

## Long COVID: Symptoms, Etiology and Management Plans from the EU

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## 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'

The #LongCovid #COVID19 is starting to be addressed on major newspapers in Italy 🇮🇹 too: ~20% of tested patients remain covid + for at least 40 days 🙌. Prof from Tor Vergata University of Rome notes: there is a lot we don't know about this virus.

rep.repubblica.it  
L'infettivologo: "Il 20% dei malati resta positivo al virus per 40 giorni"  
Paul Garner, professore di malattie infettive alla Liverpool School of Tropical Medicine, a sette settimane dal primo tampone è ancora positivo. E non è un ...

7:17 PM - May 20, 2020 · Twitter for Android

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

### Mater 100 cohort

Symptom	Frequency
Cough	72
Fever	65
SOB	37
Fatigue	28
Myalgia	27
Headache	24
Sore throat	16
Nausea	15
Diarrhoea	14
Abdominal pain	10
Chest pain	9
Reduced Consciousness	5
Rhinorrhoea	4
Loss of taste / smell	2

### 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

- 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



## ANTICIPATE COHORT

**SF-12**

**PCS:** Physical component score

**MCS:** Mental component score

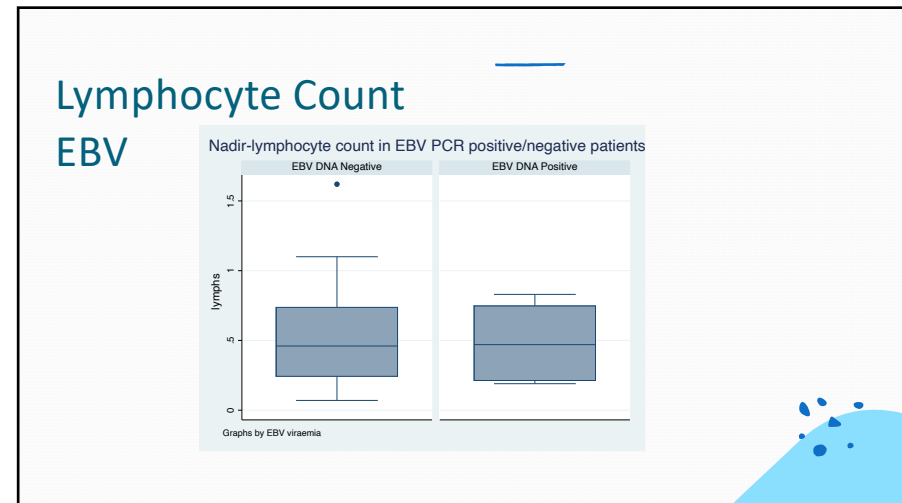
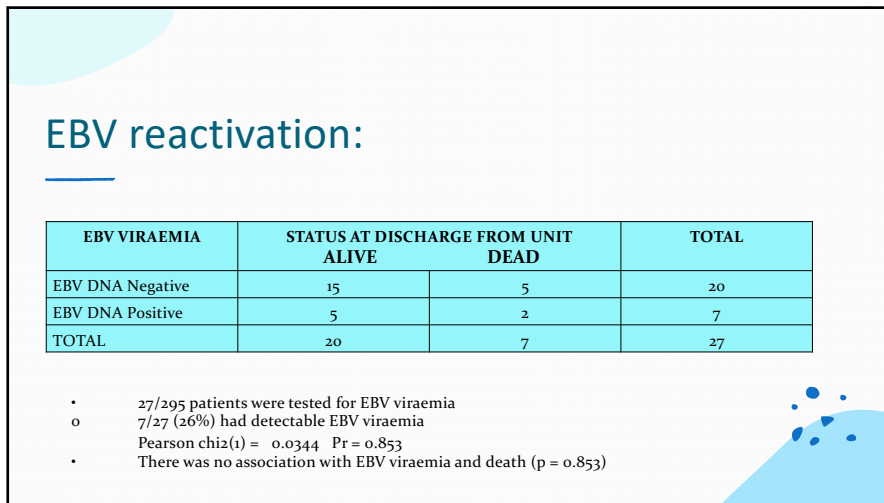
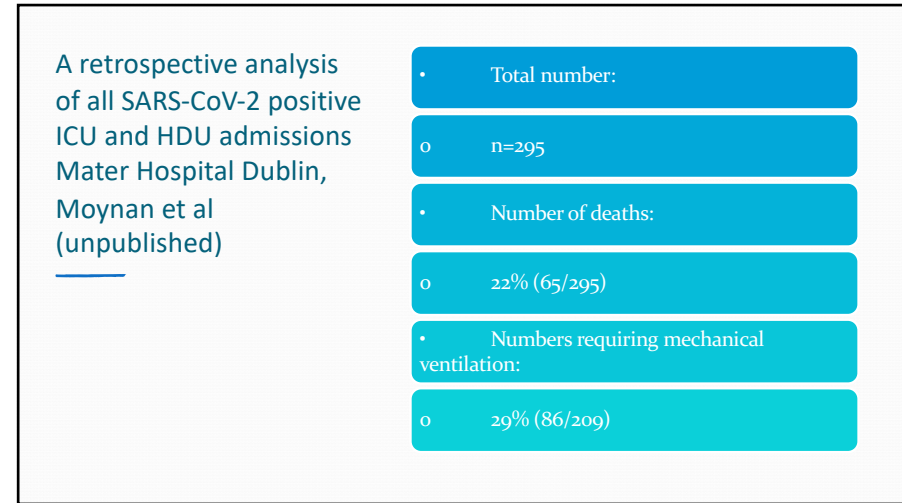
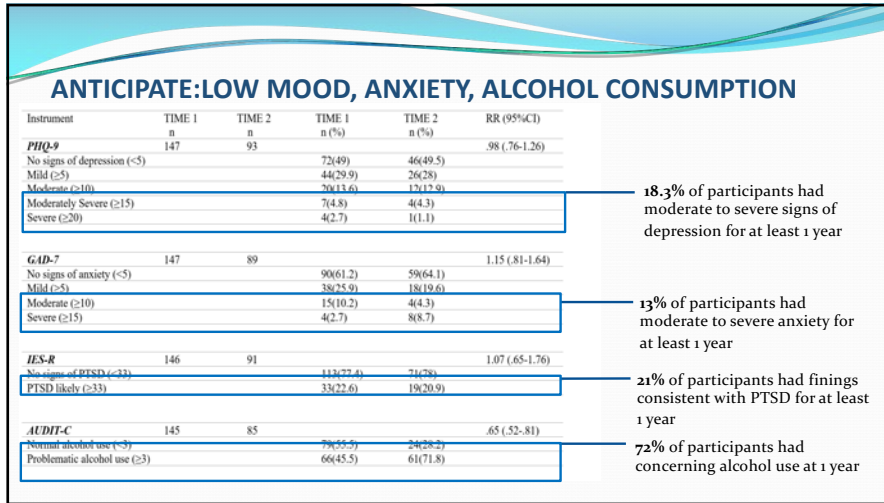
• Score for average well person is 50

## ANTICIPATE COHORT SF-12 outcomes at 12 months

7-14 month follow up	N(%)	SF-12 PCS			SF-12 MCS		
		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





## CMV viral reactivation:

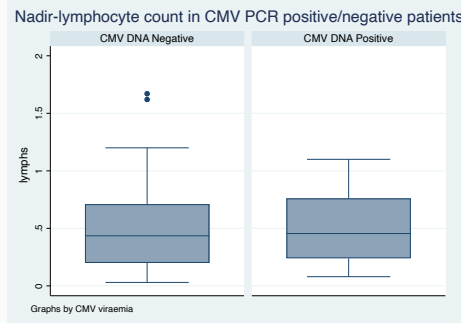
CMV VIRAEMIA	STATUS AT DISCHARGE FROM UNIT		TOTAL
	ALIVE	DEAD	
CMV DNA Negative	33	19	52
CMV DNA Positive	9	6	15
TOTAL	42	25	67

67/295 patients were tested for CMV viraemia  
 Of those who were tested: 15/67 (22.3%) had a detectable CMV viraemia  
 Pearson  $\chi^2(1) = 0.0596$  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
<b>TOTAL</b>	<b>15</b>

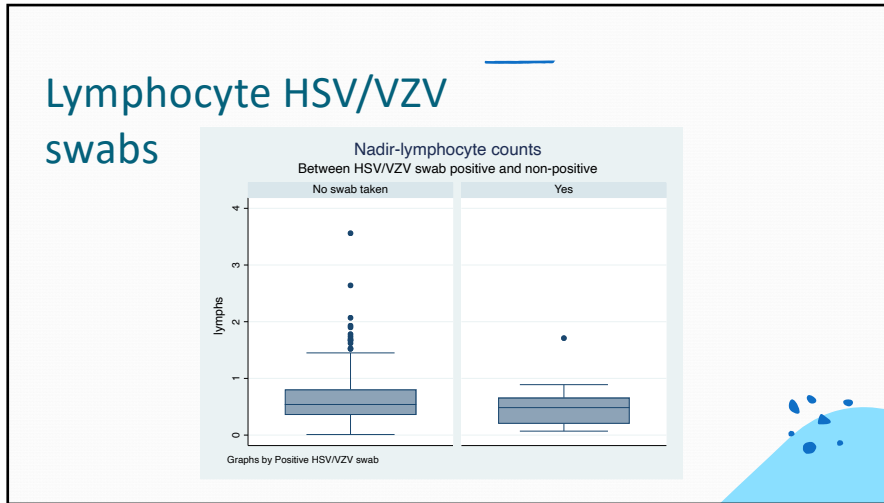
## Lymphocyte Count CMV



## HSV/VZV Viral Swabs

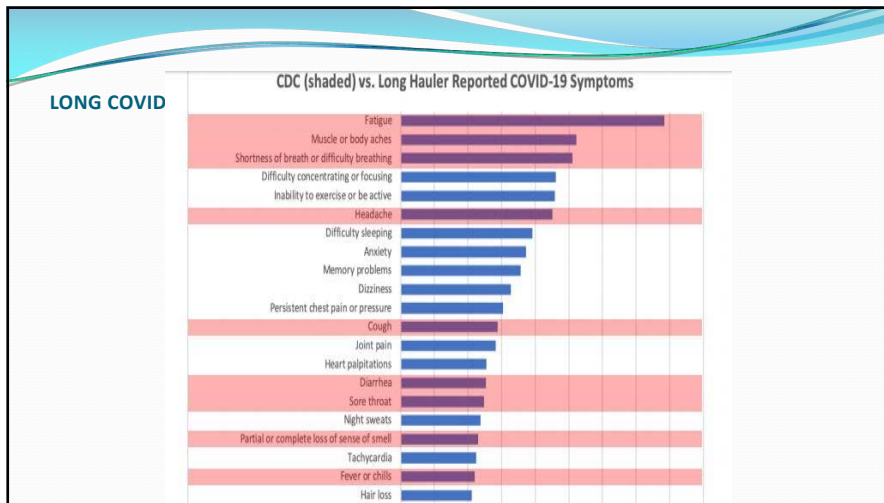
- 26/295 (9%) of the cohort developed skin lesions that swabbed positive for either HSV-1/HSV-2 or VZV
- 11/26 of the patients who swabbed positive for HSV/VZV on skin lesions received mechanical ventilation
- Pearson  $\chi^2(1) = 0.0525$  Pr = 0.819
- There was no association between HSV/VZV reactivation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

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



### 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



### 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
- Rheumatological
  - Arthralgia/arthritis; myalgias
- Neurological
  - Cognitive-confusion/memory difficulties/disorientation
  - Pain-headaches/cranial or peripheral neuropathies
  - tremors

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## 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).

## PET Brain Scans and Chronic Lyme

Journal of Neuroinflammation  
BMC

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

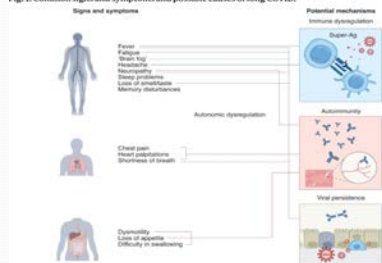
12 patients with PTLDS had symptoms of fatigue and at least one other finding (memory change, difficulty with wordfinding), were compared to controls; controlling for age, BMI, and genotype, individual linear regression models fit for individual ROIs showed significant differences in the cerebellum,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

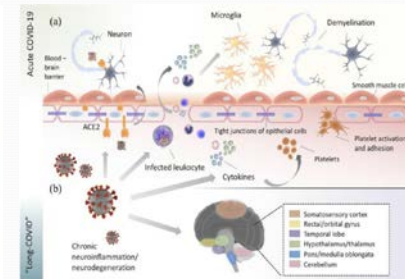
Petter Brodin<sup>1</sup>, Giorgio Casati, Liam Townsend, Chiara O'Farrelly, Ivan Tancoski, Judith Löffler, Rapa Tine

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 Patakidinou, Eleni Bakola, Nikolaos Smyrnis,



## Long Covid or post-acute sequelae 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 sequelae 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

<p>Fatigue, low exercise tolerance, deconditioning (eg, post-ICU)</p>	<p>“Battery flat,” unable to do usual activities. Trying to do more may worsen symptoms. In some cases, fatigue does not improve with rest</p>	<p>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</p>	<p>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</p>
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### 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)
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### 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)
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### 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
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### 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
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### 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
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### 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) <sup>24</sup> (protocol in supplementary file). <sup>25</sup> 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
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### 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
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### 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
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### 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
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### Symptom management (11)

Allergic-type symptoms	Skin rashes (eg, urticaria), conjunctivitis, abdominal bloating, regurgitation	Confirm urticaria clinically (eg, dermatographism). 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)
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### 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)
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### 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
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## 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
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## Patients' accounts of long covid symptoms and accessing services, from research interviews with people with long covid

- "I had an odd rash for quite a while; it kept coming and going ... very itchy cough ... very mild asthma ... I started getting the odd headache again .... Pins and needles, feet going completely numb ... all sorts of odd symptoms, I just kept putting it down to grief until a couple of months in, a friend said, 'Look, do you think this could be covid?'"
- "The fatigue is literally like hitting a wall. I can't stay awake any more. It's just like, wow, I have to go to bed."
- "I'd had 11 days of feeling great. And after [a particular] weekend I crashed again. And again it seemed to last for weeks of having these waves of symptoms: shortness of breath, diarrhoea, muscle aches, complete fatigue."

## Patients accounts (2)

- "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

- 8 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 Tube
- 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/acscchemneuro.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 associated 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 symptoms, 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.

**Enter the Brain**  
Genetic material from the virus, and viral proteins, have been found in cells that line passages deep within the brain. Researchers suspect that the virus may reach these cells through tears and other routes that connect the brain and the rest of the body. It can also infect astrocytes, a critical neural support cell.

**High Levels of Virus Detected**  
High levels of virus-infected cells were observed in nasal mucus, suggesting that the virus may be able to reach the brain through the nasal cavity.

**Autonomic Nerve**  
In COVID patients with neurophysiological symptoms, proteins specific to SARS-CoV-2 were found in small bundles of autonomic nerves that connect from their chest and abdomen, as long as three months after their 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.

**Researcher's Research**  
Studies of long COVID patients with cognitive problems found signs that immune system cells from blood vessels had moved into the brain. These cells are not supposed to be in that region and are known to trigger inflammation. This suggests that the virus may be causing damage to the brain's blood vessels.

**Neurological Attack**  
Reports of people who have died from COVID show signs of an assault from vasculopathy, a type of immune system cell that reacts to viruses and other pathogens. The cells surround and destroy the endothelium, the thin lining of blood vessels, especially around brain blood vessels.

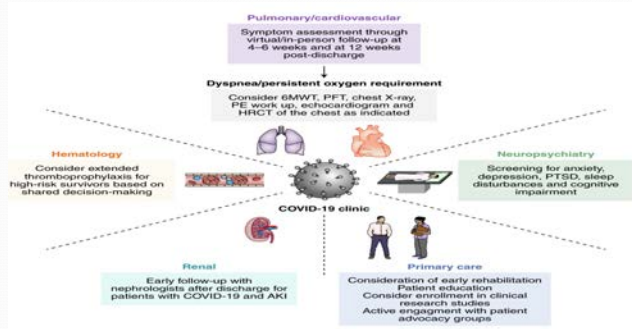
**Healthy Brain Blood Vessel**  
Healthy brain blood vessels have a thin lining of endothelial cells that allows for smooth blood flow.

**Brain Blood Vessel After Infection**  
After infection, immune cells (macrophages and microglia) enter the vessel, causing inflammation and damage to the endothelial lining.

## 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 and reactivation of latent infections)
  - Interventions to repair the mitochondria

## Home exercises

- Rebuild the diaphragm: Philips Respironics IMT Threshold Trainer
- Apply principles of nasal breathing: 'the oxygen advantage' by Patric McKeown. Specifically nasal breathing when 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://hzhcardiacphysio.com/specialist-cardiac-physiotherapist/>



## 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)	1 <sup>st</sup> follow up median(IQR)	P value	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 your health now limit you in your 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	-3.806	-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



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.

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Mangiferin: a natural miracle bioactive compound against lifestyle related disorders  
[Muhammad Imran](#), <sup>1,2</sup> [Muhammad Saïd Arshad](#), <sup>1,2</sup> [Munoz-Solis-Ber](#), <sup>3</sup> [Gopalika Kaur](#), <sup>4</sup> [Mahmoud Elmaghrabi](#), and <sup>5</sup> [Mahmoud Elmaghrabi](#)

[Lipids Health Dis.](#) 2017; 16: 84.  
 Published online 2017 May 2. doi: [10.1186/s12944-017-0449-y](https://doi.org/10.1186/s12944-017-0449-y)

- Mangiferin (2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) can be isolated from higher plants as well as the mango fruit and their byproducts (i.e. peel, seed, and kernel). It possesses several health endorsing properties such as antioxidant, antimicrobial, antidiabetic, antiallergic, anticancer, hypocholesterolemic, and immunomodulatory. It suppresses the activation of peroxisome proliferator activated receptor isoforms by changing the transcription process.... Additionally, mangiferin enhances the capacity of the monocyte-macrophage system and possesses antibacterial activity against gram-positive and gram-negative bacteria.

## 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, amyotrophic 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

Long COVID: The Nature of Thrombotic Sequelae Determines the Necessity of Early Anticoagulation Chengyue Wang<sup>1,2</sup>, Chengyuan Yu<sup>1,3</sup>, Haijiao Jing<sup>1</sup>, Xiaoming Wu<sup>1</sup>, Valerie A. Novakovic<sup>4</sup>, Rujuan Xie<sup>2\*</sup> and Jialan Shi<sup>1,4,5\*</sup>  
Front. Cell. Infect. Microbiol., 05 April 2022  
Sec. Clinical Microbiology  
Volume 12 - 2022 | <https://doi.org/10.3389/fcimb.2022.861703>

- After vascular endothelial injury, there may be weakened anticoagulant properties, increased permeability and leukocyte adhesion. TF expression on ECs surface is up-regulated. Antithrombin III, TF pathway inhibitor and protein C system are damaged and lose anticoagulant properties. Injured ECs can release vWF, factor VIII and PS exposure to promote a hypercoagulable state. Furthermore, ECs can increase the expression of chemokines on their surface, promote neutrophil recruitment, and participate in thrombosis. SARS-CoV-2 and cytokines (such as TNF- $\alpha$ , IL-1, IL-6) damage the vascular endothelium, resulting in ECs contraction, connections separating and the appearance of intracellular gaps
- As the disease progresses, injury to circulating blood cells and vascular endothelium can activate cytokines release, resulting in extensive capillary ECs damage, increasing the transport channel diameter and vessels permeability, and albumin leakage in the blood vessels

Degradative Effect of Nattokinase on Spike Protein of SARS-CoV-2  
Takashi Tanikawa<sup>\*</sup>, Yuka Kiba<sup>\*</sup>, James Yu<sup>\*</sup>, Kate Hsu<sup>\*</sup>, Sminder Chen<sup>\*</sup>, Aysuke Ishii<sup>\*</sup>, Takami Tokogawa<sup>\*</sup>, Ryuichiro Suzuki<sup>\*</sup>, Yutaka Inoue<sup>\*</sup>, Masashi Kitamura<sup>\*</sup> 2022 Aug 24;27(17):5405. doi: 10.3390/molecules27175405

- SARS-CoV-2 has a spike protein (S protein), and cleavage of the S protein is essential for viral entry. Nattokinase is produced by *Bacillus subtilis* var. *natto* and is beneficial to human health.
- When cell lysates transfected with S protein were incubated with nattokinase, the S protein was degraded in a dose- and time-dependent manner. Immunofluorescence analysis showed that S protein on the cell surface was degraded when nattokinase was added to the culture medium.
- These findings suggest that nattokinase exhibits potential for the inhibition of SARS-CoV-2 infection via S protein degradation

## Gut Microbiota Dynamics in Relation to Long-COVID-19 Syndrome: Role of Probiotics to Combat Psychiatric Complications

Maha F. Alenazy,<sup>1</sup> Haya I. Aljohar,<sup>2</sup> Ashwag R. Alruwaili,<sup>3</sup> Maha H. Daghestani,<sup>4</sup> Mona A. Alonazi,<sup>5</sup> Ranyah S. Labban,<sup>6</sup> Afaf K. El-Ansary,<sup>7</sup> and Hanan A. Balto<sup>8</sup> *Metabolites*. 2022 Oct; 12(10): 912.

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Increasing numbers of patients who recover from COVID-19 report lasting symptoms, such as fatigue, muscle weakness, dementia, and insomnia, known collectively as post-acute COVID syndrome or long COVID. In this review, these symptoms are discussed in connection to the COVID-19 and long-COVID-19 immune changes, highlighting oral and psychiatric health, as this work focuses on the gut microbiota's link to long-COVID-19 manifestations in the liver, heart, kidney, brain, and spleen. This review focuses on current knowledge about the use of probiotics as adjuvant therapies for COVID-19 patients that might help to prevent long-COVID-19 complications.



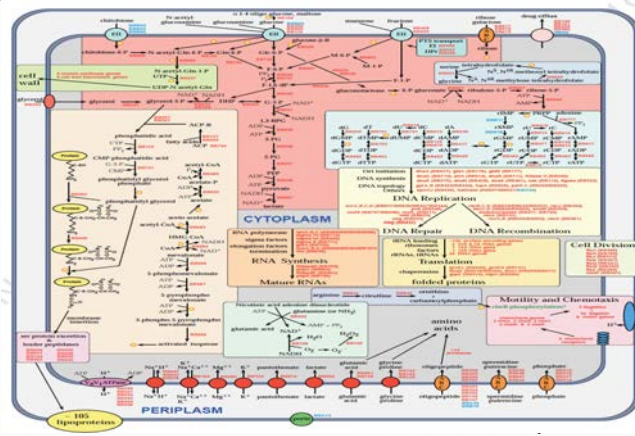
## Management of Long COVID? Lessons from Lyme disease, which has similar characteristics

- 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 gut 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, Cryptolepis, TCM herbs)
- Medicinal mushrooms may have future role in strengthening and modulating the immune system (Reishi, Lions Mane, Cordyceps)

## ITS COMPLICATED



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## 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
- Support for treatments that have initial evidence of benefit (low dose naltrexone, melatonin, NAC)
- Taking on board new science: it's the Brain that seems to be damaged, and a 'neuro-rehab' strategy with support from medical and complementary medicine is the way forward, until the 'magic cure' is found