UNITY HEALTH TORONTO

Managing Post COVID-19 Condition Therapeutic Education Program

FAQ Session

Welcome

Agenda

- Introduction of team members
- Review of commonly asked questions

Introduction of Team Members

Inflammation and the Post COVID Condition

What does the literature say about the relationship between the Post-COVID Condition (PCC) and inflammation in the brain/body?

Physiological causes of Long COVID symptoms

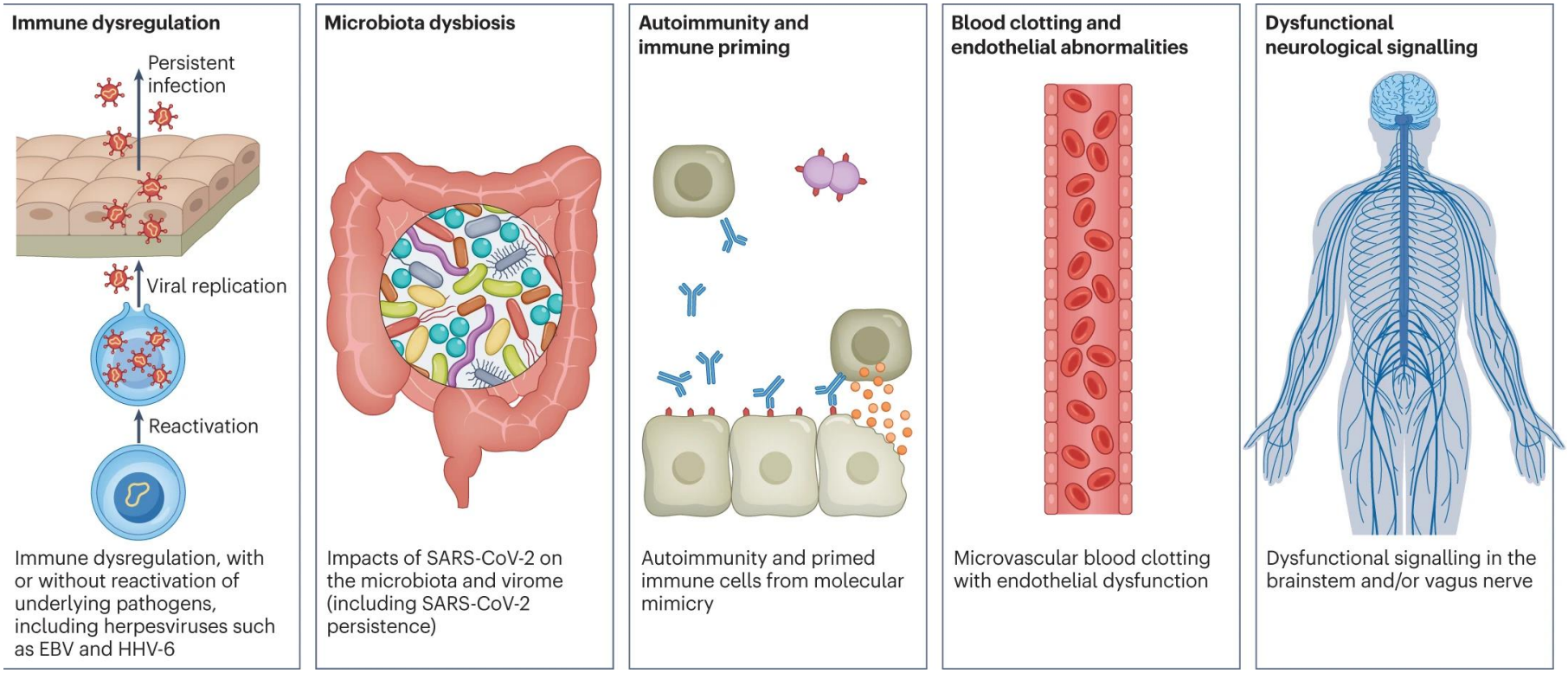


Fig. 3: Hypothesized mechanisms of long COVID pathogenesis.

Davis, H.E., McCorkell, L., Vogel, J.M. et al. (2023).

Potential Mechanisms for Long COVID

1) **Immune Dysregulation** - with or without activation of underlying pathogens, i.e. EBV, HHV-6

2) **Endothelial Dysfunction** – microclots and hyper-activated platelets

3) **Mitochondrial Dysfunction** – exercise intolerance, impaired O2 extraction

4) **Mast Cell Activation Syndrome (MCAS)**
   - Mast cells are allergy cells responsible for immediate allergic reactions through release of mediators stored inside the cell
   - Release occurs when allergy antibodies (IgE) present on the mast cell surface binds to allergens and results in a release of mediators (degranulation)
   - MCAS can results symptoms related to heart, skin, lung, GI

Long COVID and the Brain

Proposed mechanisms affecting brain function:

1. Neuroinflammation
2. Endothelial dysfunction – damage to the neural blood vessels through coagulopathy resulting in injury to neurons
3. Hypometabolism in the brain and brainstem
4. Cerebral spinal fluid abnormalities identified in the lumbar punctures samples in non-hospitalized patients
5. SDAT (Senile dementia of Alzheimer's type)-like signaling in PCC patients with predominant neuro symptoms
    - Peptides that self-assemble into amyloid clumps that are toxic neurons

Research on Long COVID and the Brain

UK Biobank Study (Douaud, G., Lee, S., Alfaro-Almagro, F. *et al.*, 2022):

- MRI of brains of healthy volunteers before COVID, compared to repeat MRI scans of same volunteers after contracting SARS-CoV-2 and developing LC symptoms including brain fog
- MRIs show decreased grey matter in the ortbitofrontal cortex and parahippocampal gyrus; overall decrease in brain size

Research on Long COVID and the Brain

Yale Medical School - NAC and Guanfacine open-label study (Arman Fesharaki-Zadeh, Naomi Lowe, Amy F.T. Arnsten, 2023):

- The prefrontal cortex (PFC) preferentially affected, with evidence of increased Kynurenine production

Hypothalamus-Pituitary-Adrenal Axis Dysfunction

- Supported by low blood cortisol levels in PCC patients > 1 year post-infection
- This should be compensated by increased ACTH (adrenoorticotropic hormone) production by the pituitary gland, but not occurring in some PCC patients. This may reflect and underlying neuroinflammatory process

Take away message on brain fog

- There are studies confirming the neuroanatomical pathways by which SARS CoV-2 has effected or changed the brain
- The term "brain fog" may not capture the very real effects of the virus on the brain
- Research is being conducted to identify supplements/medications that may provide some benefit but the research is in its early stages with small sample sizes, therefore findings should not be generalized to all patients with PCC.

Medications and Vitamins

What are some common medications and supplements that are being prescribed to help improve symptoms?

Some patients have tried a combination of these supplements with varied success:

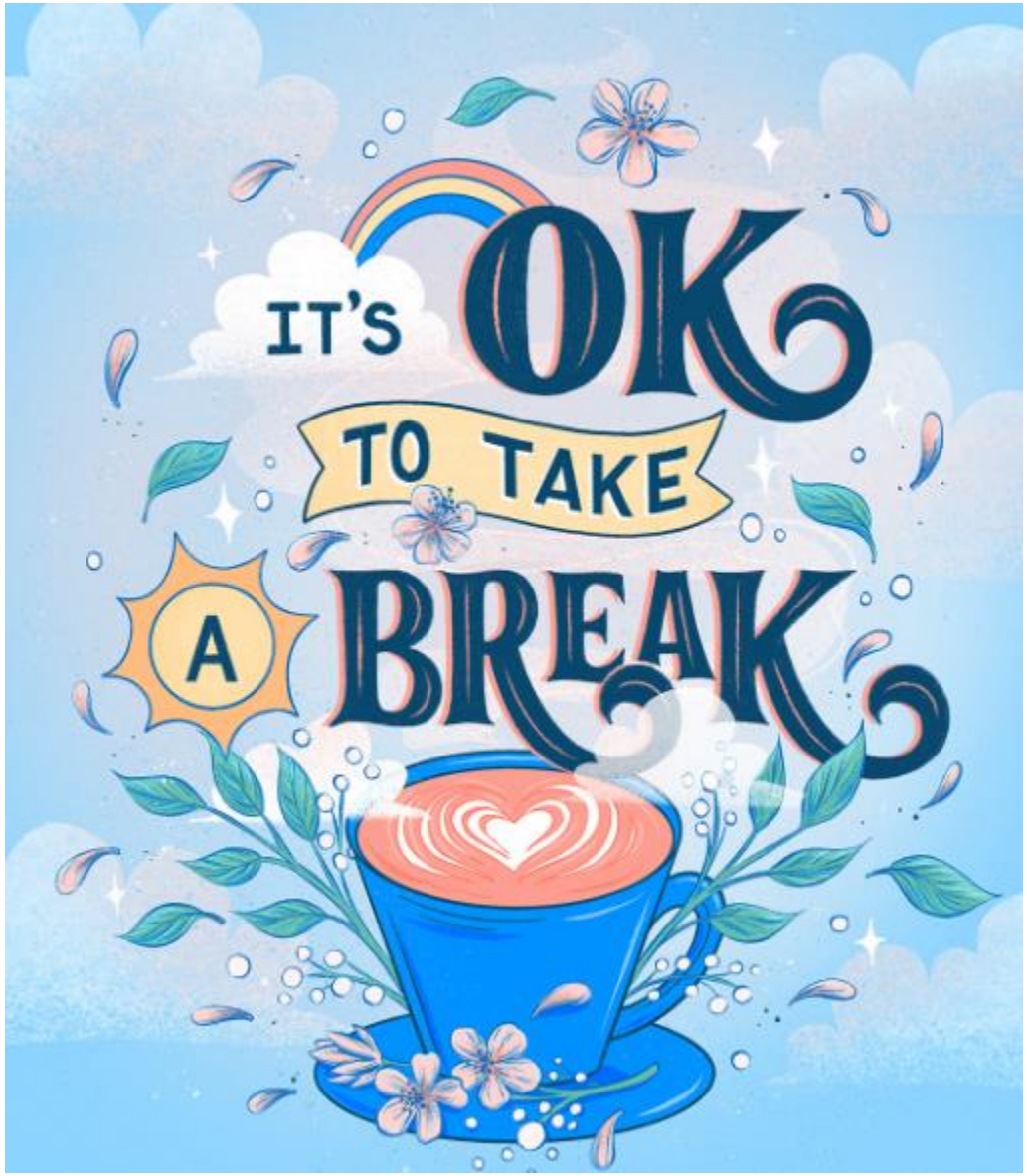
Purpose	Supplement
Mitochondrial booster to treat mitochondrial dysfunction	MitoMatrix (contains N-acetylcysteine (NAC), Coenzyme Q10, L-Acetyl Carnitine, Alpha Lipoic Acid)
Reduction of inflammatory biomarkers linked to persistent dysregulation of inflammation	Theracurmin (more bioavailable than other forms of high-dose turmeric)
Histamine Blockers: treatment of Mast Cell Activation Syndrome (MCAS) symptoms	H1 Blocker – Claritin, Reactin H2 Blocker – Pepcid (Famotidine)

*Please consult your primary care provider to determine if these are appropriate for you.

Three of the prescription medications trialed for some of the patients with varied success:

Drug	Potential side effects
NAC 600 mg + Guanfacine 1 mg (month 1) → 2 mg (month 2)	Hypotension (low BP) causing dizziness/lightheadedness from the use of Guanfacine (α2A-adrenoceptor agonist)
Methylphenidate: - **Adderal XR** - **Concerta** - **Alertec (Modafinil)**	As a result of sympathomimetic activity, there is a risk of insomnia, anxiety, palpitations and worsening of tachycardia/dysautonomia/POTS symptoms which may already exist
Low Dose Naltrexone (LDN) Start at 1 mg; increase up to 5-7 mg (compounding pharmacy required)	Seemingly minimal – only 2/52 participants in the O'Kelly study (above) reported adverse SE

*Please consult your primary care provider to determine if these are appropriate for you.


IT'S OK
TO TAKE
A BREAK

Vaccinations and boosters

What does the research say about vaccinations and booster shots for people who already have long-COVID/PCC?

- Boosters are safe for people with Long COVID
- Help reduce risk of re-infection, important benefit due to evolving variants
- Iwasaki Study:
    - 30-40% reports symptomatic improvement
    - 10-15% may feel worse, some feel find no difference in symptoms

Vaccinations and boosters

Will vaccinations prevent people from getting Long COVID?

- Gao & Liu Study (2022)
  - Vaccinated group had 20% lower risk of developing Long COVID vs. unvaccinated group
  - Vaccination showed protective effects in patients with 2 doses but not 1 dose
  - Vaccination was effective against Long COVID in patients vaccinated before or after SRAS-Cov-2 infection
  - Vaccination reduced risk of these Long COVID symptoms: cognitive dysfunction, myalgia and problems sleeping

Gao P, Liu J, Liu M. Int J Environ Res Public Health. 2022 Sep 29;19(19):12422

Exercise and the Post COVID Condition

How do I know when I can add gentle exercises to my routine and avoid PEM/symptom exacerbation?

- If you continue to experience PEM/PESE with your basic daily routine, progressive exercise is not recommended
- Focus on restorative activities or things that help you feel better, i.e. if you are feeling muscle tightness/stiffness doing gentle stretching or movement in a seated or lying position can be helpful.
- For most people, gentle stretching and movement in short duration is tolerated but monitor your symptoms to see what your body can tolerate

Exercise and the Post COVID Condition

- When you start anything new, start slow and monitor your symptoms. If symptoms are triggered, it is likely not tolerated.
- Ways to adapt activities:
  - Frequency
  - Duration
  - Intensity
- If an activity is tolerated, stay at the same level for about 2 weeks before considering how you might increase, i.e. change only one of frequency, duration, intensity

Recovery and Post COVID Condition

Has anyone in your clinic recovered fully from Long COVID?

- We have seen a spectrum with regards to recovery

- Main themes for those who have seen an improvement:
  - They continue to monitor their energy use and activities
  - They remember to pace, plan, and prioritize as part of their efforts to avoid PEM episodes

- The majority of patients who come through the program likely have more severe long COVID symptoms vs patients with milder Long COVID that we do not see in the program

Three key messages about Long COVID

1. Long COVID/PCC is a complex condition with symptoms that are episodic and unpredictable
    - A post-viral syndrome, which is a multi-system, neuro-immune illness
    - Results in profound fatigue not alleviated by rest

Key messages (cont'd)

2. Avoid PEM
    - Best practice draws on management approaches for related condition like ME/CFS, mTBI, chronic PCS, Fibromyalgia/chronic pain
    - Progress activity gradually, modulating physical and cognitive activity levels in response to symptoms

Key messages (cont'd)

3. Attending this program does not cure long COVID
    - The program provides education/tools to manage the condition
    - Discharge from the program is based on completion of the education modules and not as a result of any improvement in health status or return to pre-COVID function
    - Most patients require additional time and support for recovery following discharge

*These messages are included in the discharge letter we send to your family doctor

Accessing Testing and Treatment

If my doctor is not confident in PCC, how do I continue to advocate for my care?

- Consider the urgency of your symptom
- Resources for your family doctor:
  https://www.ontariofamilyphysicians.ca/tools-resources/covid-19-resources/long-covid-qa.pdf

  https://www.ontariohealth.ca/sites/ontariohealth/files/2021-12/PostCovidConditionsClinicalGuidance_EN.pdf

Future Steps

As the clinic closes, where can we go for continued care?

- *Four Villages Community Health Centre*
  https://4villageschc.ca/programs/adults/
- *Private Clinics for Post-COVID Condition*
  (i.e. Lifemark, Cornerstone)
- *Chronic Disease Self Management Programs*
  https://selfmanagementontario.ca/
- *Chronic Pain Clinics and Self Management*
  https://tapmipain.ca/
- *The ME Association of Ontario*
  National ME/FM Action Network
  https://www.meao.ca/
  http://www.mefmaction.com/

References

Arman Fesharaki-Zadeh, Naomi Lowe, Amy F.T. Arnsten. Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in "Long-COVID19", Neuroimmunology Reports, Volume 3, 2023, 100154, ISSN 2667-257X. https://doi.org/10.1016/j.nerep.2022.100154. (https://www.sciencedirect.com/science/article/pii/S2667257X22001000)

Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133-146(2023). doi: https://doi.org/10.1038/s41579-022-00846-2

Douaud, G., Lee, S., Alfaro-Almagro, F. *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* **604**, 697–707 (2022). https://doi.org/10.1038/s41586-022-04569-5

Gao P, Liu J, Liu M. Effect of COVID-19 Vaccines on Reducing the Risk of Long COVID in the Real World: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022 Sep 29;19(19):12422. doi: 10.3390/ijerph191912422. PMID: 36231717; PMCID: PMC9566528.

Resources

Mechanism of Long COVID (Post-COVID Condition – PCC):

1 - Long COVID: major findings, mechanisms and recommendations (*this is the article Dr. Cheng referred most to): https://www.nature.com/articles/s41579-022-00846-2

2 - Understanding Long COVID: Mitochondrial Health and Adaptation – Old Pathways, New Problems:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9775339/

3 – One of Long COVID's worst symptoms is also its most misunderstood:

https://www.theatlantic.com/health/archive/2022/09/long-covid-brain-fog-symptom-executive-function/671393/

4 – Could microclots help explain the mystery of Long COVID?

https://www.theguardian.com/commentisfree/2022/jan/05/long-covid-research-microclots

5 - Long COVID Now Looks like a Neurological Disease, Helping Doctors to Focus Treatments:

https://www.scientificamerican.com/article/long-covid-now-looks-like-a-neurological-disease-helping-doctors-to-focus-treatments/

6 – Mast cell activation symptoms are prevalent in Long COVID:

https://www.sciencedirect.com/science/article/pii/S1201971221007517?via%3Dihub

7 – Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation:

https://www.sciencedirect.com/science/article/pii/S1201971220307323?via%3Dihub

Resources (cont'd)

Articles (research and otherwise) on Medications / Supplements:

1 - The Long COVID Clinical Trials: Big Drugs, Big Studies... and More: https://www.healthrising.org/blog/2023/01/13/long-covid-clinical-trials-big-drugs-big-studies-and-much-more/

2 - MediciNova gains approval from Health Canada for long COVID therapy trial: https://www.clinicaltrialsarena.com/news/medicinova-long-covid-therapy/

3 - Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in "Long-COVID 19":

https://www.sciencedirect.com/science/article/pii/S2667257X22001000

4 - Yale Researchers Discover Possible 'Brain Fog' Treatment for Long COVID:

https://medicine.yale.edu/news-article/potential-new-treatment-for-brain-fog-in-long-covid-patients/#:~:text=Guanfacine%20and%20NAC%20Relieve%20Long%20COVID%20Brain%20Fog&text=Since%20then%2C%20Fesharaki%2DZadeh%20has,2%20mg%20after%20one%20month.

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

https://pubmed.ncbi.nlm.nih.gov/35814187/

6 – Repurposing drugs for post-COVID 19 fatigue: methylphenidate, duloxetine & Brexipiprazole:

https://journals.lww.com/americantherapeutics/Fulltext/2022/04000/Repurposing_Drugs_for_Post_COVID_19_Fatigue.9.aspx

Resources (cont'd)

Management:

A Case study of Successful Application of the Principles of ME/CFS Care to an Individual with Long COVID: https://www.mdpi.com/2227-9032/11/6/865

Experience of Brain Fog:

One of Long COVID's Worst Symptoms is also Its Most Misunderstood by Ed Yong, The Atlantic, September 12, 2022.

https://www.theatlantic.com/health/archive/2022/09/long-covid-brain-fog-symptom-executive-function/671393/

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FAQ with Dr. Cheng and the Post COVID Condition Team

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