Responses to Participants' Questions

This document provides responses to questions raised by seminar participants related to the following presentations:

- **Presentation 1:** ***Comparing ME/CFS and PASC/Long COVID: Lessons Learned from ME/CFS***
  Nancy Klimas, MD

- **Presentation 2:** ***PASC-CFS: Implications, Data, and Next Steps***
  Benjamin H. Natelson, MD

- **Presentation 3:** ***Pathophysiology of Exercise Intolerance in ME/CFS and PASC***
  David M. Systrom, MD

Presentation 1: Questions and Responses

Q1. The International Consensus Criteria (ICC) is one step in subgrouping patients. We are now seeing how patient selection using the ME ICC is providing results specific to that patient group. Is the ME ICC along with the ME International Consensus (IC) Primer being considered to screen PASC patients?

Response: It is being tested as a potential screening tool, but it has not been validated in the PASC population yet.

Q2. The ME IC Primer provides a list of viruses to be tested for. Are PASC patients getting that virus testing to see what may be reactivating and is treatable?

Response: It depends on the study. In our CDC-funded study, we're testing for viral reactivation of latent viruses.

Q3. The National Centre for Neuroimmunology and Emerging Diseases out of Griffith University in Australia is doing research into the transient receptor potential melastatin (TRPM) channels that are malfunctioning in people with ME affecting many processes, including mitochondrial function and possible involvement in low natural killer (NK) cell

function. Is low NK cell function seen in PASC? Is anyone doing TRPM channel research in PASC?

Response: I don't know if TRPM work is being done in PASC. The ME/CFS work of the Griffith University group is excellent and it is helping sort out the underlying mechanisms for NK cell dysfunction in ME/CFS.

Q4. Has there been an increase in diagnosis of narcolepsy in PASC patients (the way there was an increase post H1N1 flu)?

Response: We have not yet seen anything in PubMed (the published literature) that addresses this question.

Q5. Have you seen any cases of ME/CFS with chronic active virus still present in the body?

Response: Dr. John Chia[1] has great data on enterovirus restricted to the gastrointestinal tissue. Others have focused on herpes family viruses (HHV6, EBV, CMV) and ParvoB19. There is a lot of work published in this area, but it remains controversial. Only a few very small clinical trials are looking at this and usually only treating herpes family viruses.

Q6. I am interested in your slide on Mapping Active Genes to Active Pathway elements. Do the location of the points on those maps represent anything (specifically the clumps) or are they random locations to show connections between genes?

Response: Each dot represents something we measured, such as a set of genes regulating something specific (for example, a cytokine) or a measured cell type (for example, an activated T cell) or a neuropeptide (for example, testosterone). The lines represent communication between these measures, and the thicker the line the stronger the connection.

Q7. How often have you observed Gulf War illness (GWI) and/or ME tip into amyotrophic lateral sclerosis (ALS)? Oversimplifying, but presumed mechanism would be chronic severe oxidative stress and neuroinflammation across time.

[1] Dr. John Chia is the President of EV Med Research, Owner/Physician at Infectious Disease Med, and Assistant Professor at the UCLA School of Medicine. He is an infectious disease specialist and studies the role of enteroviral infections in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). https://www.enterovirusfoundation.org/overview

Response: The ALS cases in the GWI patients tended to appear in the first 10 to 15 years after the toxic exposures, which is the same as brain cancer. It's rare, but a real worry. What we are worrying about now is neurodegenerative illness, such as Parkinson's disease, as it's been 31 years since the Gulf War.

Q8. Why are we assuming that Long COVID is post viral and not viral persistence?

Response: We don't know. It's too early in PASC research to determine if there is a large group or subgroup that have viral persistence.

Presentation 2: Questions and Responses

Q10. What is the tragus device called?

Response: The device is called a parasym. It's available in the UK or EU without a prescription.

Q11. Assuming post-exertional malaise (PEM) reflects an underlying pathology, one might expect study participants who experience PEM would show different results from those who do not. Have you subsetted your ME/CFS cohorts to analyze the differences in these two subsets? If so, what did you see?

Response: Nearly all our ME/CFS patients have PEM. We're using a wrist-mounted computer to capture activity and symptoms and should be able to use these data to correlate with PEM and with symptom burden.

Q12. You have a number of encouraging hypotheses that involve impairments—mitochondrial dysfunction, poor oxygen extraction, hyperventilation—and you are testing therapies such as vagus nerve stimulation. I know it's still early, but given what you know, would you say there may be existing therapies or medications that will be effective treatments? Or does someone have to invent something from scratch? And will there ever be a "cure" or do you see a future of "managing symptoms"?

Response: Right now, in my practice, I spend a lot of time with each patient to try to arrive at a personalized approach to their problem. We apply the same approach with PASC as with ME/CFS, as I've described in my book, *Your Symptoms Are Real*. Right now, there is no FDA-approved treatment for either PASC or CFS, but that doesn't stop our efforts.

Q13. Assuming the vagus nerve modulation approach works, what do you think is the underlying mechanism of the pathophysiology of the vagus nerve/or other neurologic dysfunction?

Response: We don't know a lot about fatigue. However, with pain, descending pathways controlling pain are affected so they do not work well, so individuals with ME/CFS and fibromyalgia have whole body pain. We believe the vagus nerve modulation targets those areas and opens up systems that are blocked. Descending pathways controlling pain are ameliorated by treatment.

Q14. What kind of efforts are currently made to understand how to treat post-exertional malaise?

Response: Donna Mancini[2] has conducted a trial to raise eTCO2 in patients with heart failure by practicing breathing against resistance, using a rethreshold IMT breathing device or an N-95 mask covered with a cloth mask. No trials have yet been done in PASC.

Q15. How [do you] distinguish ongoing memory problems, etc., due to CFS versus onset of Alzheimer's disease?

Response: The neuropsychological deficiencies in Alzheimer's disease are distinct from those seen in CFS.

Q16. How do you differentiate clinically POTS and ME/CFS?

Response: POTS and orthostatic hypocapnia are evidence of orthostatic intolerance (OI), which can be a part of CFS. Many CFS patients have OI. What we don't know is the number of patients who have POTS who do not have CFS. However, many young people have markedly elevated heart rates with standing or leaning but do not experience any symptoms. We would not make the diagnosis of OI unless the patient reports feeling ill when upright and not moving.

Presentation 3: Questions and Responses

Q17: VO2 peak is reduced in the dyspnea group in your preload study. What are the preload values at the same VO2 (or work rate) rather than at peak?

Response: VO2 is low at rest and throughout incremental exercise.

Q18. Is dyspnea something that in ME can be intermittent? If so, what does this mean?

[2] Dr. Donna M. Mancini is a professor of medicine and cardiology, and population health science and policy at the Icahn School of Medicine at Mount Sinai. She is a heart failure and transplant cardiologist who conducts clinical research focused on heart failure, exercise physiology, risk stratification for selection of heart transplant and LVAD candidates, and novel post-transplant immune therapy and care.

Response: Yes, and it can track with other indices of dysautonomia; for example, high heart rate and low blood pressure.

Q19. What is the current hypothesis on the mechanisms causing sudden hyperventilation, in PASC for instance, in people previously not hyperventilating?

Response: We don't know, but it's an area ripe for research and treatment. Presumably, that hyperventilation relates to dyspnea as one of the PASC symptoms. Some of the other diseases we've talked about are associated with hyperventilation. In mitochondrial disease, hyperventilation is ubiquitous. In all forms of heart failure and pulmonary disease where there is a component of impaired oxygen delivery, there is also hyperventilation. That signal may come from the periphery. What may be at play in some of these patients is muscle metaboreflex.

All Presenters: Questions and Responses

Q20. How can one treat hyperventilation?

Responses:

- **Dr. Systrom:** We need to know the cause first. There has been some luck with sertraline.
- **Dr. Klimas:** There are different reasons for hyperventilation. If the underlying acid base balance in the patient is normal, then I would recommend exercises like the Buteyko method to retrain the underlying regulatory signals. Another similar breathing method, vagal breathing, emphasizes working the diaphragm and can help retone the vagal nerve and in turn help improve the sympathetic/parasympathetic balance.

Q21. What steps are being taken—or will be taken—to drive the results of PASC/PASC-CFS studies to further ME/CFS research and to help treat ME/CFS patients in a timely manner?

Responses:

- **Dr. Systrom:** Although one would hesitate to use the term, if there is any silver lining of Long COVID, it has helped with research funding that will help both ME/CFS and PASC.
- **Dr. Klimas:** I'm hopeful that PASC investigators will learn the benefit of including ME/CFS control groups in their studies. We have had very few clinical trials in this field, and there are so many things we could be doing. I'm hopeful that pharmaceutical industries and funding agencies will see through PASC how people's lives are impacted when they have diseases like this.
- **Dr. Natelson:** The silver lining of Long COVID for me is that ME/CFS is recognized as real. Those of us who have cared for these patients for decades know it's real, but there's an avalanche of research coming down the pike.

Seminar Slides

To request a copy of the R3 seminar slides, please email RECOVER_ACC@rti.org.

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- Information about RECOVER study protocols and measures: https://recovercovid.org/research-works.
- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs
- CDC information: Information for the general public and for healthcare providers about post-Covid conditions: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/

References

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Natelson, B. H. (2007). *Your symptoms are real: What to do when your doctor says nothing is wrong*. Hoboken, New Jersey: John Wiley & Sons, Inc.