Long COVID from a Clinical Perspective

- Professor John (Jack) S. Lambert, Consultant in Infectious Diseases, Mater and Rotunda Hospitals, and Full Professor, UCD School of Medicine, Dublin, Ireland

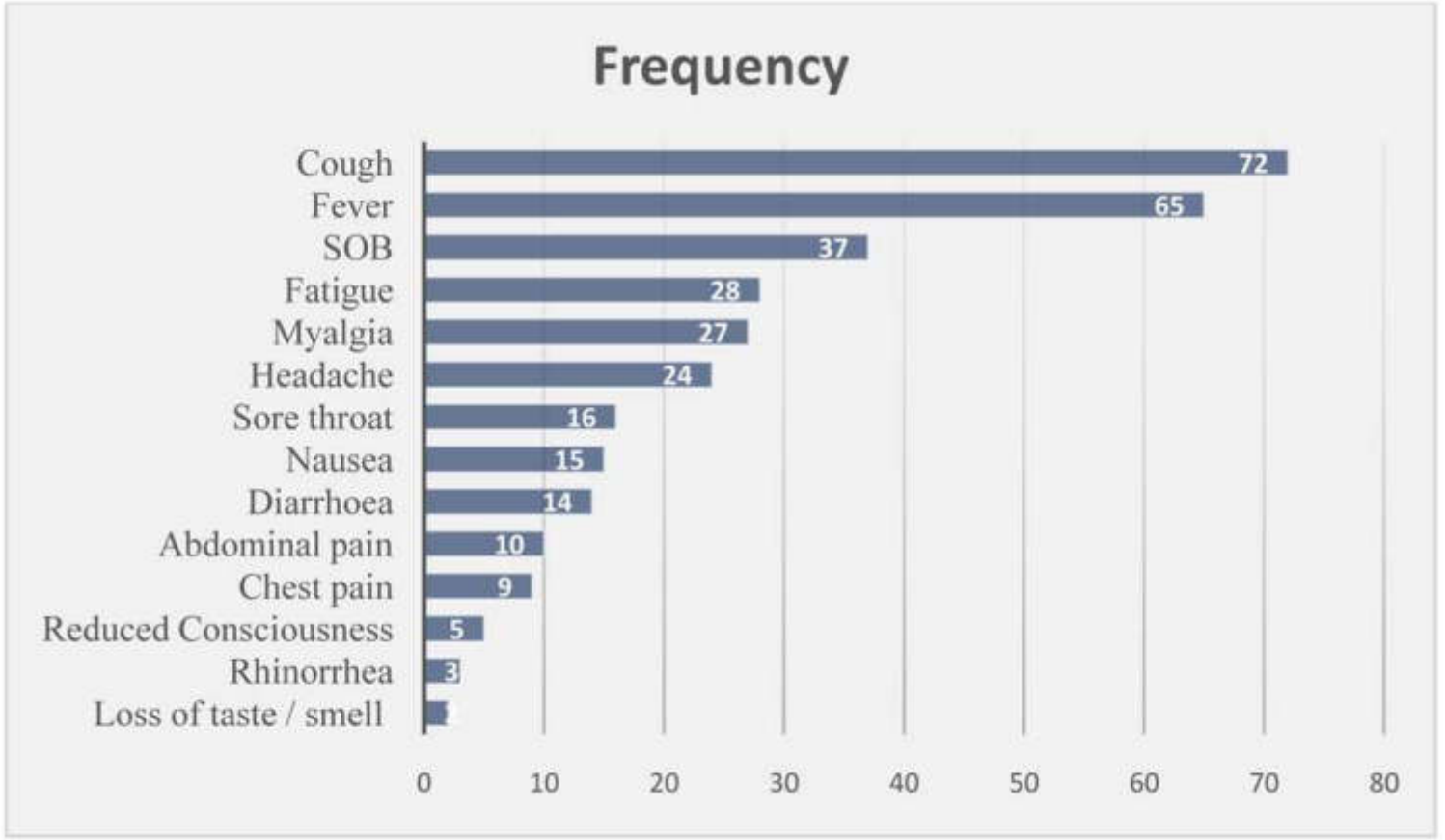
LONG COVID/ LONG HAUL COVID

Phrase first coined by Dr who had COVID, first described in tweet in May 2020

‘sick three months post initial COVID19’

First 100 patients admitted to the Mater Hospital with COVID-19

Mater 100 cohort



Anticipate cohort

1 year follow up of patients post COVID-19 in long covid clinic
Mater Misericordiae University Hospital: 150 patients/Mater staff members included
Irish Health Research Bureau funded May 2020 (€200,000)

- PI Professor JS Lambert
- Co PI Professor W Cullen, Professor of General Urban Family Medicine UCD

(image from The Guardian newspaper)

ANTICIPATE: Longitudinal follow up of patients POST COVID-19

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Assessing the impact of COVID-19 at 1-year using the SF-12 questionnaire: Data from the Anticipate longitudinal cohort study

Brendan O'Kelly[1,3,*], Louise Vidal[3], Gordana Avramovic[3], John Broughan[3], Stephen Peter Connolly[1], Aoife G Cotter[1,2,3], Walter Cullen[3], Shannon Glaspy[3], Tina McHugh[3], James Woo[1], John S. Lambert[1,3]

[1] Infectious Diseases Department, Mater Misericordiae University Hospital, Dublin 7, Ireland
[2] Centre for Experimental Pathogen Host Research, University College Dublin, Dublin 4, Ireland
[3] School of Medicine, University College Dublin, Dublin 4, Ireland

ANTICIPATE COHORT

SF-12

PCS: Physical component score

MCS: Mental component score

- Score for average well person is 50

ANTICIPATE COHORT SF-12 outcomes at 12 months

		SF-12 PCS			SF-12 MCS		
7-14 month follow up	N(%)	3 month	7-14 month	P value	3 month	7-14 month	P value
Total	94	**42.96(10.87)**	**45.39(10.58)**	**0.02**	47.63(11.1)	48.87(9.6)	0.311
Female	65(69)	43(11.2)	45.6(10.5)	0.026	47.2(10.8)	49.57(9)	0.121
Male	29(31)	42.2(10.12)	44.4(10.72)	0.304	48.5(12.2)	47.1(10.9)	0.569
Post COVID-19 syndrome	24(25.5)	**34.95(10.2)**	**37.2(10.4)**	0.219	47.2(9.3)	46.4(10.7)	0.72
No symptoms	70(74.5)	45.5(9.7)	46.1(10.9)	0.596	47.7(11.8)	48.3(10)	0.891
P value		<0.001	<0.001			0.504	

ANTICIPATE:LOW MOOD, ANXIETY, ALCOHOL CONSUMPTION

HRB Open Research

SUBMIT YOUR RESEARCH

BROWSE GATEWAYS & COLLECTIONS HOW TO PUBLISH

Home » Browse » Mental health and alcohol use among patients attending a post-COVID-19...

Check for updates

RESEARCH ARTICLE

Mental health and alcohol use among patients attending a post-COVID-19 follow-up clinic: a cohort study [version 1; peer review: awaiting peer review]

John Broughan [1], Geoff McCombe [1], Brendan O'Kelly[1,2], Gordana Avramovic[1,2], Ronan Fawsitt[3,4], Shannon Glaspy [1,2], Mary Higgins[1,5], Tina McHugh[1,2], Louise Vidal[2], James Woo[2], John S Lambert [1,2], Walter Cullen[1]

Author details

ANTICIPATE:LOW MOOD, ANXIETY, ALCOHOL CONSUMPTION

Instrument	TIME 1 n	TIME 2 n	TIME 1 n (%)	TIME 2 n (%)	RR (95%CI)
PHQ-9	147	93			.98 (.76-1.26)
No signs of depression (<5)			72(49)	46(49.5)	
Mild (≥5)			44(29.9)	26(28)	
Moderate (≥10)			20(13.6)	12(12.9)	
Moderately Severe (≥15)			7(4.8)	4(4.3)	
Severe (≥20)			4(2.7)	1(1.1)	
GAD-7	147	89			1.15 (.81-1.64)
No signs of anxiety (<5)			90(61.2)	59(64.1)	
Mild (≥5)			38(25.9)	18(19.6)	
Moderate (≥10)			15(10.2)	4(4.3)	
Severe (≥15)			4(2.7)	8(8.7)	
IES-R	146	91			1.07 (.65-1.76)
No signs of PTSD (<33)			113(77.4)	71(78)	
PTSD likely (≥33)			33(22.6)	19(20.9)	
AUDIT-C	145	85			.65 (.52-.81)
Normal alcohol use (<3)			79(55.5)	24(28.2)	
Problematic alcohol use (≥3)			66(45.5)	61(71.8)	

18.3% of participants had moderate to severe signs of depression for at least 1 year

13% of participants had moderate to severe anxiety for at least 1 year

21% of participants had finings consistent with PTSD for at least 1 year

72% of participants had concerning alcohol use at 1 year

A retrospective analysis of all SARS-CoV-2 positive ICU and HDU admissions Mater Hospital Dublin, Moynan et al (unpublished)

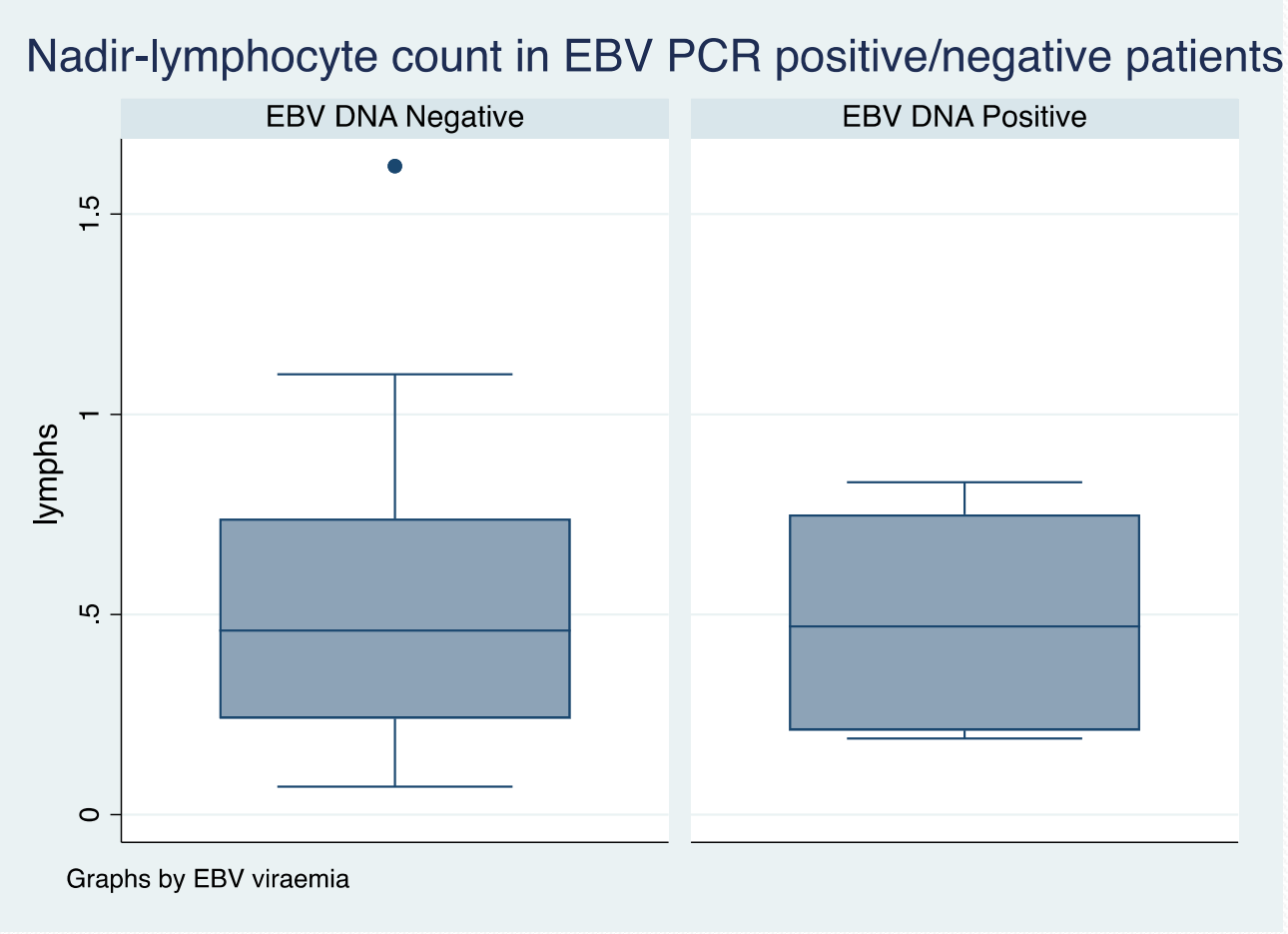
- Total number:
  - n=295
- Number of deaths:
  - 22% (65/295)
- Numbers requiring mechanical ventilation:
  - 29% (86/209)

EBV reactivation:

EBV VIRAEMIA	STATUS AT DISCHARGE FROM UNIT ALIVE	DEAD	TOTAL
EBV DNA Negative	15	5	20
EBV DNA Positive	5	2	7
TOTAL	20	7	27

- 27/295 patients were tested for EBV viraemia
- 7/27 (26%) had detectable EBV viraemia
  Pearson chi2(1) = 0.0344 Pr = 0.853
- There was no association with EBV viraemia and death (p = 0.853)

Lymphocyte Count EBV



CMV viral reactivation:

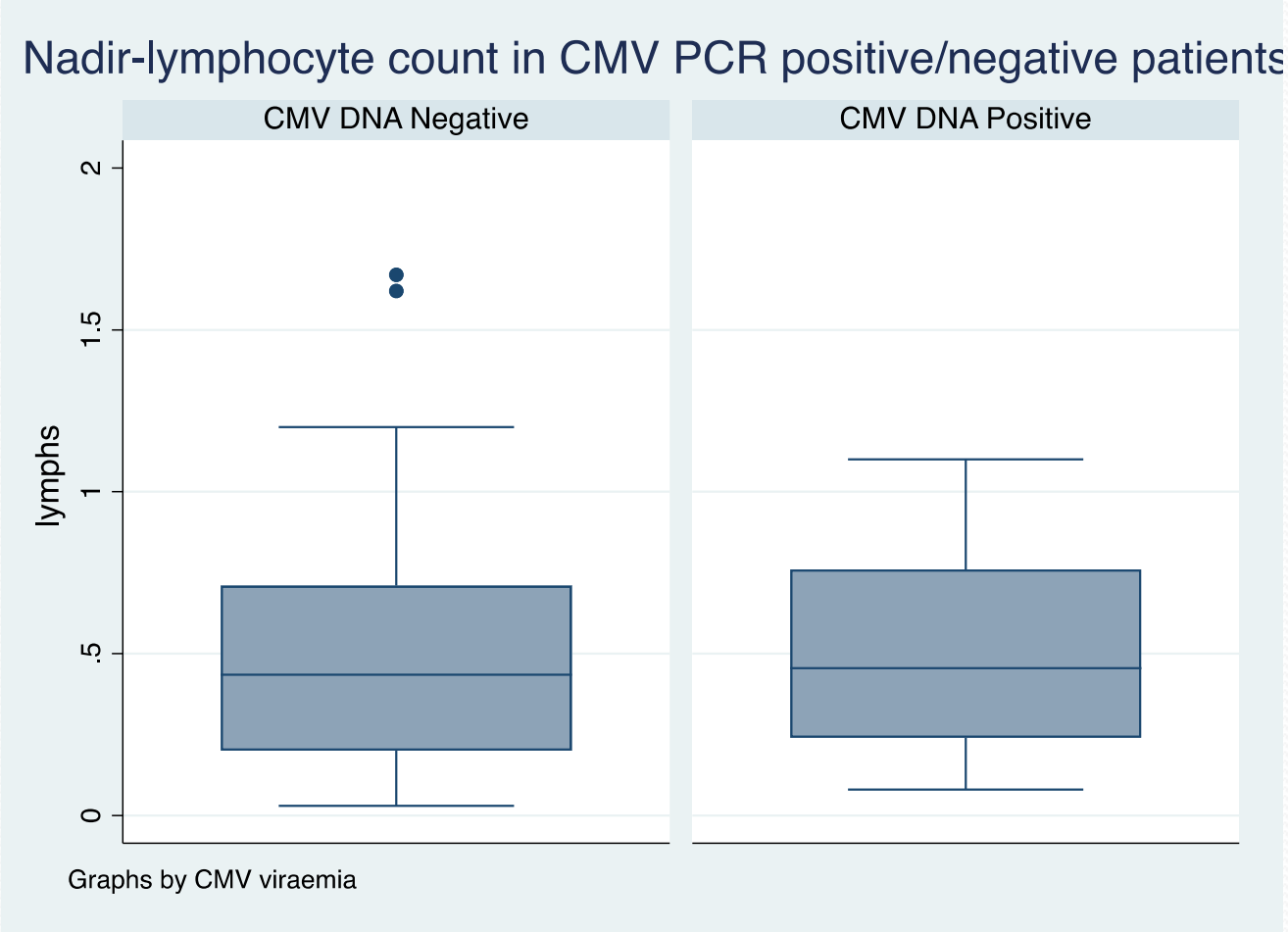
CMV VIRAEMIA	STATUS AT DISCHARGE FROM UNIT		TOTAL
	ALIVE	DEAD	
CMV DNA Negative	33	19	52
CMV DNA Positive	9	6	15
TOTAL	42	25	67

67/295 patients were tested for CMV viraemia
Of those who were tested: 15/67 (22.3%) had a detectable CMV viraemia
Pearson chi2(1) = 0.0596 Pr = 0.807
6/15 patients with CMV viraemia died
A chi-squared test was run to determine the relationship between the categorical variables (death and CMV viraemia) but there was no statistical significance with P = 0.807

Patients who reactivated CMV; risk factors:

Chemotherapy/transplant (iatrogenic immunosuppression)	3
VV-ECMO recipient	6
Non-iatrogenic immunosuppression/non VV-ECMO	6
TOTAL	*15*

Lymphocyte Count CMV

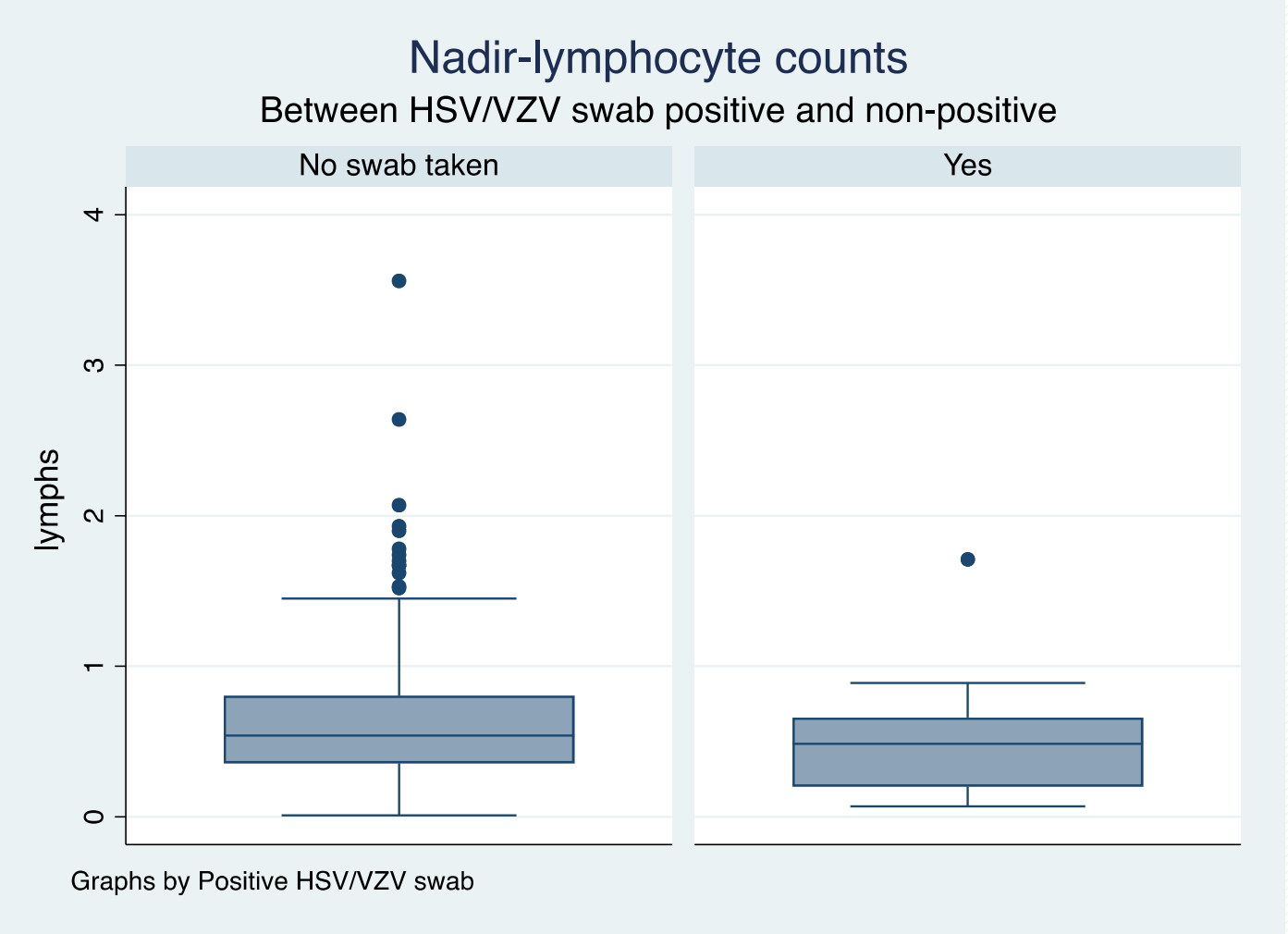


HSV/VZV Viral Swabs

- • 26/295 (9%) of the cohort developed skin lesions that swabbed positive for either HSV-1/HSV-2 or VZV
- • 11/26 of the patients who swabbed positive for HSV/VZV on skin lesions received mechanical ventilation
- Pearson chi2(1) = 0.0525 Pr = 0.819
- There was no association between HSV/VZV reactivation and mechanical ventilation

HSV/VZV SWAB	INVASIVE VENTRILATION NO	YES	TOTAL
HSV Positive	14	10	24
VZV Positive	1	1	2
TOTAL	15	11	26

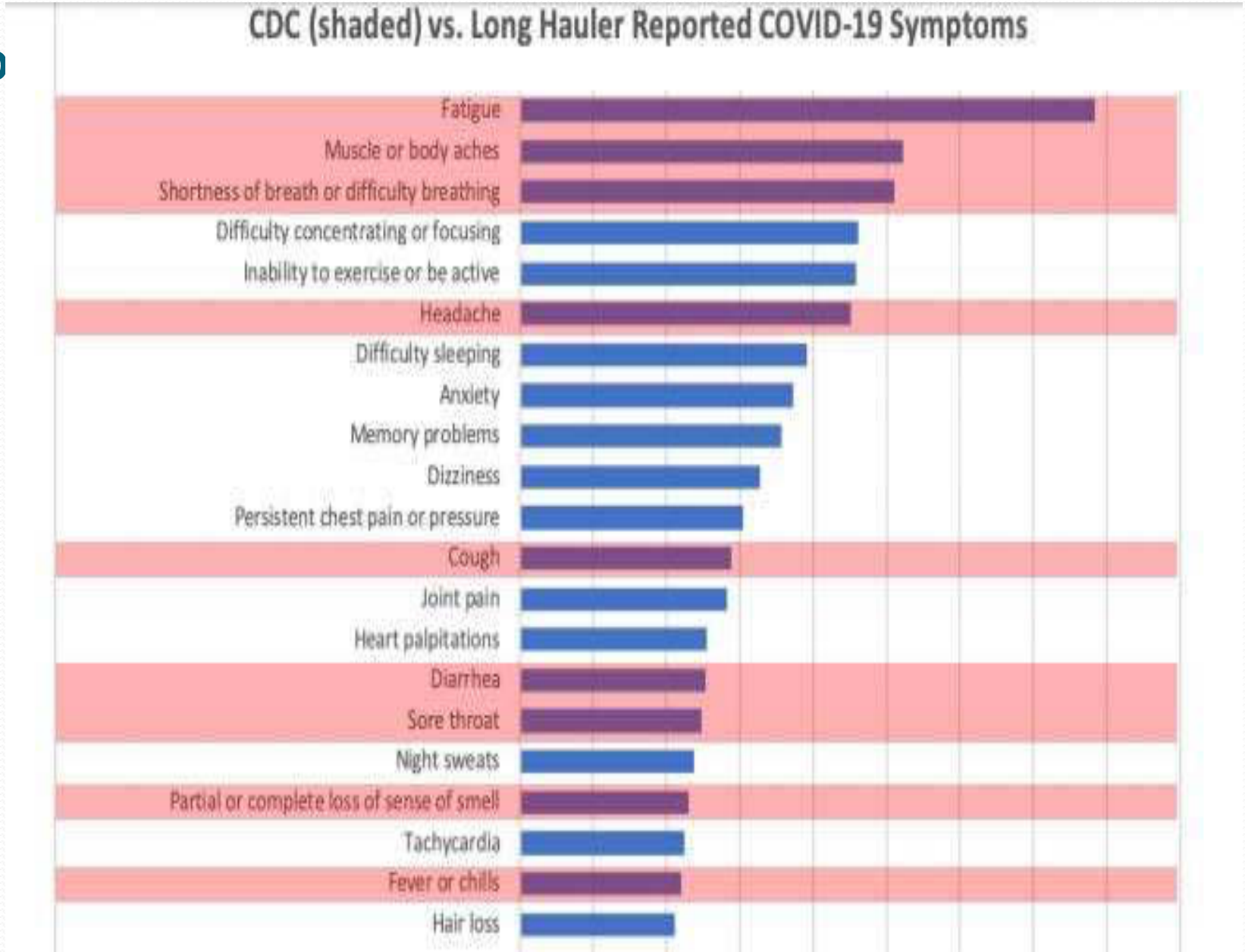
Lymphocyte HSV/VZV swabs



Which patients progress to long covid?

Anyone can, not just those hospitalised; just as likely with mild symptoms, not significantly protected from by COVID19 vaccines

LONG COVID


CDC (shaded) vs. Long Hauler Reported COVID-19 Symptoms
Fatigue
Muscle or body aches
Shortness of breath or difficulty breathing
Difficulty concentrating or focusing
Inability to exercise or be active
Headache
Difficulty sleeping
Anxiety
Memory problems
Dizziness
Persistent chest pain or pressure
Cough
Joint pain
Heart palpitations
Diarrhea
Sore throat
Night sweats
Partial or complete loss of sense of smell
Tachycardia
Fever or chills
Hair loss

Lyme Disease-clinical manifestations

Post Treatment Chronic Lyme disease

Research studies using PCR, culture or antigen positivity as the marker of infection

- General/constitutional
  - Fatigue/weight loss
- Rheumatolgical
  - Arthralgia/arthritis; myalgias
- Neurological
  - Cognitive-confusion/memory difficulties/disorientation
  - Pain-headaches/cranial or peripheral neuropathies
  - tremors

:

PET Scans of the Brain and LONG COVID

Guedj et al Eur J Nuclear Med and Molec Imaging (2021)

- Compared to healthy subjects, patients with LC exhibited bilateral hypo-metabolism in the bilateral rectal/orbital, gyrus, including the olfactory gyrus; the right temporal lobe, including the amygdala and the hippocampus, extending into the right thalamus; the bilateral pons/medulla brainstem; the bilateral cerebellum.
- These clusters of hypo-metabolism were significantly associated with more numerous functional complaints, and all associated with the occurrence of certain symptoms (hyposmia/anosmia, memory/cognitive impairment, pain and insomnia.

Journal of Neuroinflammation BMC

PET Brain Scans and Chronic lyme

Imaging glial activation in patients with post-treatment Lyme disease symptoms: a pilot study using [^{11}C]DPA-713 PET
Jennifer M. Coughlin 2018

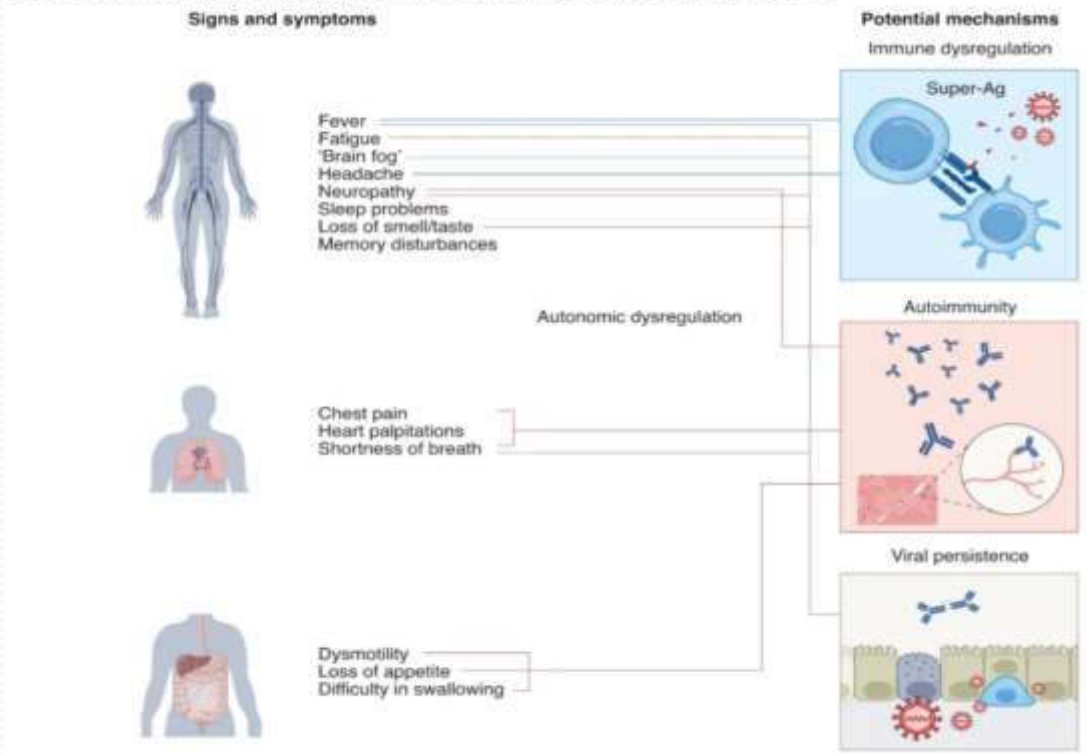
12 patients with PTLDS had symptoms of fatigue and at least one other finding (memory change, difficulty with wordfinding), were compared to controls; controlling for age, BMI, and genotype, individual linear regression models fit for individual ROIs showed significant differences in the cerebellum, frontal cortex, parietal cortex, thalamus, temporal cortex, and cingulate cortex.

Pathogenesis of LONG COVID

Studying severe long COVID to understand post-infectious disorders beyond COVID-19

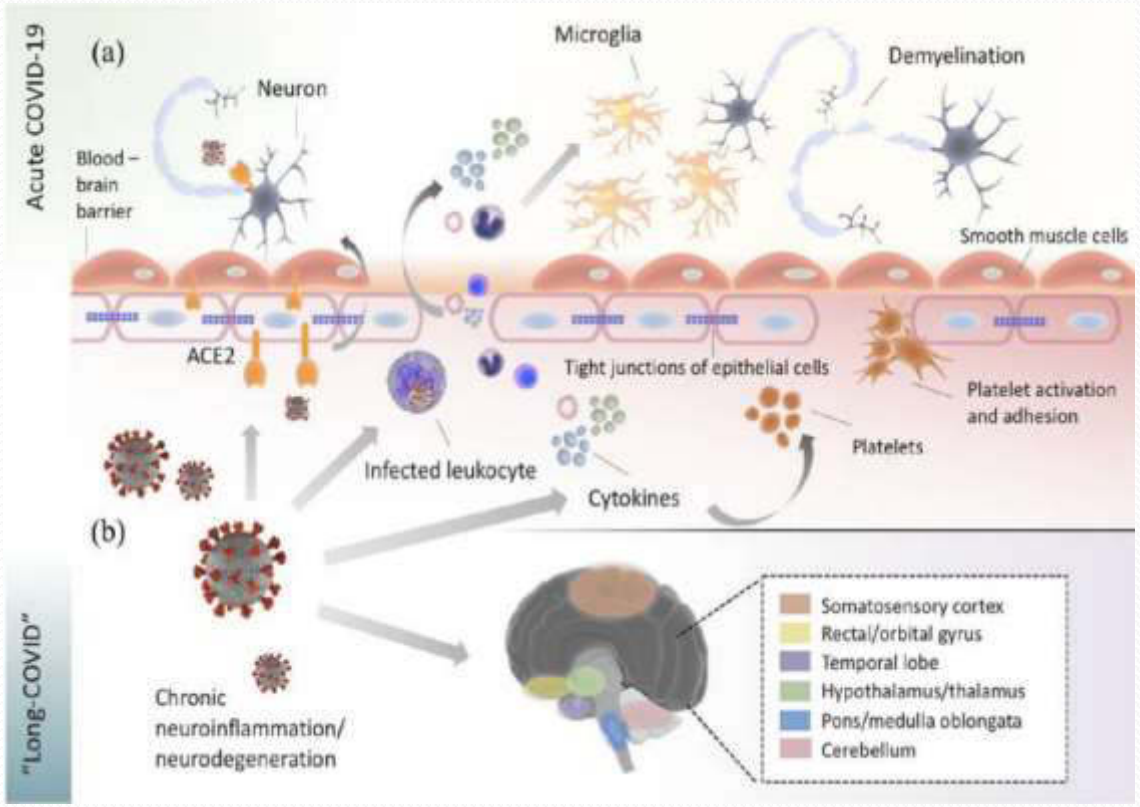
Petter Brodin, Giorgio Casari, Liam Townsend, Cliona O'Farrelly, Ivan Tancevski, Judith Löffler-Ragg, Trine

Fig. 1: Common signs and symptoms and possible causes of long COVID.



Neurological manifestations of long-COVID syndrome: a narrative review

Maria-Ioanna Stefanou, Lina Palaiodimou, Eleni Bakola, Nikolaos Smyrnis,



Long Covid or post-acute sequellae of covid-19: an overview of biological factors that may contribute to persistent symptoms (Proal et al, frontiers of microbiology, June 2021, vol.12, article 698169

- This paper details mechanisms by which RNA viruses have been connected with long-term consequences. Potential contributors to post acute sequellae symptoms (PASC) include consequences from acute COVID-19 injury to one or multiple organs, persistent reservoirs of COVID-19 in certain tissues, re-activation of neurotrophic pathogens such as herpesviruses under conditions of COVID-19 immune dysregulation; COVID- 19 interactions with host microbiome/virome communities, clotting/coagulation issues, dysfunctional brainstem/vagus nerve signaling, ongoing activity of primed immune cells, and autoimmunity due to molecular mimicry between pathogen and host proteins.
- 'The individualized nature of PASC symptoms suggest that different therapeutic approaches may be required to best manage care for specific patients with the diagnosis.'

Long covid—an update for primary care

- *BMJ* 2022; 378 doi: https://doi.org/10.1136/bmj-2022-072117 (Published 22 September 2022)Cite this as: *BMJ* 2022;378:e072117

- *Trisha Greenhalgh, professor of primary care health sciences*
- *Manoj Sivan, associate professor in rehabilitation medicine*
- *Brendan Delaney, professor of medical informatics and decision making*
- *Rachael Evans, associate professor in respiratory medicine, associate professor in respiratory medicine*
- *Ruairidh Milne, person with long covid and, emeritus professor of public health*

Questions patients ask
Why did I get long covid, and what caused it?

- Symptoms (especially fatigue) may persist after many infectious illnesses, including other coronaviruses such as SARS and MERS. But no clear explanation exists for why a particular individual develops long covid while another recovers quickly.
- Long covid is more common in those who had more severe acute disease but may occur after mild or even asymptomatic disease. It is more common in people who were hospitalised, aged 35 to 69, female, living in deprived areas, working in healthcare, social care, or education, with high body mass index, and with more than one pre-existing, activity limiting health condition.

Questions (2)

- The underlying cause of long covid is not fully known, but several interacting mechanisms likely contribute. A chronic, low grade inflammatory response is correlated with the severity of ongoing symptoms in patients who were hospitalised. Some patients have evidence of multi-organ microvascular disease characterised by immunothrombosis and endothelial dysfunction, and some show an autoimmune response, where the body starts to recognise its own tissues and organs as foreign. Some patients have covid induced neurological damage, particularly to the autonomic nervous system, which controls involuntary functions like heart rate. Being chronically ill and with unpredictable relapses may lead to loss of work, income, and social interaction, which in turn can lead to poor mental health. Structural inequalities such as poverty, overcrowding, poor working conditions, and inability to access services are important in the development and course of covid-19 and may form an important context for long covid.

Symptoms, investigation, and management of long covid

Fatigue, low exercise tolerance, deconditioning (eg, post-ICU)	“Battery flat,” unable to do usual activities. Trying to do more may worsen symptoms. In some cases, fatigue does not improve with rest	Bloods as appropriate (eg, full blood count, urea and electrolytes, renal, thyroid, vitamin D, C reactive protein, B12, ferritin). Exclude other causes of fatigue. Monitor symptom severity and frequency and pattern of relapses (eg, using the C19-YRS outcome measure). Consider autonomic dysfunction	Holistic management is key. Self-management to function within available energy limits (eg, prioritising, planning, building in breaks and rests, knowing when to stop). Signpost to resources

Symptoms management (2)

Post-exertional symptom exacerbation (PESE)	“Crash,” “relapse” worsening of symptoms (physical, cognitive, or emotional), or new symptoms, following exertion	Monitor symptom severity and frequency and pattern of relapses (eg, using C19-YRS). A patient activity diary can record triggers (for relapse)	Signpost to resources. Pacing in phases (see WHO self-management booklet, box, Resources for patients)

Symptoms management (3)

Exertional breathlessness	Short of breath predominantly with physical activity	Guided by specific symptoms. Assess impact on function (eg, using item 1 of C19-YRS). Haemoglobin, spirometry, full lung function tests as indicated. Natriuretic peptides and echocardiogram as indicated if heart failure suspected. Pulse oximetry and sit-to-stand test for exertional hypoxia. Chest x ray image (especially if patient was hospitalised) if persistent lung damage suspected and to exclude other causes. D dimer if acute pulmonary embolism suspected (note that a negative result does not exclude chronic pulmonary emboli)	Refer according to clinical concern (eg, worsening symptoms, resting or exertional hypoxia, unexplained abnormal spirometry, abnormal chest x ray image)

Symptoms management (4)

Altered breathing/breathing pattern disorder	Pressure in chest (“covid squeeze”), shallow breathing, breathlessness with or without exertion, sense of needing to work harder to take a breath, or air hunger (“can’t get enough air”)	Exclude other causes of breathlessness as listed above, especially causes of episodic breathlessness such as asthma or recurrent pulmonary embolism	Recommend breathing control exercises, signpost to online resources for breathing pattern disorder, and if no improvement refer to specialist

Symptom management (5)

Chest pain	Pain in specific positions, pain on exertion, “lung burn,” pressure (“like an elephant sitting on my chest”)	Guided by specific symptoms. Chest pain may indicate microvascular angina, myocardial infarction, myo- or pericarditis, pulmonary embolism or costochondritis. ECG, troponin, D dimer, oximetry (including sit-to-stand test), vitamin D, imaging as indicated	Chest pain with angina-like features warrants referral to a rapid access chest pain clinic. Consider colchicine or anti-inflammatory analgesics for inflammatory type pain once other causes excluded

Symptom management (6)

Throat and voice symptoms	“Covid strangle”—sore or dry throat with sensation of choking; altered voice	Full history and assessment to explore differential diagnosis (eg, covid related vocal cord pathology, gastro-oesophageal reflux, sinus disease, strained voice, dehydration)	If not improving, refer to ear, nose, and throat or speech and language therapist as appropriate

Symptoms management (7)

Autonomic dysfunction	Palpitations, dizziness, orthostatic tachycardia, gastro-intestinal disturbance, generalised pain	NASA 10-minute lean test to check for postural orthostatic tachycardia syndrome (POTS)24 (protocol in supplementary file).25 Investigations for other causes of autonomic dysfunction/POTS if positive. 24 hour ECG and blood pressure	Fluids, electrolytes, compression garments, lifestyle adaptation, and specialist rehabilitation if tolerated. Various drugs are under investigation. Specialist referral if symptoms severe or diagnosis in doubt

Symptom management (8)

Neurocognitive dysfunction	“Brain fog” (poor short term memory, concentration, problem solving, and executive function). Mental fatigue	Brief cognitive screening test (eg, mini mental state examination). Fatigue investigations as above. If memory loss pre-dated covid-19 and is now worsening, follow usual investigations and pathway	Strategies of pacing and energy conservation, to-do list diary, avoid multitasking. If unable to work or have a safety critical occupation, refer for formal neuropsychological testing

Symptom management (9)

Dizziness and vertigo	Unpleasant episodes, “room spinning,” nausea	Full history to identify timing and triggers and ascertain if resolving. Clinical examination (eg, nystagmus, other neurological signs, postural drop in blood pressure)	Precautionary measures to avoid falls, head tilt and balance exercises, encouraging movement and activity focusing on environmental cues. Refer to audiology if indicated

Symptom management (10)

Loss of smell	Loss of enjoyment of food and mealtimes. Phantosmia (a persistent, disagreeable background smell) or parosmia (distorted sense of smell)	Clinical examination to exclude nasal polyps, chronic sinusitis, and rare inflammatory or neoplastic conditions of nasal cavity and cranial nerves	Smell training (see box, Resources for patients). Experiment with different foods and menus to find palatable options. Steroid nasal spray may help in some cases

Symptom management (11)

Allergic-type symptoms	Skin rashes (eg, urticaria), conjunctivitis, abdominal bloating, regurgitation	Confirm urticaria clinically (eg, dermographism). If present, may indicate mast cell overactivity. Resurgent atopy (eg, hay fever recurring after many years) is common post covid	Antihistamines (obtainable over the counter) may help. A clinical trial of specific antihistamines is underway (STIMULATE-ICP). Allergy or immunology referral if fulfils local criteria (eg, anaphylaxis)

Symptoms management (12)

Poor sleep	Unrefreshing sleep, exhaustion, exacerbation of fatigue and brain fog, vivid dreams or nightmares	Assess daytime somnolence (eg, using Epworth sleepiness scale); exclude underlying causes (eg, obstructive sleep apnoea using STOP-Bang questionnaire. Assess psychological health. Covid related sleep disorder often overlaps with autonomic dysfunction and mast cell disorder	Sleep hygiene measures (eg, structured routines, exercise as able, avoid shift work if possible, avoid caffeine and alcohol), short daytime naps. Melatonin may help restore circadian rhythms in some cases (exclude other causes before prescribing)

Symptom management (13)

Mental health	Anxiety, depression, post-traumatic stress disorder (PTSD). Loss of identity and purpose	Full history (hear the patient's story; witness their experience; affirm their lived experience). Carefully distinguish anxiety from POTS (see above). Assess risk of self-harm and risk to any dependents	Whole person care. Adjusting to illness. Talking therapy, meditation, and medication if indicated. Mental health referral or social prescribing if appropriate

Symptoms management (14)

Joint and muscle pain	Generalised, focal, or regional pain. May be in “coat hanger” distribution. May progress to chronic pain	Investigations guided by history and clinical examination. C reactive protein (if inflammatory disorder suspected), creatine kinase (if myositis suspected). Additional tests as indicated for rheumatological disorders	Non-steroidal anti-inflammatory drugs. Mobilisation within personal limits. Consider trial of neuropathic agents (amitriptyline, gabapentin, pregabalin) in chronic cases, especially if neuropathic symptoms

Patients accounts

- “I think it [consultation with general practitioner] was a really positive experience and I felt really listened to, and she was able to be honest at that point and said I don’t really know what I can do to help you but you can phone me or email me at any point.”
- “My last interaction with my GP was in June. I asked about my lungs, and he said, ‘What do you want me to do about it? You tell me. I have no idea.’ It felt very dismissive […]. ‘Nothing’s got any evidence so, yeah sorry, I can’t help.’ I went back to work after five weeks still very unwell because nobody believed in long covid in May, they just didn’t believe it.”

The Irish Long Covid Plan

- 9 funded pulmonary centres, 6 ID centres, 1 Neuro Centres
- Post acute COVID (first three months) clinic, seeing patients with brain fog and tinnitus, ordering pulmonary function tests, telling patients to look up tinnitus on U Tub
- Exhausted patients being sent to 'graded exercise' rehabilitation, and following a day in such a programme, being bedridden for two weeks
- ICU nurse, out of work two years, with tachycardia to 170, bradycardia to 35, told by private cardiologist who found all of her tests normal, 'you are just anxious'.
- 9 yo with long covid, dizzy, poor balance, seen by peds neurologist who says nothing is wrong, discharges from clinic, refers to psychiatrist
- 50 yo ambulance driver, infected on job, out of work 2 years, unable to function; told to return to work by occ health; working one day Monday 12 hours, spends Tues and Wed in bed following 'crash' to recover rest of week

The Scientific Medical Literature on Neurological complications of COVID/Long COVID

- Neurological complications were being reported in scientific publications dating back to Autumn of 2020
- Yong SJ. Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. ACS Chem Neurosci. 2021 Feb 17;12(4):573-580. doi: 10.1021/acschemneuro.0c00793. Epub 2021 Feb 4. PMID: 33538586; PMCID: PMC7874499.
- Johansson et al Neurological manifestations of COVID19: a comprehensive literature review and discussion of mechanisms. J Neuroimmunol. 2021 Sept 15:358: 577658.
- Mehrabani et al Neurological complications assocaiated with COVID19; molecular mechanisms and therapeutic approaches. Rev Med Virol. 2022. Feb 9;e2334
- Li et al. An Overview of Neurological and Psychiatric Complications During Post-Covid period: a Narrative Review. J Inflamm Res. 2022; 15: 4199-4215

Scientific American February 2023

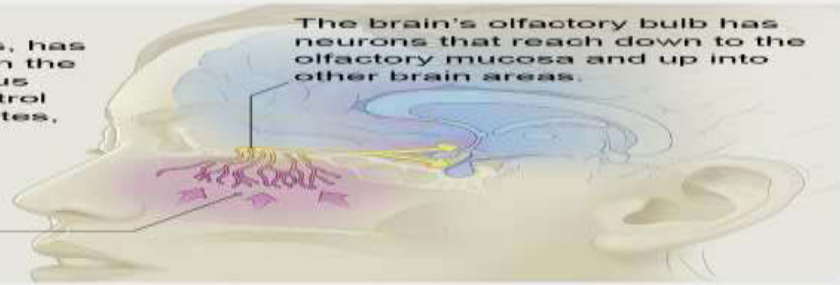
- **NEUROSCIENCE**
- 'Long COVID Now Looks like a Neurological Disease, Helping Doctors to Focus Treatments'
- The causes of long COVID, which disables millions, may come together in the brain and nervous system
- Affecting 16 M in the USA, with 2-4 million yet to return to work
- Several early studies showed that COVID attacks endothelial cells, which line blood vessels. That can lead to clotting and oxygen deprivation in multiple organs, including the brain. Even subtle disruption of endothelial cells in the brain could contribute to cognitive dysfunction.

How SARS-CoV-2 Can Harm the Brain and Nerves

Researchers have found evidence that the COVID-causing virus, SARS-CoV-2, can reach the brain and other parts of the central nervous system. This contact may lead to persistent and devastating symptoms of long COVID, which—more and more scientists say—appears to be a neurological disease. Cognitive symptoms include difficulty thinking and remembering things. And physical ailments, such as pain, extreme fatigue and a racing heartbeat, are tied to problems with the autonomic nervous system, which ordinarily runs our bodies on autopilot.

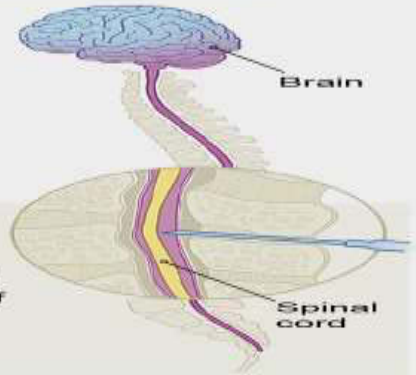
Into the Brain

Genetic material from the virus, and viral proteins, has been found in cells that line passages deep within the nose. Neurons project into this lining, and the virus can travel through them into brain areas that control breathing and the heart. It can also infect astrocytes, a crucial neural support cell.



Lingering Virus

In COVID patients with neuropsychiatric symptoms, proteins specific to SARS-CoV-2 appeared in small packets of cellular material that came from their neurons and astrocytes as long as three months after initial infection. This indicates the virus persists in the central nervous system for a long time. Another study found genetic material from the virus in a patient's brain almost eight months after symptoms began.



Immune System Abnormalities

Studies of long COVID patients with cognitive problems found signs that immune system cells from blood vessel walls had moved into the brain. These cells are not supposed to be in that organ and can cause damaging inflammation there. Patients without cognitive difficulties had lower levels of this unusual immune activity.

Cerebrospinal fluid collected from patients' spinal cords via a lumbar puncture (spinal tap) included proteins associated with inflammation.

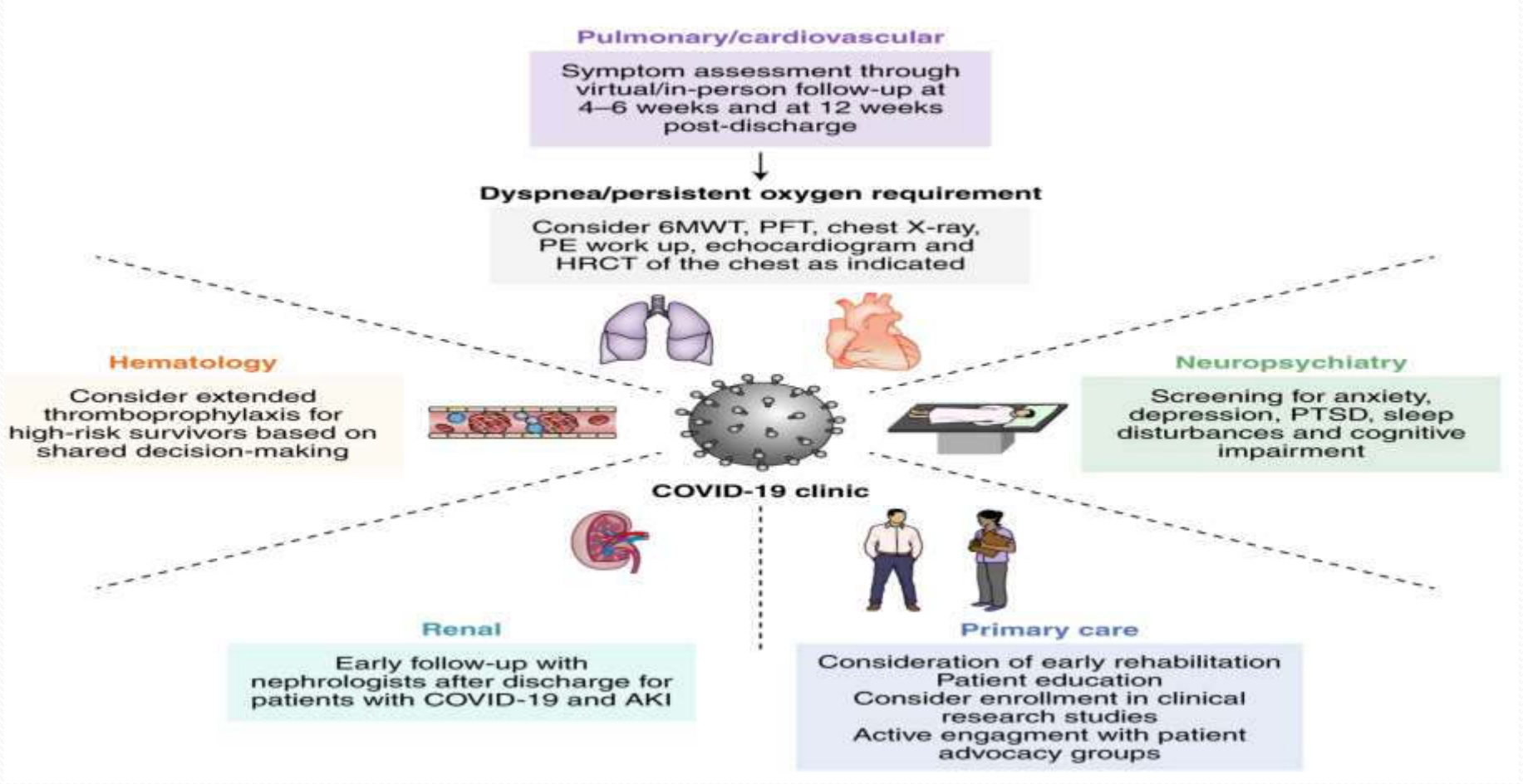
Macrophage Attack

Brains of people who have died from COVID show signs of an assault from macrophages, a type of immune system cell that reacts to invaders such as viruses. The cells surround and destroy the interlopers. But macrophages also damage nearby tissue, especially around brain blood vessels, says Avindra Nath, a neurologist at the National Institutes of Health.

What underlies LC manifestations?:

- Deficiencies in zinc, selenium, magnesium, Co-enzyme Q10 seen
- Probiotics have been shown to speed up recovery from COVID19
- Inflammation and auto-immunity underlie many of the LC clinical manifestations
- Damage to the mitochondria with 'crashing' is common
- There may be issues with 'microclots'
- Re-activation of other infections may occur in the setting of COVID19 induced lymphopenia
- Besides brain inflammation, the cranial nerves are also involved, not just CN1 and 2, but also CN10 the vagus nerve
- Sympathetic/parasympathetic dysregulation is common

WHAT HELPS? Multidisciplinary involvement



What Helps (2)?

- CAMS advice (Complementary Alternative Medicine)
- Lifestyle counselling including:

--Diet

--Sleep

--Stress management

--Interventions to target brain and cranial nerve inflammation (neuro-rehabilitation)

--Interventions to repair the immune system (immune crashing)

Home exercises

- Rebuild the diaphragm: Philips Respironics IMT Threshold Trainer
- Apply principles of nasal breathing: 'the oxygen advantage' by Patric McKeown. Specifically nasal breathing wshen walking and taping mouth shut at night with a light tape, until the habit is embedded
- https://www.youtube.com/watch?v=DLQ2rjAAj5E listen from minute 34, they talk about the importance of nasal breathing and how the sympathetic system is not working in LD patients.
- Karen Craddocks cardiovascular rehab programme: https://h2hcardiacphysio.com/specialist-cardiac-physiotherapist/

Brain, Behavior, & Immunity - Health
Volume 24, October 2022, 100485

Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study

Brendan O'Kelly [a, b], Louise Vidal [b], Tina McHugh [b], James Woo [a], Gordana Avramovic [b], John S. Lambert [a, b]

What is low dose naltrexone (LDN)?

- Naltrexone is an opiate receptor antagonist at doses of 50mg, but at lower doses of 1mg-4.5mg it appears to have unique immune modulation activity and is termed LDN
- LDN has been shown to be beneficial for a number of conditions including Crohn's disease, induction of remission and reduction in need for anti-inflammatory medications, chronic fatigue syndrome, fibromyalgia, reduction in use of disease modifying drugs in rheumatoid arthritis, multiple sclerosis and complex regional pain syndrome although studies are small *(Bolton et al.,2020; Lie et al., 2018; Raknes et al., 2018; Raknes and Smabrekke, 2019; Younger et al., 2014)*

What helps? Low dose Naltrexone – possibly

Likert scale	Baseline questionnaire median(IQR)	1st follow up median(IQR)	P value Baseline to 1st questionnaire	Z score (based on negative ranks)	Effect size (Rosenthal coefficient)
	N=52	N=38			
I feel I have recovered from COVID-19 (1-5)	1.5(1-2)	2(2-4)	<0.001	-4.492	-0.515
Does you health now limit you in you in daily activities? How much (1-3)	1(1-2)	2(1-2)	0.001	-3.207	-0.368
In the past 4 weeks do you have a lot of energy? (1-6)	3(2-3)	3(3-4)	0.001	-3.334	-0.382
In the past 4 weeks rate your overall mood(1-5)	2(2-3)	3(2-3)	.054	-1.925	-0.221
In the past 4 weeks rate you pain/discomfort(1-5)	2(2-3)	4(3-4)	<0.001	-4.66	-0.534
In the past 4 weeks rate your level of concentration(1-5)	2(1-2)	2(2-3)	0.001	-3.337	-0.382
Have you trouble staying or falling asleep(1-4)	2(1-3)	3(1-3)	<0.001	-3.896	-0.447

Safety and efficacy of low dose naltrexone in a LONG COVID cohort; an interventional pre-post study

Highlights:

- Low dose naltrexone (LDN) is safe to use in patients with long covid (LC)
- In patients with LC for a median 11 months, LDN reduced symptoms at 2 months,
- In this cohort, LDN also improved well-being in 6 of 7 parameters at 2 months

Just Herbs
EUROPE

www.just-herbs.eu

Advisor (disclaimer:does not accept financial remuneration as advisor):

Monica Wilde (MSc FLS),
is a research herbalist specialising in the field of Lyme disease. Based in Scotland, she helps Lyme patients through her clinic, ensuring that their herbal protocol is appropriate and effective. Herbal medicine is a holistic form of healing where the physical, mental, social and spiritual aspects of each person are taken into account. From a biochemical perspective, treatments that involve both prescription drugs, herbal and mineral supplements need to be undertaken with care to keep patients safe. Monica undertakes herbal research and provides support and training opportunities for other herbalists and practitioners in this area.

Just Herbs
EUROPE

www.just-herbs.eu
www.just-herbs.co.uk

‘

to support cognitive health, immune function and energy’

www.just-herbs.eu

Sublyme Essential

A unique, complex, multifunctional and essential food supplement for supporting overall cognitive, musculoskeletal and immune health, and reduce histamine overreactivity.

A professional blend of milk thistle from *Silybum marianum*, curcumin from *Curcuma longa,* N-acetyl L-Cysteine (NAC), quercetin from *Sophora japonica,* green tea extract from *Camellia sinensis,* bromelain from pineapple, and japanese knotweed from *Fallopia japonica* in capsule form.

Free from fillers, gluten, GMO, dairy, added sugars or colourings. This product does not contain any known allergens.

Vegetarian and vegan friendly formula.

N-acetyl cysteine (NAC), to assist with ‘crashing’

- NAC (which is converted to glutathione intracellularly) has been shown to improve markers of oxidative stress in an animal model of Huntington disease and cell lines derived from patients with Huntington disease and mitochondrial respiratory chain disorders. There have been case reports using NAC to treat primary mitochondrial disorders, for example, in mitochondrial disease patients who have liver dysfunction. NAC has been used in controlled trials in several conditions with likely secondary mitochondrial involvement, including Alzheimer disease, amyotropic lateral sclerosis, and autism.

. Improvement in some measures of cognitive ability was observed in Alzheimer disease patients. Autistic patients have shown improvement in some aberrant behaviors, especially irritability, following treatment with NAC

Management of Long COVID? Lessons from Lyme disease, which has similar characteristics

- Infections trigger a cascade of disseminated spread to multiple organs/tissues
- A cascade of inflammatory and autoimmune processes develop
- Microbes may cause damage at mitochondrial/cellular level.
- Patients are often lymphopenic with deranged lymphocyte markers.
- Lymphopenia causes reactivation of 'dormant' infections ie shingles, EBV, HSV, CMV
- Management must address the issue of persistent infection, deranged immune system, 'immune crashing', and neuro-inflammation
- Pacing and not 'pushing' is required. Don't advise 'graded exercise'.

Suggested protocol

- Multivitamin with coenzyme Q10 or Sublyme vitality (which contains 34 products)
- Probiotic or KEFIR (targeting the microbiome)
- Sub-Lyme essential capsules (cognitive, anti-inflammatory, mitochondrial, immune support)
- Low Dose Naltrexone 1mg, titrate up to 2mg, to 3mg, to 4.5mg, each dose over 2 to 4 weeks
- For sleep disturbances, Melatonin 3mg HS, titrate up to 10mg as needed
- For mood problems consider SSRI (serotonin replacement)
- Allergic symptoms H2 blocker (telfast, diphenhydramine)
- Vagal nerve exercises, transauricular VNS
- In select cases ASA 75mg, nattokinase to deal with issues of microclots, circulatory problems
- Consultation with Herbalists (Mangiferon, Cryptolepsis, TCM herbs)
- Medicinal mushrooms may have future role in strengthening and modulating the immune system (Reishi, Lions Mane, Cordyceps)

Mater COVID19 publications to date (17)

Cullen W, Avramovic G, Broughan J *et al.* Study Protocol: Prospective, observational, cohort study of COVID-19 in General Practice (North Dublin COVID-19 Cohort ['ANTICIPATE'] Study). *HRB Open Res* 2020, **3**:67 (https://doi.org/10.12688/hrbopenres.13135.1)

O'Kelly B, Cronin C, Connolly SP *et al.* What is the clinical course of patients hospitalised for COVID-19 treatment Ireland: a retrospective cohort study in Dublin's North Inner City (*the 'Mater 100'*) [version 1; peer review: awaiting peer review]. *HRB Open Res* 2020, 3:80 (https://doi.org/10.12688/hrbopenres.13138.1)

O'Kelly B, McGettrick P, Angelov D, Fay M, McGinty T, Cotter AG, Sheehan G, Lambert JS. Outcome of a patient with refractory Hodgkin lymphoma on pembrolizumab, infected with SARS-CoV-2. Br J Haematol. 2020 Jul;190(1):e1-e3. doi: 10.1111/bjh.16798. Epub 2020 May 25. PMID: 32379903; PMCID: PMC7267253.

Avramovic G, McHugh T, Connolly SP, Cullen W, Lambert JS. Anticipate study protocol: Baseline profile and care outcomes of patients attending Mater Misericordiae University Hospital with COVID-19 infection. HRB Open Res. 2021 Jan 18;3:52. doi: 10.12688/hrbopenres.13091.2.

Connellan D, Diffley K, McCabe J, Cotter A, McGinty T, Sheehan G, Ryan K, Cullen W, Lambert JS, Callaly EL, Kyne L. Documentation of Do-Not-Attempt-Cardiopulmonary-Resuscitation Orders amid the COVID-19 Pandemic. Age Ageing. 2021 Apr 28:afab075. doi: 10.1093/ageing/afab075.

Broughan J, McCombe G, Avramovic G, Crowley D, Downey C, Downey O'Sullivan J, Fawsitt R, McHugh T, O'Connor E, Perrotta C, Cotter AG, Lambert JS, Cullen W. General practice attendances among patients attending a post-COVID-19 clinic: a pilot study. BJGP Open. 2021 May 11:BJGPO.2021.0016. doi: 10.3399/BJGPO.2021.0016.

Safieh J, Broughan J, McCombe G, McCarthy N, Frawley T, Guerandel A, Lambert JS, Cullen W. Interventions to Optimise Mental Health Outcomes During the COVID-19 Pandemic: A Scoping Review. Int J Ment Health Addict. 2021 Jun 15:1-22. doi: 10.1007/s11469-021-00558-3.

O'Kelly B, Cronin C, Connellan D, Griffin S, Connolly SP, McGrath J, Cotter AG, McGinty T, Muldoon EG, Sheehan G, Cullen W, Doran P, McHugh T, Vidal L, Avramovic G, Lambert JS. Antibiotic prescribing patterns in patients hospitalized with

Mater publications to date (cont)

O'Kelly B, McLaughlin R, O'Doherty R, Carroll H, Murray R, Dilworth R, Corkery L, Cotter AG, McGinty T, Muldoon EG, Cullen W, Avramovic G, Sheehan G, Sadlier D, Higgins M, O'Gorman P, Doran P, Inzitari R, Holden S, O'Meara Y, Ennis S, Lambert JS. Rapid and Laboratory SARS-CoV-2 Antibody Testing in High-Risk Hospital Associated Cohorts of Unknown COVID-19 Exposure, a Validation and Epidemiological Study After the First Wave of the Pandemic. Front Med (Lausanne). 2021 Aug 26;8:642318. doi: 10.3389/fmed.2021.642318. PMID: 34513853; PMCID: PMC8427142.

Costello S, O'Kelly B, Avramovic G, McHugh T, Cullen W, Lambert J, Ryan, K. Cross-sectional study of palliative care to hospitalised patients with COVID-19. IMJ (Accepted Sept '21)

Lim J, Broughan J, Crowley D, O'Kelly B, Fawsitt R, Burke MC, McCombe G, Lambert JS, Cullen W. COVID-19's impact on primary care and related mitigation strategies: A scoping review. Eur J Gen Pract. 2021 Dec;27(1):166-175. doi: 10.1080/13814788.2021.1946681. PMID: 34282695; PMCID: PMC8293960.

Kenny G, McCann K, O'Brien C, Savinelli S, Tinago W, Yousif O, Lambert JS, O'Broin C, Feeney ER, De Barra E, Doran P, Mallon PWG; All-Ireland Infectious Diseases (AIID) Cohort Study Group. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. Open Forum Infect Dis. 2022 Mar 7;9(4):ofac060. doi: 10.1093/ofid/ofac060. PMID: 35265728; PMCID: PMC8900926.

Broughan J, McCombe G, O'Kelly B, Avramovic G, Fawsitt R, Glaspy S, Higgins M, McHugh T, Woo J, Vidal L, Lambert JS, Cullen W (In review), *Mental health and alcohol use among patients attending a post-COVID-19 follow-up clinic: A cohort study.* HRB Open Research, 2022.

O'Kelly B, Vidal L, Avramovic G, Broughan J, Cotter AG, Cullen W, McHugh T, O'Gorman T, Woo J, Lambert JS. Predictors and Outcomes for COVID-19 Re-Admissions in the Anticipate Cohort. Ir Med J. 2022 May 25;115(5):599. PMID: 35696289.

O'Kelly B, Vidal L, Avramovic G, Broughan J, Connolly SP, Cotter AG, Cullen W, Glaspy S, McHugh T, Woo J, Lambert JS. Assessing the impact of COVID-19 at 1-year using the SF-12 questionnaire: Data from the Anticipate longitudinal cohort study. Int J Infect Dis. 2022 May;118:236-243. doi: 10.1016/j.ijid.2022.03.013. Epub 2022 Mar 14. PMID: 35301101; PMCID: PMC8920113.

Brennan A, Broughan J, McCombe G, Brennan J, Collins C, Fawsitt R, Gallagher J, Guérandel A, O'Kelly B, Quinlan D, Lambert JS, Cullen W. Enhancing the management of long COVID in general practice: a scoping review. BJGP Open. 2022 Jun 30:BJGPO.2021.0178. doi: 10.3399/BJGPO.2021.0178. Epub ahead of print. PMID: 35256357.

Brendan O'Kelly, Louise Vidal, Tina McHugh, James Woo, Gordana Avramovic, John S. Lambert, Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study, Brain, Behavior, & Immunity - Health, 2022, 100485, ISSN 2666-2546 https://doi.org/10.1016/j.bbih.2022.100485

What should the future look like?

- The establishment of multi-disciplinary clinics that can support patients with Long Covid, Long Lyme, CFS/ME as they have similar pathogenesis
- Guidelines for GPs to support these patients, not to just prescribe medicines to control the symptoms (as there is significant collateral damage from these medicines)
- Pathways of referral for all patients with Long COVID. Currently GP's and occupational health have no way to refer patients; in many cases not at all, and in some cases, a one year waiting list to 'designated centres'. Private clinics are 'testing testing testing' €€€
- The HSE needs to support/pay for treatments that have initial evidence of benefit (low dose naltrexone, melatonin, NAC). Hyperbaric oxygen also has benefit in 'CFS'.
- Taking on board new science: it's the Brain, not the heart and lungs that are the target. The Irish post acute clinics were doomed to failure before they started.
- Other countries models of care have also focused on the heart and the lungs, based on the 'first wave'; France being an exception, where they have a 'neuro-rehab model'. USA is coming on board with the 'neuro-rehab model'. (UCLA, other centres)

The Mater Long Covid Business plan: a model for care

- A multi-disciplinary clinic at the Mater, service both N Dublin and beyond
- Request for neuro-rehab consultant 1.0 FTE; Id consultant 0.5 FTE, neurology consultant 0.5 FTE; psychologist 1.0 FTE; physiotherapy 1.0 FTE, occupational therapy 1.0 FTE, clinical nurse specialist 1.0 FTE; GP liason team GP 0.5 FTE, community nurse trainer 1.0 FTE; work with Mater post acute LC HSE fully funded pulmonary consultant 1.0FTE, currently running clinic 3 hours twice monthly, seeing almost zero LC patients
- Plan to run 3 clinics per week, providing appointments for 60-80 per week, 3300 per year; maximise outpatient management with virtual consultations three days weekly, which will support an additional 3300 per year; liase with GP, provide training/guidelines/referrals both locally and nationally to support their management of patients in their GP practices
- Originally submitted July 2021 (some of us knew the science) and resubmitted July 2022 but no response from the HSE, no funding provided
- Currently only able to see patients in private clinic Dublin and Edinburgh admin@iddoctor.eu

Failure of the Irish HSE and MOH Donnelly to fund a Mater multi-disciplinary clinic focused on Neuro rehab and GP training/collaboration? Reasons given….Jan 2023 exerpts from letters to TD's

- HIQA 'Most guidelines are recommending a holistic, person centred approach to diagnosis, management and treatment, with emphasis on shared decision making, which is consistent with the HSE's Interim model of care'
- 'The HSE are content that the interim model of care is in line with international best practice and will continue the review that Interim Model as new evidence emerges'
- The HSE has reviewed the Mater business case and has internally communicated with other departments of the HSE that the Mater business case would have required alignment with the HSE interim model of care prior to recommending for funding' (but no direct communication has taken place with the Mater)

HIQA conclusions:

- ‘In terms of service planning, the included guidelines and or models of care highlighted the need for a focus on continuation and coordination of care for individuals with long COVID. This should be facilitated through a comprehensive, multidisciplinary service that includes core team members, such as physicians with relevant experience and specialists in allied health, clinical psychology, nursing, pharmacy and rehabilitation medicine’.

The emperor has no clothes…..

COVID19 acts fast, don’t defend your mistakes, change course, listen to patients (PPI), take on new science. The HSE/NHS needs a new plan that keeps pace with the science.