

Responses to Participants' Questions

The overarching goal of the R3 Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses* to questions raised by seminar participants related to the following presentations at the R3 Seminar *Impacts of SARS-CoV-2 Infection on Brain, Immunity, and Metabolism* held on December 12, 2023:

- ***Investigating the Metabolic and Immunological Basis of Long COVID***
Catherine Blish, MD, PhD
- ***The Role of Metabolic Inflammation and Lipid Abnormalities in PASC***
Cliff Rosen, MD
- ***Neurological Complications of COVID-19***
Avindra Nath, MD
- **Discussant: Sudha Seshadri, MD**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What is the average duration of Long COVID symptoms?

Response:

Dr. Blish: While we currently don't know the answer to that question, my hope is that the RECOVER consortium will be able to provide an answer and define a consistent syndrome, description, or biomarker. So far, it's been very difficult, and I think many of us believe that's because there's heterogeneity in the manifestations of Long COVID.

Long COVID isn't one thing. Both Drs. Rosen and Nath alluded to this. Dr. Nath described four kinds of Long COVID. But it's possible that there are four kinds, or eight, or maybe there are 10 kinds of Long COVID. I think it is likely that the underlying pathophysiology driving each of these subtypes may be slightly different, and the resolution therein is going to be different.

In our data describing a small cohort of 100 patients, we note that altered taste and smell and cough resolved, almost universally. Unfortunately, brain fog seemed to be getting worse over the 1-year duration of our study. So, if you lost your smell, then there is reason to celebrate that your symptoms will resolve. However, if brain fog is

the primary manifestation, we don't know what the natural history of that's going to be. And that's where we're going to need data for people across different cohorts, with different BMIs, different ethnicities, and different other risk factors, to try to figure out if there are unifying groups with predictable outcomes.

Currently, I don't think that we have a good enough grasp of what the disease is to make solid predictions. Or, at least, I don't feel like I have a good enough grasp to say respiratory COVID is caused by X, and it's going to get better in 3 months. I wish I did, but at least in our data and in my reanalysis of other people's data, I can't find a unifying group with predictable outcomes.

Q. Have you seen differences in immune responses across the lifespan? Does this impact trial design?

Response:

Dr. Blish: The problem with that is our cohort is 100 people, and we don't have every analysis on every person. By the time we get into our subgroups, we're not seeing many differences by sex or by age. The finer we dice that, the more power we lose to find significant differences. So, we haven't seen dramatic age-related differences in our cohort, but we haven't looked that hard because our study is underpowered.

Q. People with hormonal metabolomic changes are at a higher risk of Long COVID. Could acute infection “unmask” syndromes or a reaction to persistent viral infection or a viral reservoir?

Response:

Dr. Rosen: That's a really difficult question, and we don't know the answer to it. Certainly, when you compare noninfected individuals as compared with individuals that are infected, their increase in incident diabetes in Long COVID patients is higher.

The question really becomes whether that is exacerbated by body or host metabolism? That is obesity, which predisposes individuals to a more chronic inflammatory type of adipose tissue, which could then lead to either viral persistence or more chronic inflammatory markers. And we don't know yet because we need longitudinal data. This is where RECOVER comes in because it not only tells us more about the long-term duration of the disease, but it also has a subcohort of individuals who were not infected, and then got infected during the last couple of epics. And those individuals are probably the most valuable group of individuals to study because they're noninfected, they're being followed, they get infected, and then they have a post COVID symptomatology.

I do want to emphasize that some people do get better, and that's very important. Although, we don't know why they get better, if this is the natural history of Long COVID, or if they're taking agents offline, through the internet, through friends, or through colleagues, that may be ameliorating their symptomatology.

Do these interventions—Vitamin D, NO1s ([N-of-Ones](#)), or other agents—that are being tested by individual patients help? We don't know, and we need a registry to really help us understand what these agents are, and if they are any better than conventional therapy.

RECOVER is the first step, and it really is extremely valuable, because I think we're still early, and we still need that natural history. And finally, it's heterogeneous, so everybody's going to be a little different. And the host response is going to be very, very important to this virus.

Q. Are patients who have recovered from worse cases of Long COVID at higher risk for subsequent bouts of Long COVID?

Response:

Dr. Rosen: Multiple infections lead to a greater risk of Long COVID. But whether you're fully recovered, and then you get another infection, and whether that predisposes one to a separate Long COVID episode.... I don't think anybody knows.

Q. Do the hormonal and metabolomic changes that Dr. Rosen mentioned have a role in changes to the brain? What does the autopsy information, which often comes from acute or subacute settings, tell us about how these different changes are relevant to the brain fog of Long COVID?

Response:

Dr. Nath: I'm pretty sure hormonal and metabolic abnormalities will be found in this patient population, and there's some work Dr. Iwasaki from Yale presented at the Keystone meeting, which is included in her [paper that just came out in Nature](#). [🔗](#) There she showed both types of abnormalities. She showed that cortisol levels were decreased. And in women, testosterone levels were decreased. Also, she suggests that these abnormalities probably make a difference. Another parallel is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) where all kinds of metabolic abnormalities have been reported, including hormonal abnormalities.

Q. Neurofilament light chain (NfL), which crosses the blood-brain barrier, can be used as a marker of acute injury? Could this be a serological biomarker of Long COVID?

Response:

Dr. Nath: There is extensive literature on NfL levels in blood and cerebrospinal fluid in a number of neurological diseases. The literature suggests that in progressive neurological disease, no matter what the underlying cause may be, if there's ongoing neural damage, neurofilament levels (light, heavy chain), and glial fibrillary acidic protein (GFAP), might be very good biomarkers. They don't quite tell you what the underlying disease is, but at

least these biomarkers tell you there's progressive disease. And now these tests have become so sensitive that you can measure them in serum. You don't need to do spinal taps on all patients. I think you're absolutely right that patients with Long COVID should also be monitored with these biomarkers.

Q. Could declining mitochondrial function explain some Long COVID symptoms?

Responses:

Dr. Rosen: Well, there was that paper I illustrated that suggested that mitochondrial genes were downregulated. And I think there's a bit of evidence that was shown at Keystone, from a group in the Netherlands and now [published](#), that showed decreased mitochondrial function in muscle tissue, from muscle biopsies of people with Long COVID.

Dr. Nath: It's a tricky thing to study. Because if you get muscle deconditioning, and you're not moving around, you're not doing much exercise, your muscle is going to show decreased metabolic function related to mitochondrial dysfunction. But that could be explained by deconditioning. One needs to be careful how to interpret mitochondrial function. We did a lot of mitochondrial DNA sequencing from the muscles of chronic fatigue patients and were unable to find any specific abnormalities. But mitochondrial functional studies using the Seahorse technology did show abnormalities. The extent to which it may reflect deconditioning is not fully understood.

Q. Are there any treatment trials that are of particular interest to the panel?

Response:

Dr. Rosen: The [metformin study](#) is very interesting. A number of my patients have been put on metformin now. It may actually improve mitochondrial function, as well as all the other things that metformin does. And I'll only say that providers are desperate for interventions. So, it's really important that these clinical trials be done and done well.

Q. Have there been any reviews on EMDR/Eye Movement Integration for Long COVID patients?

Response:

Dr. Seshadri: There are two studies/reviews, which are by no means exhaustive: PMID [37727746](#) and PMID [35153919](#).

Q. Dr. Blish mentioned some potential factors affecting the immune situation in Long COVID patients, such as timing of sampling. Is there is any meta-epidemiological kind of study looking into the effect of those variables?

Response:

Dr. Blish: I don't believe that a formal meta-analysis has been done yet, but there are many ongoing studies, and I'm certain they will address the sample timing. This will be a major strength of the RECOVER study because it has standardized and intensified the follow-up periods to allow researchers to address this question.

Q. Why is it still unknown if adipose tissue is a reservoir if that site is so easily biopsied and conceivably studied?

Responses:

Dr. Blish: The work is ongoing, but it has been challenging to obtain and analyze the biopsies. It's also easier to prove that it's present because we just need to detect it once. But to be convinced that it's not present, we will need a reasonable sample size to ensure that a negative result is not just sampling error.

Dr. Rosen: So far it's been difficult to detect intact virus in fat tissue. First, we don't have enough biopsies done. Second, it's tricky to determine if the virus is in the fat or in the immune cells surrounding the fat cells. And finally, part of the problem is that there's a variable length of time after infection when people are biopsied, and maybe the virus is there but disappears over time.

Q. Which studies are currently underway that are looking at declines (persistent or otherwise) in mitochondrial function?

Response:

Dr. Rosen: Many studies are looking at mitochondria in circulating immune cells, in fat tissue, and in muscle tissue.

Q. Other than cortisol levels, what hormonal and immune profiling is being done with RECOVER?

Response:

Dr. Rosen: Estrogen, testosterone, ACTH, and hemoglobin A1C.

Q. Can you discuss the use of cortisol to reduce Long COVID symptoms?

Responses:

Dr. Rosen: No clinical trials have been undertaken, although low cortisol levels have been reported in Long COVID patients. The results in ME/CFS are quite variable, but Long COVID is probably different. We need a randomized controlled trial.

Dr. Nath: In my experience, in the few patients in whom it has been tried, it has not been found to be effective.

Q. Can brain fog be indexed by high temporal resolution functional neuroimaging; for example, fMRI, EEG, MEG?

Response:

Dr. Nath: Yes, these techniques are worthy of exploring as a research tool to investigate brain fog, but they are not yet fully developed to be useful in clinical care.

Q. Any thoughts on transcranial direct current stimulation (tDCS) as a potential intervention for Long COVID cognitive symptoms, such as brain fog, memory changes, fatigue, slowed attention, etc.?

Response:

Dr. Nath: Yes, there are good reasons to explore tDCS as an intervention in the context of research studies on Long COVID.

Q. What type of robust diagnostic criteria have we developed to quantify cognitive impairment (brain fog, loss of memory, etc.) due to Long COVID? Are there any straightforward blood tests patients can request from their GP to test for Long COVID?

Response:

Dr. Nath: The cognitive impairment seems variable among patients with Long COVID; hence, it's been difficult to develop diagnostic criteria. Unfortunately, currently there are no blood tests for Long COVID.

Q. What is the impact of long-lasting COVID on the brain and cognition. Can COVID trigger and/or accelerate dementia?

Response:

Dr. Nath: Yes, there's much concern in the research community that COVID might trigger or accelerate dementia and other neurodegenerative diseases.

Q. Please comment on the role of microglial inflammation in Long COVID and whether low dose naloxone (Narcan) might play a role in helping. I've heard hypotheses regarding glial inflammation as a sequela and the role of naloxone and I'm not sure if either is true.

Response:



Dr. Nath: Yes, we coauthored a [paper in Cell](#) last year showing microglial cell activation in Long COVID. I agree that anti-inflammatory agents need to be explored as a potential therapeutic in this condition.

Q. How does the spike protein affect nerve/brain cells and is there any evidence that the COVID vaccine would have the same effect?

Response:

Dr. Nath: This would be highly unlikely. The amount of protein produced by the vaccine is so small and in a localized area at the site of injection that it would not be expected to reach the brain.

To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research> 
- 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/>
- For medical/scientific terminology: <https://medlineplus.gov/healthtopics.html>