispot	CPDA	£83
☐	6w	Ehrlichia & Anaplasma iSpot	CPDA	£135
☐	7a	Anaplasma phagocyt. IgM/IgG antibodies	Serum	£87
☐	7b	Ehrlichia chaffeensis IgM/IgG antibodies	Serum	£87
☐	9a	Bartonella henselae Elispot	CPDA	£83
☐	9w	Bartonella henselae iSpot	CPDA	£135
☐	9	Bartonella (henselae + quintana) IgG antibodies	Serum	£87
☐	10	Bartonella (henselae + quintana) IgM antibodies	Serum	£87
☐	12a	Babesia microti Elispot	CPDA	£83
☐	12w	Babesia microti iSpot	CPDA	£135
☐	12	Babesia IgG/IgM antibodies	Serum	£87
☐	15	Chlamydia pneumoniae Elispot	CPDA	£83
☐	15w	Chlamydia pneumoniae iSpot	CPDA	£135
☐	16	Chlamydia pneumoniae IgG/IgA antibodies	Serum	£60
☐	17	Chlamydia trachomatis Elispot	CPDA	£83
☐	17w	Chlamydia trachomatis iSpot	CPDA	£135
☐	18	Chlamydia trachomatis IgG/IgA antibodies	Serum	£60
☐	19a	Mycoplasma pneumoniae Elispot	CPDA	£83
☐	19w	Mycoplasma pneumoniae iSpot	CPDA	£135
☐	19	Mycoplasma pneumoniae IgG/IgA antibodies	Serum	£60
☐	21	Yersinia enterocolitica Elispot	CPDA	£83
☐	21w	Yersinia enterocolitica iSpot	CPDA	£135
☐	22	Yersinia enterocolitica IgG/IgA antibodies	Serum	£60
☐	23a	Rickettsia Elispot	CPDA	£83
☐	23w	Rickettsia iSpot	CPDA	£135
☐	23	Rickettsia IgG antibodies (rickettsii + typhi)	Serum	£87
☐	24	Rickettsia IgM antibodies (rickettsii + typhi)	Serum	£87
☐	101	Campylobacter jejuni IgG/IgA Immunoblot	Serum	£131
☐	102	Helicobacter pylori ELISA IgG/IgA antibodies	Serum	£63
		VIRUSES		
☐	26	EBV Elispot (2 antigens: lytic + latent)	CPDA	£132
☐	27	EBV IgG/IgM + anti-EBNA antibodies	Serum	£138
☐	28b	HSV 1 + 2 Elispot	CPDA	£132
☐	28w	HSV 1 + 2 iSpot	CPDA	£225
☐	28	HSV 1 + 2 IgG/IgA/IgM antibodies	Serum	£83
☐	29	CMV Elispot (2 antigens: lytic + latent)	CPDA	£132
☐	30	CMV IgG/IgM + anti-EBNA antibodies	Serum	£62
☐	31a	Varicella Zoster Virus (VZV) Elispot	CPDA	£83
☐	31w	Varicella Zoster Virus (VZV) iSpot	CPDA	£135
☐	31	VZV IgG/IgM/IgA antibodies	Serum	£83
☐	33	Coxsackievirus A7 + B1 IgG/IgA antibodies	Serum	£124
☐	86	Echovirus IgG/IgA antibodies	Serum	£86
☐	95	Enterovirus IgG/IgA antibodies	Serum	£49
☐	34a	HHV-6 Elispot	CPDA	£83
☐	34w	HHV-6 iSpot	CPDA	£135
☐	34	HHV-6 IgG/IgM antibodies	Serum	£78
☐	35a	HHV-7 Elispot	CPDA	£83
☐	35w	HHV-7 iSpot	CPDA	£135
☐	35b	HHV-7 IgG antibodies	Serum	£44
☐	36	HHV-8 IgG antibodies	Serum	£44

	TEST NO.	TEST NAME	MATERIAL	PRICE
☐	50	Parvovirus B19 IgG/IgM antibodies	Serum	£50
☐	94	TBE IgG/IgM antibodies	Serum	£62
		TICKPLEX ANTIBODY SCREENING		
☐	74	Tickplex Basic IgG/IgM antibodies (Borrelia)	Serum	£120
☐	75	Tickplex Plus IgG/IgM antibodies (Borrelia, Bartonella, Babesia, Ehrlichia, Coxsackie, EBV, Parvovirus B19, Mycoplasma fermentans/pneumoniae, Rickettsia)	Serum	£585
		YEASTS & MOULDS		
☐	103	ToxiPlex Basic (Mycotoxins: Aflatoxin B1, Deoxynivalenol, Fumonisin (B1&B2), Ochratoxin A, Zearalenone)	Serum	£232
☐	70a	Candida albicans Elispot	CPDA	£83
☐	70w	Candida albicans iSpot	CPDA	£135
☐	70	Candida IgG/IgA/IgM antibodies	Serum	£105
☐	72a	Aspergillus Peptide Mix 1&2 Elispot	CPDA	£167
☐	72w	Aspergillus Peptide Mix 1&2 iSpot	CPDA	£225
		AONM TEST PANELS		
☐	77	Panel A2 Standard Virus Panel	CPDA & Serum	£479
☐	78	Panel B2 Extended Virus Panel		£737
☐	79	Panel C2 Comp. Bacteria Panel	CPDA, Serum, EDTA & Hep	£910
☐	80	Panel D2 Stealth Pathogen Panel		£844
☐	201	Post COVID Viral Reactivation Panel: Light	CPDA & Serum	£344
☐	202	Post COVID Viral Reactivation Panel: Advanced		£606
		COMPLEMENTARY AND ADDITIONAL TESTS		
☐	2b	Immune Profile (CD19/CD3-/CD57+/CD56+/CD45+ Cells)	Hep & EDTA	£169
☐	105	RANTES	Serum	£62
☐	38	CCP antibodies	Serum	£38
☐	39	Antinuclear Antibody (ANA) titer	Serum	£25
☐	40	ds-DNA antibodies	Serum	£26
☐	42	c- and p-ANCA	Serum	£50
☐	43	C-Reactive Protein (CRP)	Serum	£18
☐	44	Diarrhoea/Coeliac Disease	Serum	£90
☐	45	Organ Profile: FBC, CK, Sodium, Potassium, Alk Phos., AST, ALT, GGT, LDH, CHE, Amylase, Lipase, Bilirubin, Uric Acid, Creatinine, eGFR, TSH	Serum & EDTA	£74
☐	46	Total Protein, Protein Electrophoresis (Albumin, Alpha1-, Alpha2-, Beta, Gamma globulin, Total protein)	Serum	£20
☐	47	Lipid profile (cholesterol, triglycerides, HDL, LDL)	Serum	£15
☐	48	Thyroid hormones (TSH, fT3, fT4)	Serum	£64
☐	49	Thyroid antibodies (TPO abs, TG Abs, TSH receptor Abs)	Serum	£125
☐	61	Reverse T3	Serum	£49
☐	87	Zonulin antibodies	Serum	£64
☐	88	TNF Alpha antibodies	Serum	£38
☐	89	Interleukin 6 (IL-6) antibodies	Serum	£64
☐	90	Interleukin 2 (IL-2) Receptor antibodies	Serum	£64
☐	92	Anti-DNase B	Serum	£18
☐	93	Anti-Streptolysin O	Serum	£21
☐	96	Immunoglobulin levels IgA/IgM/IgG	Serum	£39
		VITAMINS		
☐	51	Vitamin D3 (25 OH)	Serum	£42
☐	52	Vitamin B6 Pyroxidine	EDTA	£49
☐	53	Vitamin B12	Serum	£22
☐	54	Vitamin B9 Folate	Serum	£22
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Armin Labs via AONM

		VIRUSES
☐	26	EBV Elispot (2 antigens: lytic + latent)
☐	27	EBV IgG/IgM + anti-EBNA antibodies
☐	28b	HSV 1 + 2 Elispot
☐	28w	HSV 1 + 2 iSpot
☐	28	HSV 1 + 2 IgG/IgA/IgM antibodies
☐	29	CMV Elispot (2 antigens: lytic + latent)
☐	30	CMV IgG/IgM + anti-EBNA antibodies
☐	31a	Varicella Zoster Virus (VZV) Elispot
☐	31w	Varicella Zoster Virus (VZV) iSpot
☐	31	VZV IgG/IgM/IgA antibodies
☐	33	Coxsackievirus A7 + B1 IgG/IgA antibodies
☐	86	Echovirus IgG/IgA antibodies
☐	95	Enterovirus IgG/IgA antibodies
☐	34a	HHV-6 Elispot
☐	34w	HHV-6 iSpot
☐	34	HHV-6 IgG/IgM antibodies
☐	35a	HHV-7 Elispot
☐	35w	HHV-7 iSpot
☐	35b	HHV-7 IgG antibodies
☐	36	HHV-8 IgG antibodies

Viral Persistence & Reactivation

Nutri Link
Linking Science and Nutrition

- Given the ability of coronaviruses to infect and reinfect individuals over a lifetime, viral persistence seems likely to play a role in PASC.
- There is ample evidence for persistence of SARS-CoV-2 viral RNA and proteins in several tissues, including respiratory tract, GI tract, olfactory mucosa, and the central nervous system.
- The mechanisms of persistence may involve replication or the action of viral replication machinery; however, exactly how viral components persist in individuals is still unclear.
- The presence of persistent viral antigen and RNA may be the result of incomplete immunity where holes in the immune response permit viral persistence, but there also appears to be evidence that persistent inflammation as a reaction to persistent antigen is causing pathology.

Viral Persistence & Reactivation

- A deeper understanding of the adaptive immune responses, including T-cell and B-cell responses, may provide rationales for targeted therapies either to enhance clearance of persistent antigens, or to limit persistent inflammatory responses that are causing damage.
- The evidence for reactivation of other latent viruses also appears to be implicated; these provide a rationale for more extended testing for reactivation of EBV and other viruses during PASC or similar post-viral syndromes.
- Treatment of these viral co-infections may also provide an avenue for therapeutic trials where evidence of persistent viral activation is present.

Viral Persistence & Reactivation

Nutri Link
Linking Science and Nutrition

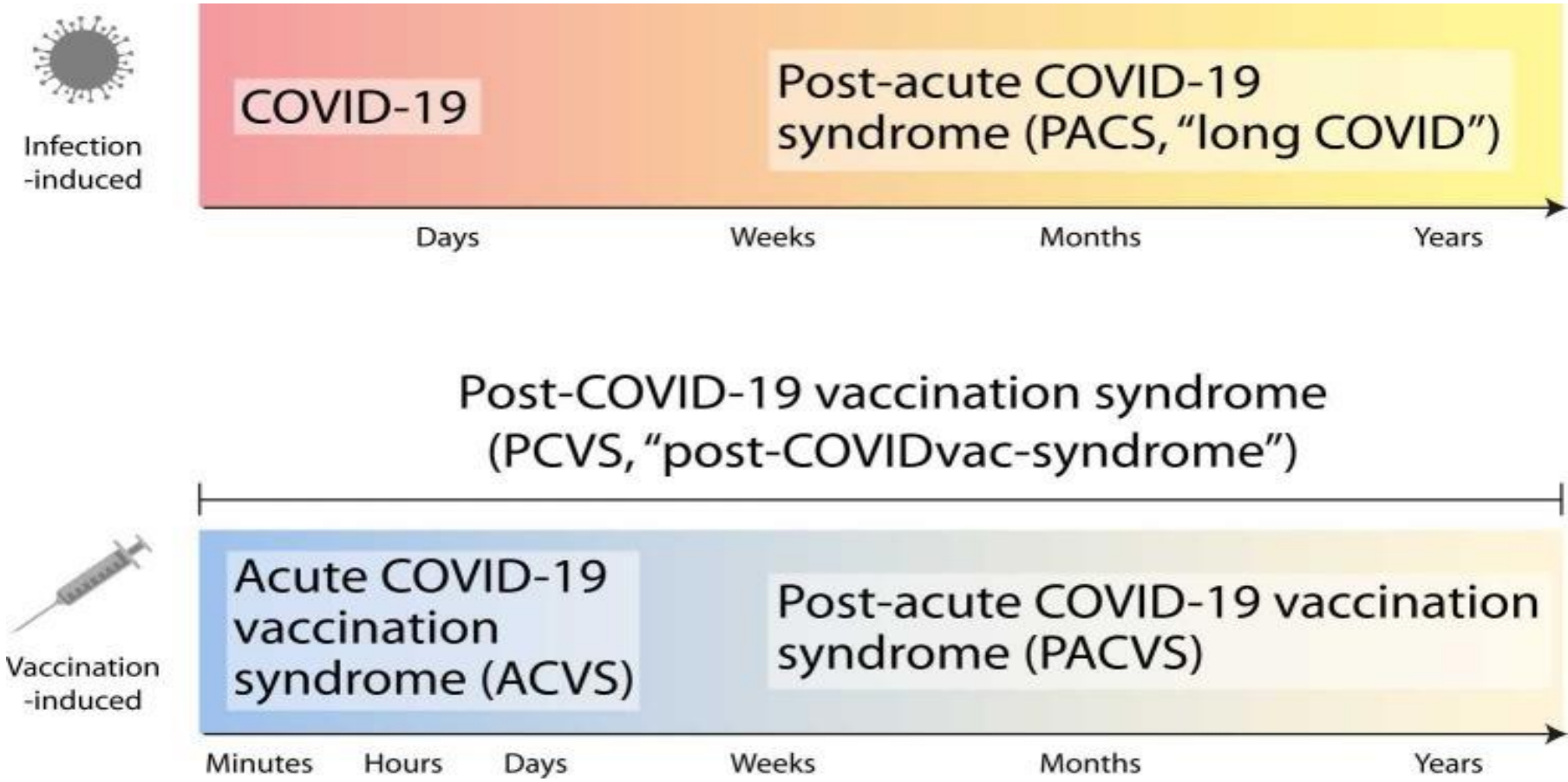
- From a medical perspective, a major challenge of the treatment of PASC is that it appears to be a highly diverse condition, potentially with several different pathogenetic mechanisms that each will require a distinct treatment approach.
- From a nutritional / naturopathic perspective, there is no such challenge. It is evident that an anti-inflammatory approach is to be implemented, alongside natural remedies that have been shown to break down spike protein, and where appropriate natural anti-virals.
- There is also a robust logic to heal the intestinal lining in which may be embedded mRNA remnants.

Nutri Link
Linking Science and Nutrition

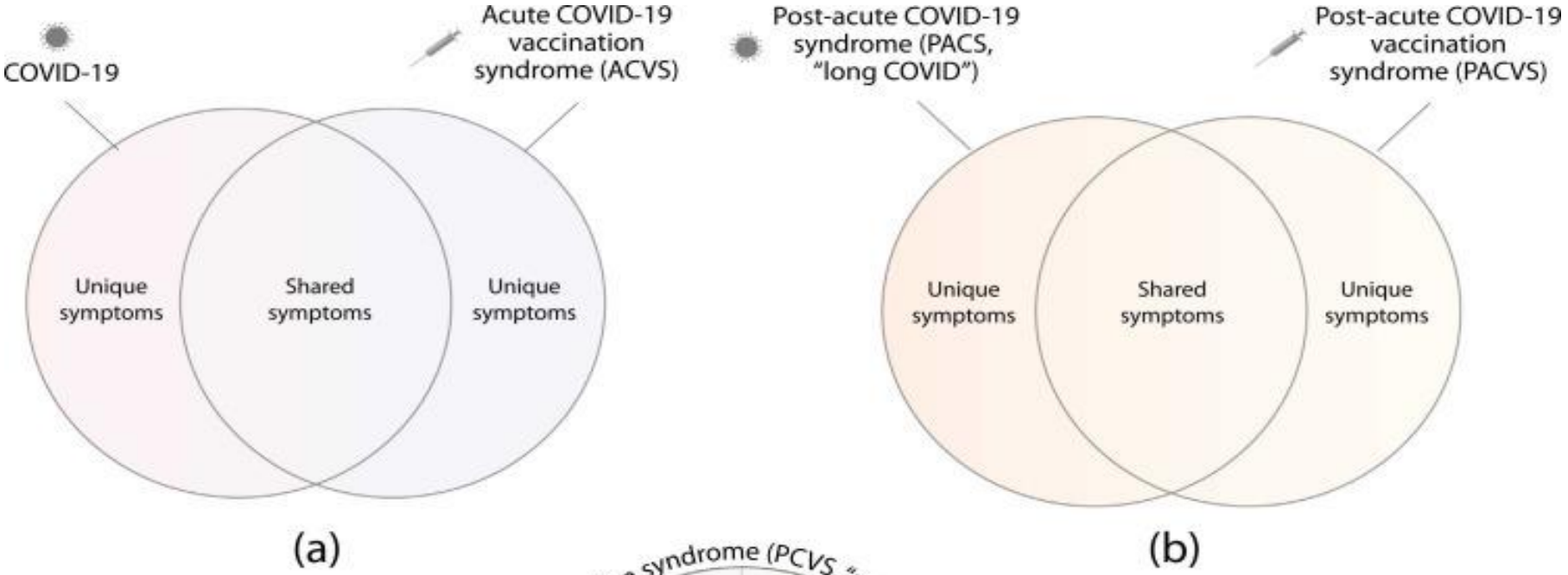
Post-COVID-19 vaccination syndrome
PCVS

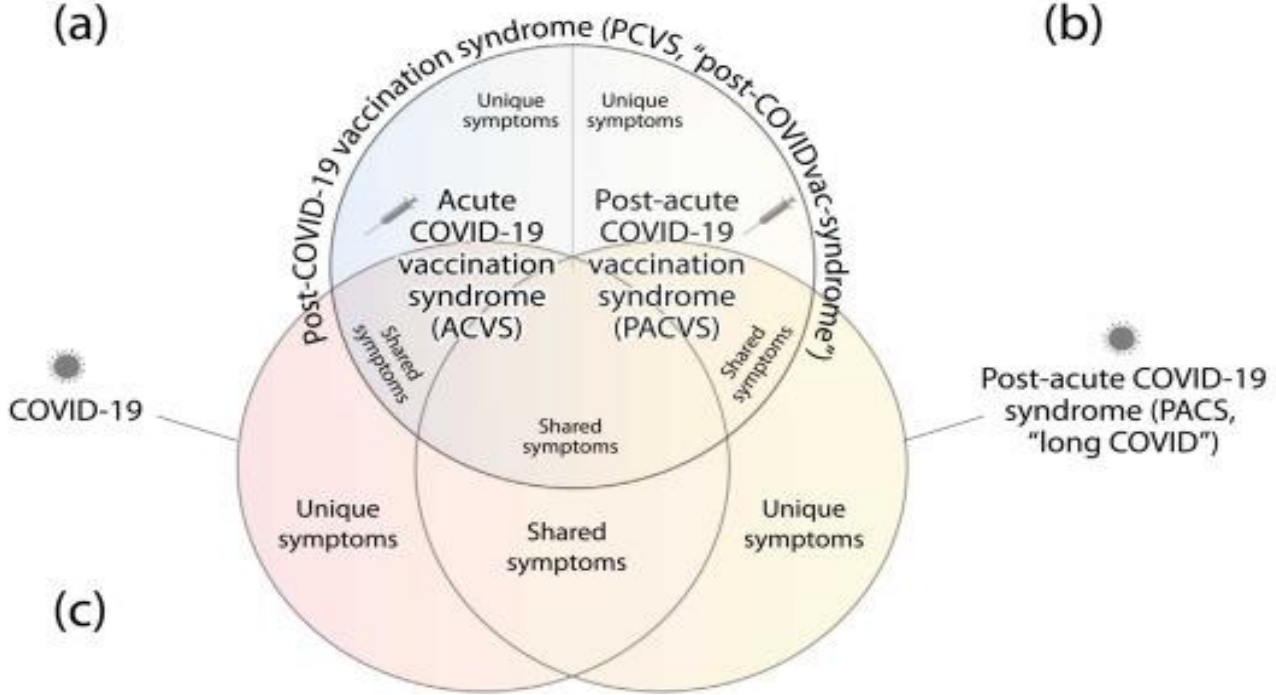
Post-COVID-19 vaccination syndrome, PCVS

- Definition of the terminology of syndromes with respect to the causative factor (infection/vaccination) und their general temporal manifestation. The colour gradient shows that it is a spectrum where the initial syndrome can change to the following syndrome.



Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper





Visualisation of the terminology in the form of Venn diagrams based on overlapping symptoms, in terms of

(a) COVID-19 and ACVS,
(b) PACS and PACVS, and
(c) COVID-19, PCVS and PACS.

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

Nutri Link
Linking Science and Nutrition

- Although Post Acute Covid-19 Syndrome (PACS) has unique characteristics, post-acute infection syndromes (PAIS) can also be present after other types of infections.
- For example, “post-infectious fatigue” (also termed “post-infectious fatigue syndrome”) and ME/CFS has been documented after infection with Epstein-Barr virus, influenza viruses, Dengue virus, Puumala virus, enterovirus, human parvovirus, the spirochete Borrelia, bacterium Coxiella burnetii and the protozoan Giardia.
- A relatively widespread and increasingly researched PAIS is for example the “post-treatment Lyme disease syndrome” (also known as “post-Lyme syndrome”) with fatigue also a key symptom.
- PACS is therefore a type of PAIS.

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- With regard to the COVID-19 vaccinations, the most frequent side effects are mild to moderate, non-serious and include fatigue, pain at the site of injection, fever, chills, muscle pain, joint pain, and headache lasting a few days.
- Long-lasting non-severe side effects is reported.
- Severe adverse events (side effects) can occur such as myocarditis and pericarditis.
- In the worst case, COVID-19 and ACVS (and PACVS) can lead to death. What distinguishes death in both cases is the timing between infection / vaccination and occurrence of death.
- ACVS can manifest in different ways, with for example anaphylaxis and vasovagal syncope/presyncope that can follow immediately after vaccination.

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- Severe side effects of COVID-19 vaccination have particularly an overlap with symptoms of COVID-19.
- For example, myocarditis and pericarditis have been found in association with COVID-19 and COVID-19 vaccination with the onset of cardiovascular symptoms after vaccination normally occurring a few days after vaccination.
- While COVID-19 vaccine induced myocarditis/pericarditis generally fall in the category ACVS, cases in the category PACVS seem to occur too (e.g. 3 months after vaccination).

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- The spike protein (but not the nucleocapsid protein) could be detected, for example, “within the foci of inflammation in both the brain and the heart, particularly in the endothelial cells of small blood vessels” in an individual that collapsed 2 weeks after the third dose of the COVID-19 vaccine and died 1 weeks after this incidence.
- The SARS-CoV-2 spike protein was also detected in cardiac tissue in individuals experiencing intramyocardial inflammation after COVID-19 vaccination, including a case with symptoms 21 days after vaccination and successful mRNA detection.
- Furthermore, the presence of the SARS-CoV-2 spike protein was found in varicella zoster virus (VZV) lesions in a patient suffering from VZV reactivation after COVID-19 vaccination.

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- VZV and herpes simplex virus, cytomegalovirus and Epstein-Barr virus reactivation was found to be possibly occurring due to COVID-19 and COVID-19 vaccination.
- Gold et al. found **66.7%** of long COVID patients to be positive for Epstein-Barr virus reactivation (compared to 10% in control subjects).
- Gold JE, et al. Investigation of long COVID prevalence and its relationship to Epstein-Barr virus reactivation. Pathogens. 2021;10(6). Full Paper

- There is already “epidemiological, clinical and experimental evidence that ME/CFS constitutes a major type of adverse effect of vaccines”.
- Gherardi R.K., Crepeaux G., Authier F.J. Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system. Autoimmun. Rev. 2019;18(7):691–705. View Abstract

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- According to an observation in 120 PACVS patients, the syndrome is generally characterised by fatigue with post exercise malaise, cognitive disorders, headaches, visual disturbances, joint and muscle pain, disturbances of the heat-cold regulation and sudden fast heartbeat without apparent reason (Jörg-Heiner Möller, personal communication).
- With respect to fundamental pathophysiological processes underlying COVID-19, PACS and PCVS, the following aspects are of importance:
    - Autoantibodies
    - Vascular disorders
    - Amyloid fibrin microclots
    - Hyperactivated platelets
    - Circulating SARS-CoV-2 mRNA and proteins

Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. Pathol Res Pract. 2023 Jun;246:154497. Full Paper

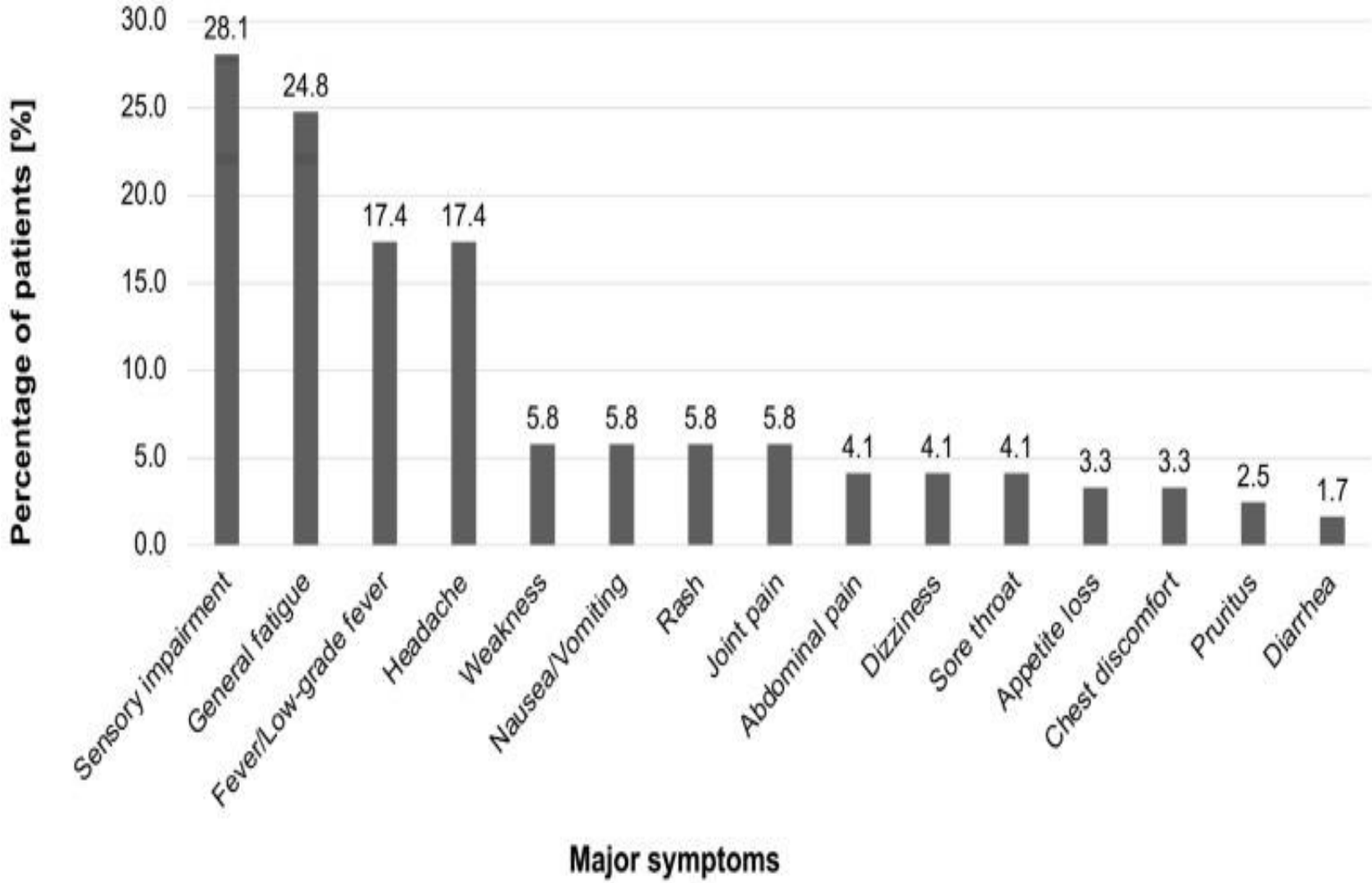
Post-COVID-19 vaccination syndrome, PCVS

- Although many adverse reactions after SARS-CoV-2 vaccination have been reported, there have been few comprehensive studies on persistent symptoms after SARS-CoV-2 vaccination.
- 15 persistent symptoms after SARS-CoV-2 vaccination were characterized. All of the symptoms had onset from 12 hours to one week after vaccination, with 10 symptoms persisting for 6 months or longer.
- The most frequent symptom was sensory impairment.

Tokumasu K, Fujita-Yamashita M, et al. Characteristics of Persistent Symptoms Manifested after SARS-CoV-2 Vaccination: An Observational Retrospective Study in a Specialized Clinic for Vaccination-Related Adverse Events. Vaccines (Basel). 2023 Oct 30;11(11):1661. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

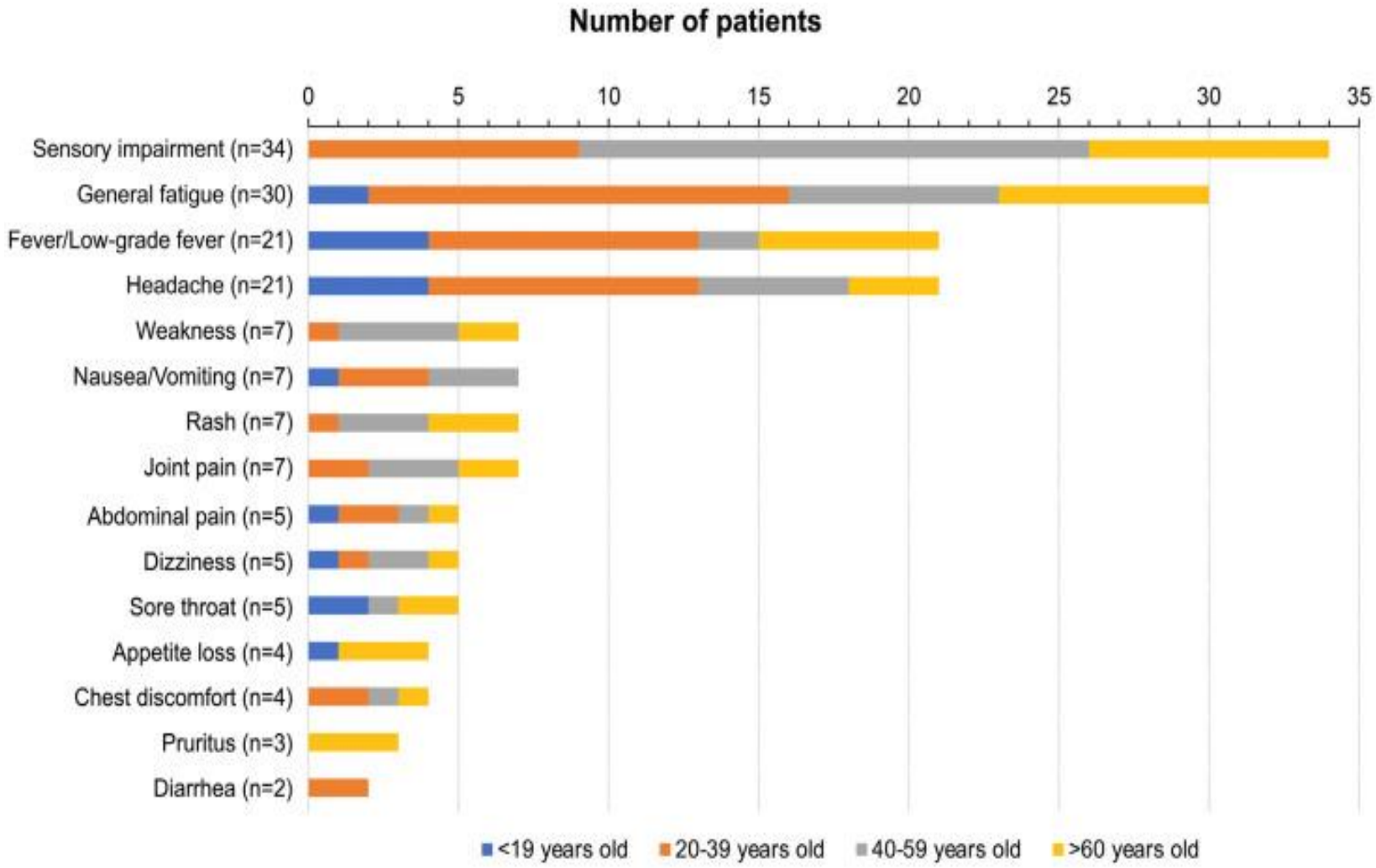
- Persistent symptoms after SARS-CoV-2 vaccination classified by frequency. The four most frequent symptoms were sensory impairment (28.1% of the patients), general fatigue (24.8%), fever/low-grade fever (17.4%), and headache (17.4%).
- We included symptoms that were observed in more than two patients.



Tokumasu K, Fujita-Yamashita M, et al. Characteristics of Persistent Symptoms Manifested after SARS-CoV-2 Vaccination: An Observational Retrospective Study in a Specialized Clinic for Vaccination-Related Adverse Events. Vaccines (Basel). 2023 Oct 30;11(11):1661. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- Age-related persistent symptoms after SARS-CoV-2 vaccination. The blue bar, orange bar, gray bar, and yellow bar indicate less than 19 years old, 20–39 years old, 40–59 years old, and over 60 years old, respectively.



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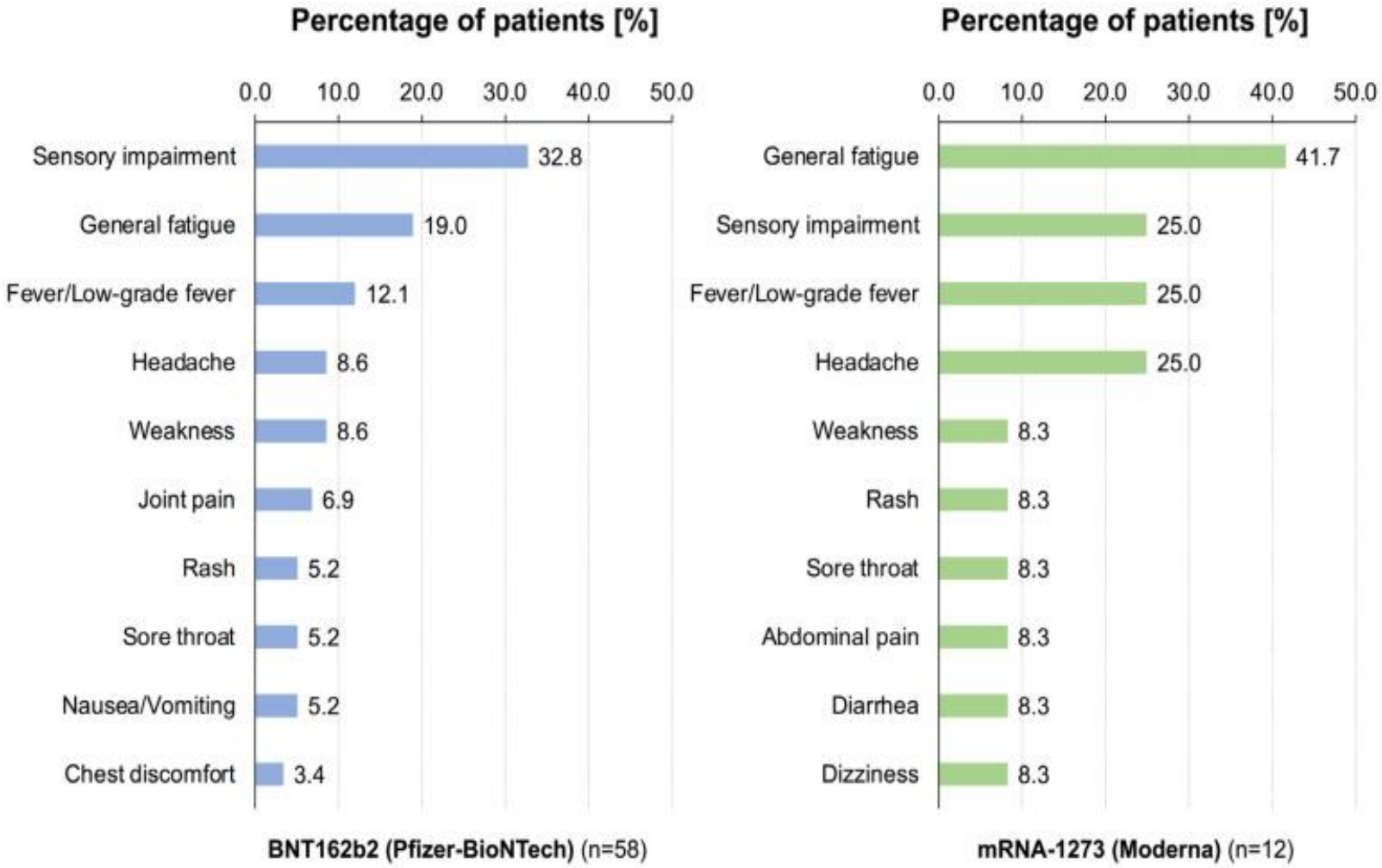
Post-COVID-19 vaccination syndrome, PCVS

- Types of vaccine-related persistent symptoms after SARS-CoV-2 vaccination.



Tokumasu K, Fujita-Yamashita M, et al. Characteristics of Persistent Symptoms Manifested after SARS-CoV-2 Vaccination: An Observational Retrospective Study in a Specialized Clinic for Vaccination-Related Adverse Events. Vaccines (Basel). 2023 Oct 30;11(11):1661. Full Paper

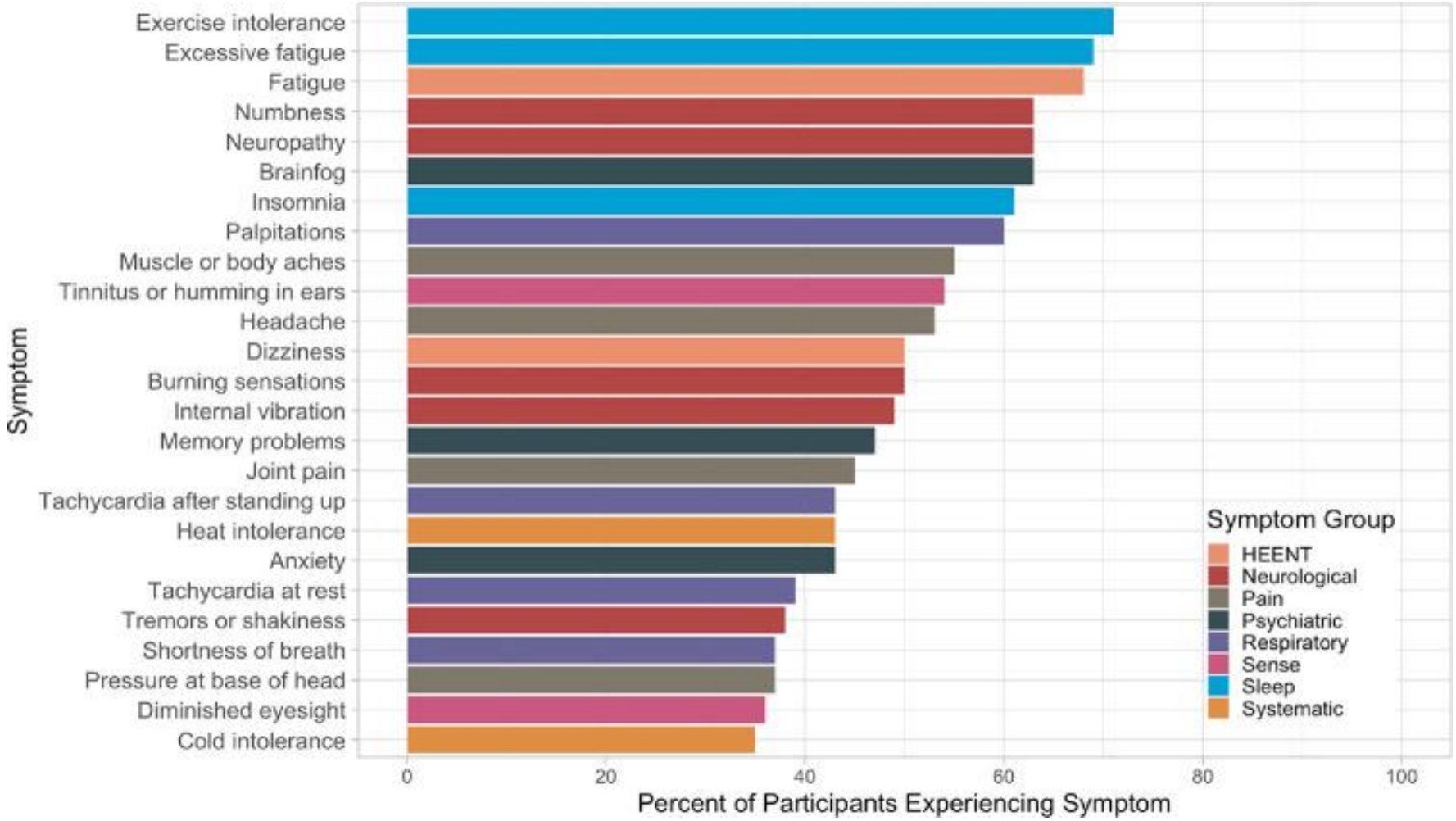
Post-COVID-19 vaccination syndrome, PCVS

- Krumholz et al 2023 241 individuals aged 18 and older who self-reported PVS after covid-19 vaccination and who joined the online Yale Listen to Immune, Symptom and Treatment Experiences Now (LISTEN) Study from May 2022 to July 2023.
- Krumholz et al summarised their demographics, health status, symptoms, treatments tried, and overall experience.
- The average number of symptoms attributed to PVS was 22.
- The most common new diagnoses in the study sample since the beginning of the pandemic were anxiety (49 (36%) participants), neurological conditions (79 [33%]), gastrointestinal issues (73 [30%]), and postural orthostatic tachycardia syndrome (POTS) (70 [29%]). There were 53 (22%) participants who reported migraine and 49 (20%) who reported depression.

Krumholz HM, Wu Y, et al. Post-Vaccination Syndrome: A Descriptive Analysis of Reported Symptoms and Patient Experiences After Covid-19 Immunization. medRxiv [Preprint]. 2023 Nov 10:2023.11.09.23298266. Full Paper - PrePrint

Post-COVID-19 vaccination syndrome, PCVS

- Top 25 most common symptoms with their corresponding symptom groups within 241 participants who reported PVS.
- People reporting PVS after covid-19 vaccination in this study are highly symptomatic, have poor health status, and have tried many treatment strategies without success.
- As PVS is associated with considerable suffering, there is an urgent need to understand its mechanism to provide prevention, diagnosis, and treatment strategies.



Krumholz HM, Wu Y, et al. Post-Vaccination Syndrome: A Descriptive Analysis of Reported Symptoms and Patient Experiences After Covid-19 Immunization. medRxiv [Preprint]. 2023 Nov 10:2023.11.09.23298266. Full Paper - PrePrint

Post-COVID-19 vaccination syndrome, PCVS

- PCVS affecting the nervous system has been studied by Gerhard et al, 2023.
- The most frequently reported symptoms were paraesthesia (56%), fatigue (46%) and cognitive impairment (36%).
- Neurological, routine laboratory, and electrophysiological examinations did not yield distinct pathological findings.
- Neuropsychological testing of a subgroup revealed deficits in attention, executive function and memory.
- “Our data does not allow conclusions whether the symptoms occurred in temporal relationship to the COVID-19 vaccination, or whether the vaccine may be considered as a triggering factor or a cause of these symptoms. While there is limited data, several pathomechanisms have been suggested to explain the occurrence of diseases following SARS-CoV-2 vaccination, e.g., molecular mimicry, production of cross-reactive (anti-idiotype) autoantibodies, involvement of vaccine adjuvants, and persistence of spike protein.”

Gerhard A, Raeder V, et al. Neurological symptoms after COVID-19 vaccination: a report on the clinical presentation of the first 50 patients. J Neurol. 2023 Oct;270(10):4673-4677. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- PCVS affecting the nervous system has also been studied by Arlt et al, 2024.

- Compared with controls, PCVS patients had a significantly greater frequency of autoantibodies against peripheral nervous system structures (9/50 (18%) vs 1/35(3%).

- Conclusion
- Our data suggest that autoantibodies against nervous system tissue could be relevant in PCVS patients.

Arlt FA, Breuer A, et a;. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Front Immunol. 2024 Aug 2;15:1404800. Full Paper

Viral Reactivation & Low Cortisol

Viral Reactivation & Low Cortisol

- The same researchers who confirmed the presence of reactivated viruses, also found lower than normal levels of cortisol in those with Long Covid compared to controls.
- “Analysis of circulating immune mediators and various hormones also revealed pronounced differences, with levels of cortisol being uniformly lower among participants with Long COVID relative to matched control groups. Integration of immune phenotyping data into unbiased machine learning models identified significant distinguishing features critical in accurate classification of Long COVID, **with decreased levels of cortisol being the most significant individual predictor**.”

Klein, J et al. Distinguishing features of Long COVID identified through immune profiling. 10 Aug 2022, https://www.medrxiv.org/content/10.1101/2022.08.09.22278592v1

If there is a Positive Viral Burden

Consider these Natural Anti-Viral Agents:

- Humic Acid Cell Membrane Active (AR) - Humic Acid x 60 Capsules | Nutri-Link (nutrilink.co.uk) – 1 with breakfast & dinner
- Humic Monolaurin Complex (AR) - Humic Monolaurin x 120 Capsules | Nutri-Link (nutrilink.co.uk) – 2 with breakfast & dinner
- Aqueous Selenium (BR) – Aqueous Selenium x 15ml | Nutri-Link.co.uk (nutrilink.co.uk) = 1 drop with two or three meals
- NAC (BR) & (AR) – 1 on empty stomach twice daily (supports Th1 immune response)
- Ashwagandha Complex (AR) (incl licorice) – 2 with breakfast & 1-2 with lunch - Ashwaganda Complex x 60 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

If there is Viral Persistence

Nutri Link
Linking Science and Nutrition

Aim to support the turnover of the gut lining to promote elimination of mRNA remnants from the intestines:

- Perm A Vite (AR) - Perm A Vite x 300g | Nutri-Link.co.uk (nutrilink.co.uk) - 1 tablespoon in liquid 10 mins before two to three meals
- Laktoferrin with Colostrum (AR) - Laktoferrin With Colostrum x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk) - 3-4 caps at night
- Bromelain Plus (BR) – Bromelain Plus x 100 Tablets | Nutri-Link.co.uk (nutrilink.co.uk) - 5 tabs on empty stomach once or twice daily (biofilm buster)
- NAC (BR) & (AR) – 1 on empty stomach twice daily (anti-viral, biofilm buster)
- Humic Monolaurin Complex (AR) - Humic Monolaurin x 120 Capsules | Nutri-Link (nutrilink.co.uk) – 2 with breakfast & dinner

Hematological Problems in Long Covid

Heme

- Each red blood cell (RBC) contains approximately 270 million hemoglobin molecules. Since each hemoglobin molecule has four heme subunits, we can calculate the total number of heme molecules per RBC:
- 270,000,000 hemoglobin molecules/RBC × 4 hemes/hemoglobin = 1,080,000,000 heme molecules/RBC
- So, there are roughly 1.08 billion heme molecules in each red blood cell.

- Amount of haemoglobin in erythrocyte - Human Homo sapiens - BNID 102740 (harvard.edu)

Heme

Nutri Link
Linking Science and Nutrition

- Heme is an essential prosthetic group found in numerous proteins across the human body.
- Here is a list of protein families and individual proteins where heme plays a crucial role:

- Globins: Hemoglobin (16 subunits) & Myoglobin
- Cytochrome enzymes: Cytochromes c (~20 types), Cytochromes b5 (~10 types), Cytochrome oxidases (~15 subunits)
- P450 enzymes: (~57 family members) e.g., CYP1A1, CYP2C9, etc.
- Nitric oxide synthase (eNOS, nNOS, iNOS): 3 isoforms
- Guanylyl cyclase: soluble guanylate cyclase (sGC), particulate guanylate cyclase (pGC)
- Sulfite reductase
- Indoleamine 2,3-dioxygenase (IDO)

- Considering these categories, approximately **150-200 distinct proteins** involve heme directly in their structure or function within the human body.

Haematological Problems in Long Covid: Iron Dyshomeostasis

Nutri Link
Linking Science and Nutrition

- Iron overload is increasingly implicated as a contributor to the pathogenesis of COVID-19.
- Indeed, several of the manifestations of COVID-19, such as inflammation, hypercoagulation, hyperferritinemia, and immune dysfunction are also reminiscent of iron overload.
- Although iron is essential for all living cells, free unbound iron, resulting from iron dysregulation and overload, is very reactive and potentially toxic due to its role in the generation of reactive oxygen species (ROS).
- ROS react with and damage cellular lipids, nucleic acids, and proteins, with consequent activation of either acute or chronic inflammatory processes implicated in multiple clinical conditions.
- Moreover, iron-catalysed lipid damage exerts a direct causative effect on the newly discovered nonapoptotic cell death known as ferroptosis.
- Unlike apoptosis, ferroptosis is immunogenic and not only leads to amplified cell death but also promotes a series of reactions associated with inflammation.

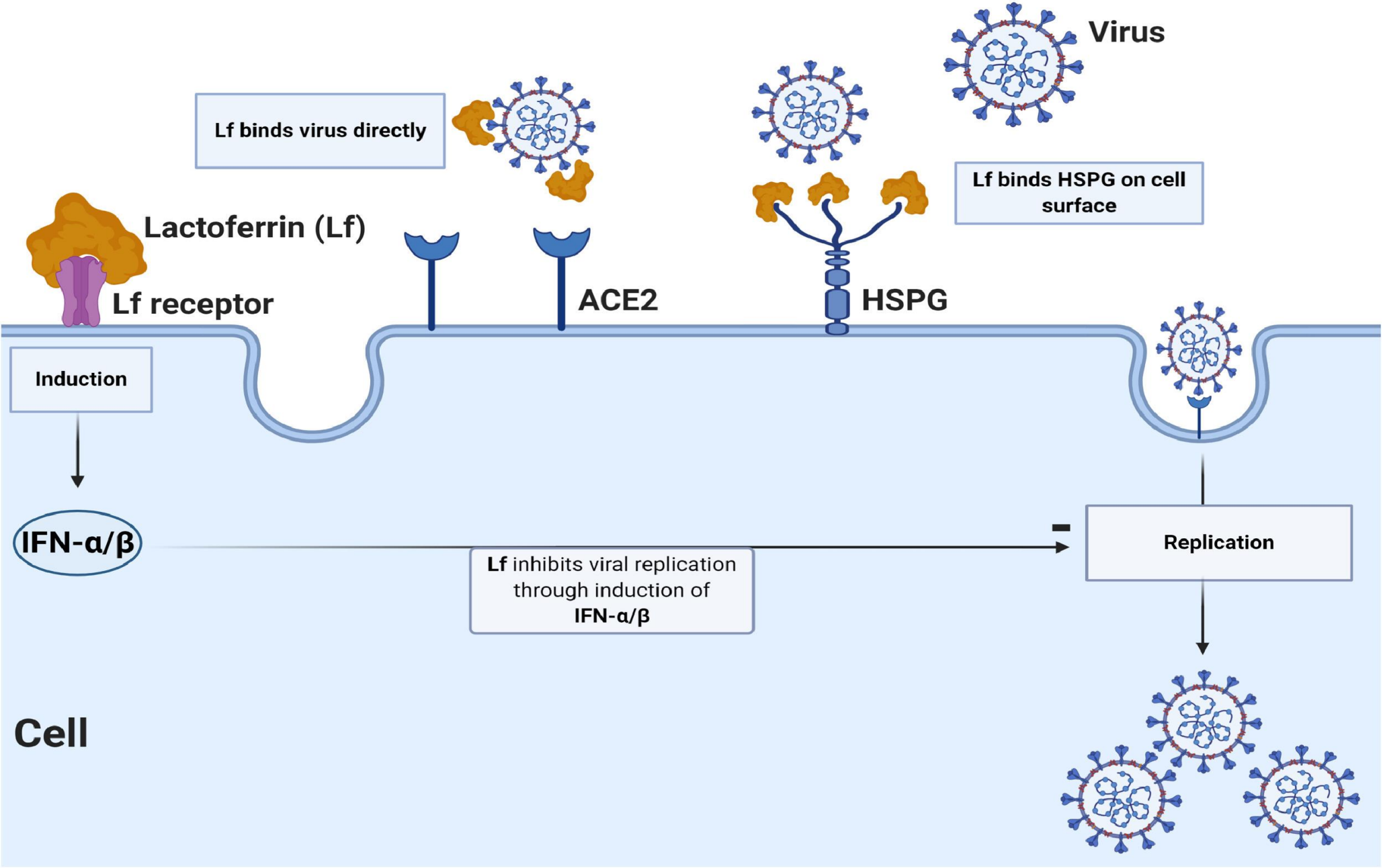
- Habib HM, Ibrahim S, Zaim A, Ibrahim WH. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. Biomed Pharmacother. 2021 Apr;136:111228. Full Paper

Haematological Problems in Long Covid: Iron Dyshomeostasis

Nutri Link
Linking Science and Nutrition

- Iron chelators are generally safe and are proven to protect patients in clinical conditions characterized by iron overload.
- There is also an abundance of evidence that iron chelators possess antiviral activities.
- Furthermore, the naturally occurring iron chelator lactoferrin (Lf) exerts immunomodulatory as well as anti-inflammatory effects and can bind to several receptors used by coronaviruses thereby blocking their entry into host cells.
- Iron chelators may consequently be of high therapeutic value during the present COVID-19 pandemic.

- Habib HM, Ibrahim S, Zaim A, Ibrahim WH. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. Biomed Pharmacother. 2021 Apr;136:111228. Full Paper



Chang R et al. Lactoferrin as potential preventative and adjunct treatment for COVID-19. International Journal of Antimicrobial Agents. Vol 56, Iss 3, 2020. View Full Paper

Lactoferrin as Antiviral Agent – Diagram Description

- Potential antiviral mechanisms of lactoferrin (Lf):
- (i) direct binding of virus by Lf;
- (ii) Lf binding heparan sulfate proteoglycans (HSPGs) on the host cell surface, reducing viral surfing and subsequent viral entry;
- (iii) Lf inhibition of viral replication via induction of intracellular cell signals. ACE2, angiotensin-converting enzyme 2; IFN, interferon.
- Zinc-saturated lactoferrin can apparently exert a more potent antiviral effect.
- Ideal dose is not known, but 300-500mg at night is proposed.

Chang R et al. Lactoferrin as potential preventative and adjunct treatment for COVID-19. International Journal of Antimicrobial Agents. Vol 56, Iss 3, 2020. View Full Paper

Haematological Problems in Long Covid: Iron Dyshomeostasis

Nutri Link
Linking Science and Nutrition

- Liu (2020) identified that the S and ORF3a proteins of SARs-CoV-2 possess picornavirus/calicivirus capsid domains, can bind hemoglobin, heme, and porphyrin.
- Liu's research suggested that the key pathogenic molecular step of COVID-19 is to attack hemoglobin causing dissociation of the porphyrins from iron and releasing iron into the circulation.
- Thus, hemoglobin loses its capacity to bind with oxygen and hinders its delivery to major organs, which is coupled with rapid multi-organ failures.
- Furthermore, amplified iron load leads to increased blood viscosity with recurrent and diffuse macro and micro circulatory thrombosis.

- Liu W., Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. 2020. View Abstract

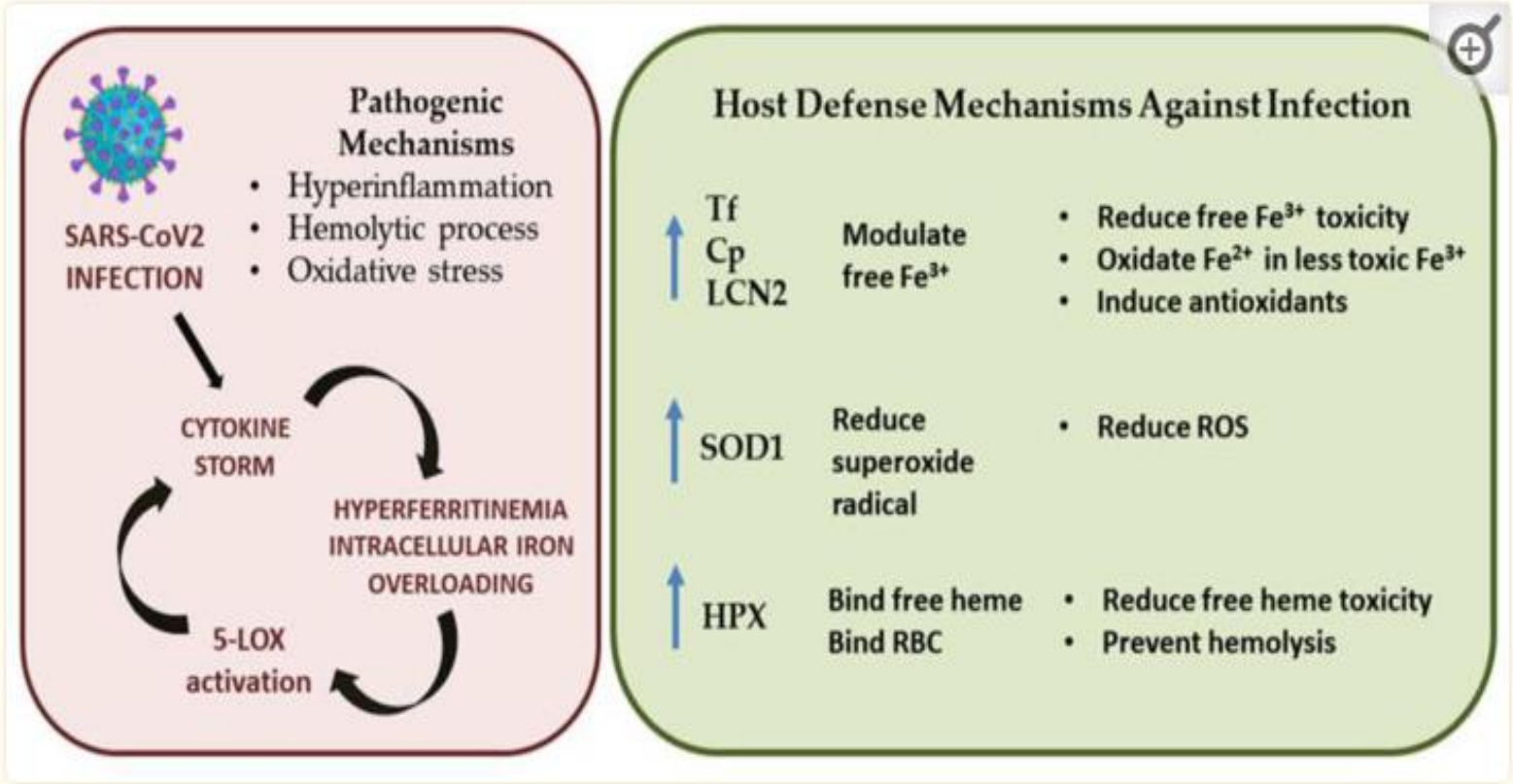
Haematological Problems in Long Covid: Iron Dyshomeostasis

- Dufrusine et al (2022) identified significant changes in proteins involved in iron metabolism using different biochemical analyses, considering ceruloplasmin (Cp), transferrin (Tf), hemopexin (HPX), lipocalin 2 (LCN2), and superoxide dismutase 1 (SOD1).
- Moreover, their results show an activation of 5-lipoxygenase (5-LOX) in COVID-19 and in long-COVID possibly through an iron-dependent post-translational mechanism.
- Furthermore, this work defines leukotriene B4 (LTB4) and lipocalin 2 (LCN2) as possible markers of COVID-19 and long-COVID and suggests novel opportunities for prevention and treatment.

- Dufrusine B, Valentinuzzi S, Bibbò S, Damiani V, Lanuti P, Pieragostino D, Del Boccio P, D'Alessandro E, Rabottini A, Berghella A, Allocati N, Falasca K, Ucciferri C, Mucedola F, Di Perna M, Martino L, Vecchiet J, De Laurenzi V, Dainese E. Iron Dyshomeostasis in COVID-19: Biomarkers Reveal a Functional Link to 5-Lipoxygenase Activation. Int J Mol Sci. 2022 Dec 20;24(1):15. Full Paper

Haematological Problems in Long Covid: Iron Dyshomeostasis

- Schematic representation of pathogenesis of SARS-CoV-2 infection and possible defense mechanisms.



- Dufrusine B, Valentinuzzi S, Bibbò S, Damiani V, Lanuti P, Pieragostino D, Del Boccio P, D'Alessandro E, Rabottini A, Berghella A, Allocati N, Falasca K, Ucciferri C, Mucedola F, Di Perna M, Martino L, Vecchiet J, De Laurenzi V, Dainese E. Iron Dyshomeostasis in COVID-19: Biomarkers Reveal a Functional Link to 5-Lipoxygenase Activation. Int J Mol Sci. 2022 Dec 20;24(1):15. Full Paper

Haematological Problems in Long Covid

- There is evidence that SARS-CoV-2 spike protein binds to heme, but the extent to which this binding causes health problems is still being researched. (Lechuga et al, 2021)
- The SARS-CoV-2 spike protein has been shown to bind to heme with a dissociation constant (KD) of 0.5 ± 0.2 µM (Freeman et al., 2023).
- Molecular modeling indicates that the heme group fits well within a pocket on the SARS-CoV-2 spike N-terminal domain lined by aromatic and hydrophobic residues (Freeman et al., 2023).
- Binding of heme to the spike protein may cause the virus to evade the adaptive and innate immunity by reducing levels of free heme during infection (Freeman et al., 2023).
- Some studies suggest that the interaction between heme and SARS-CoV-2 spike protein may lead to increased inflammation and oxidative stress, which could exacerbate symptoms of COVID-19 (Hopp et al., 2020, Hopp et al., 2020).

References

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The Hepcidin Protein

- Hepcidin is a small peptide hormone that was discovered in 2000/2001. It was initially named LEAP-1 (liver-expressed antimicrobial peptide).
- It is involved in iron trafficking and the host's response to infection.
- In fact, it has been remarked by a number of commentators that "hepcidin is to iron, what insulin is to glucose". (Grover, 2019)
- Hepcidin binds to and mediates the degradation of ferroportin (encoded by the SLC40A1 / FPN1 gene), the only known cellular iron exporter.

- Grover N. Atlas, Novo-backed biotech reels in ex-Nimbus CEO Don Nicholson as exec chairman, hooks $50M to conquer anemia. Endpoints News. 2019. Web-link

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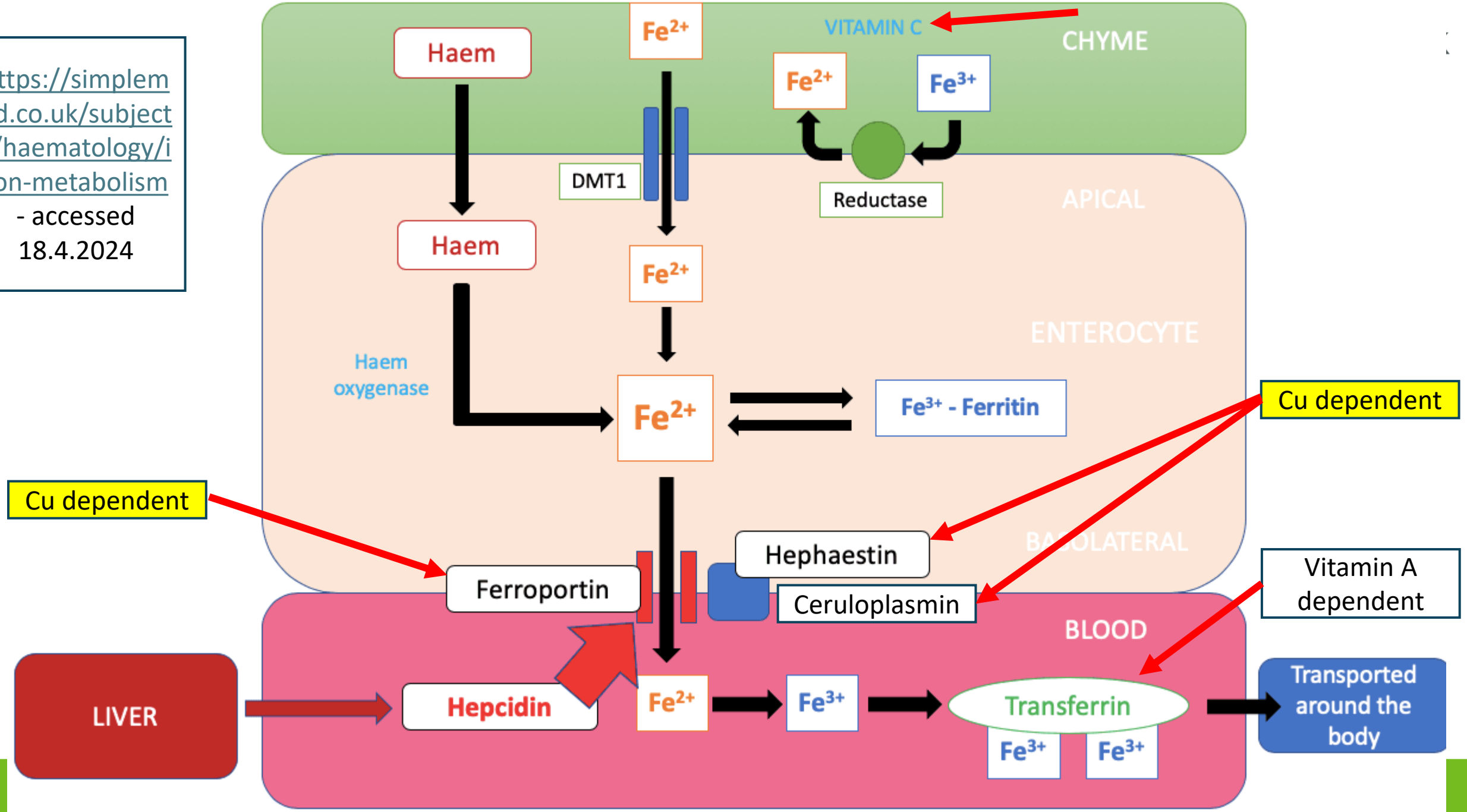

Haematological Problems in Long Covid

Nutri Link
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- According to Ehsani, 2020, the spike glycoprotein of the SARS-CoV-2 virus shares a distant sequence similarity with the hepcidin protein, which is a key regulator of iron metabolism in humans.
- This suggests a potential link between the spike protein and iron metabolism.
- Hepcidin excess may cause ferroptosis. The term ferroptosis was coined in 2012 to describe an iron-dependent regulated form of cell death caused by the accumulation of lipid-based reactive oxygen species; this type of cell death was found to have molecular characteristics distinct from other forms of regulated cell death. (Hirschhorn, 2019)

- Ehsani S. COVID-19 and iron dysregulation: distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein. Biol Direct. 2020 Oct 16;15(1):19. Full Paper
- Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med. 2019 Mar;133:130-143. View Abstract

Haematological Problems in Long Covid

- Mimicking hepcidin action, SARSCoV- 2 might remarkably increase circulating and tissue ferritin (affecting liver, spleen, bone marrow and muscles mainly), while inducing serum iron deficiency and lack of hemoglobin, by consequence.
- Hyperferritinemia gives rise to ferroptosis, with high oxidative stress and lipoperoxidation, ultimately increasing mitophagy with accelerated cell apoptosis/necrosis.
- In fact, cell iron overload is tolerated up to a threshold, as with silent hypoxia (COVID-19 first phase).
- The increasing ferroptosis-linked multi-organ oxidative stress can precipitate the inflammatory/immune over-response (the so-called interleukin storm) in later, most critical stages.
- Laboratory data show a relevantly lower hemoglobin level and higher ferritin levels in non-surviving patients, over the survivors.

- Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med. 2019 Mar;133:130-143. View Abstract

Markers relating to iron dysregulation are often aberrant

Hb	↓↑
RDW	↑
Ferritin	↑
Iron	Varies
Transferrin	"
TIBC	"
Serum copper	May be low; can also be high: that may be unbound copper
Whole blood copper	May be low
Caeruloplasmin	Often low
Retinol	Often low
ESR	↓ (1 or 2 – can indicate hypercoagulation acc. to Dr. David Berg and others)

Haematological Problems in Long Covid

- Dysregulation of iron metabolism, especially in conjunction with other factors like low copper and ceruloplasmin, raised hepcidin, reduced hephaestin, and reduced transferrin, contributes significantly to tissue damage and reduced oxygen delivery in COVID-19 and long COVID patients.

Protection from Hematological Disruption

- Glutathione (GSH) has a protective effect against oxidative stress and viral infections. Ferroptosis-induced oxidative stress is improved by GSH; moreover, GSH may reduce both hemoglobin glycation and, in combination with vitamin C, heme oxidation. (Galiniak, 2017).
- Polyphenols such as curcuminoids, anthocyanins and catechins instigate hormetic potential through NrF2-ARE pathway.
- Moreover, heme-oxygenase-1 activation by many polyphenols, curcumin above all, has been documented, which may beneficially impact hemoglobin denaturation.
- Curcuminoids, anthocyanins and catechins benefit the following biochemical processes which take place in COVID-19: i) hemoglobin oxidation, ferroptosis, and lipoperoxidation; ii) derangement of mitochondria function / biogenesis, with altered mitophagy; iii) inflammasome activation and interleukin storm; iv) SARS-CoV-2 protease activity; v) SARS-CoV-2 attack to bone marrow; vi) hepcidin upregulation and ferroportin blockage.

- Galiniak S, Bartosz G, Sadowska-Bartosz I. Glutathione is the main endogenous inhibitor of protein glycation. Gen Physiol Biophys 2017;36: 175-86. View Abstract
- Pittala V, Vanella L, Salerno L, Romeo G, Marrazzo A, Di Giacomo C, Sorrenti V. Effects of Polyphenolic Derivatives on Heme Oxygenase-System in Metabolic Dysfunctions. Curr Med Chem. 2018;25(13):1577-1595. View Abstract

Protection from Hematological Disruption

- Liposomal Glutathione (BodyBio) – 1 before two or three meals
- CurcumRx™ (BR) – 1 with each meal
- Nrf2 Renew (AR) – 1-2 with two meals

These supplements help to address these factors:

- i) hemoglobin oxidation, ferroptosis, and lipoperoxidation
- ii) derangement of mitochondria function / biogenesis, with altered mitophagy
- iii) inflammasome activation and interleukin storm
- iv) SARS-CoV-2 protease activity
- v) SARS-CoV-2 attack to bone marrow
- vi) hepcidin upregulation and ferroportin blockage

Summary

- One or more of the following may be involved in long Covid:
    - Viral Persistence
    - Viral Reactivation
    - Disordered haematology

Summary ii

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- Here's what lab tests to consider for each:

    - Viral Persistence – test for spike protein antibodies or presence of spike protein in one or more of these serum, immune cells (PBMCs), exosomes, & vaccine mRNA in PBMCs (via MMD via AONM)
    - Viral Reactivation – test for EBV, CMV, Parvovirus B19 et al. (via AONM)
    - Disordered haematology – blood test for haematology markers incl ferritin, ceruloplasmin, etc

Summary iii

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Viral Persistence

- Perm A Vite (AR) - 1 tablespoon in liquid 10 mins before two to three meals
- Laktoferrin with Colostrum (AR) - 3-4 caps at night
- Bromelain Plus (BR) - 5 tabs on empty stomach once or twice daily (biofilm buster)
- NAC (BR) & (AR) – 1 on empty stomach twice daily (anti-viral, biofilm buster)
- Humic Monolaurin Complex (AR) – 2 with breakfast & dinner

Viral Reactivation

- Humic Monolaurin Complex (AR) – 2 with breakfast & dinner
- Aqueous Selenium (BR) - 1 drop with two or three meals
- NAC (BR) & (AR) – 1 on empty stomach twice daily (supports Th1 immune response)
- Ashwagandha Complex (AR) (incl licorice) – 2 with breakfast & 1-2 with lunch

Excess Iron / Ferritin

- Laktoferrin with Colostrum (AR) – 3=4 at night
- Liposomal Glutathione (BodyBio) – 1 before two or three meals
- CurcumRx™ (BR) – 1 with each meal
- Nrf2 Renew (AR) – 1-2 with two meals
- Copper Bisglycinate (Thorne) (if low ceruloplasmin) – 1 with dinner
- *& consider need for Spike Protein Breakdown*

Summary iv

- **Spike Protein Breakdown**

- Nattokinase 50mg (1,000 FU) (AR) – 2 caps twice daily on empty stomach (8+ hours apart)(or higher dose)

- Bromelain Plus (BR) – 5 tabs on empty stomach once a day

- CurcuWIN 500 (AR) – 1 with breakfast & 1 with dinner

- Augmented NAC – 1 before breakfast & dinner by 20-15 mins

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THE END

TIME FOR QUESTIONS & COMMENTS

5. Monday 7th October 12 noon
Neurotransmitter imbalances as an explanation for multiple Long Covid symptoms.
Nutritional Therapy solutions.