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Post-COVID Syndrome

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Author: Liz Sutherland, ND

Liz Sutherland, ND had the pleasure of interviewing Heather Zwickey, PhD for the JRM Digest.

Dr. Zwickey earned her doctorate in Immunology and Microbiology from the University of Colorado Health Sciences Center with a focus on infectious disease and vaccine development. She then went on to complete a postdoctoral fellowship at Yale University where she worked on immunotherapy for cancer. Dr. Zwickey was recruited to the National University of Natural Medicine in Portland, OR, where she launched the Helfgott Research Institute and established the School of Graduate Studies, developing programs in integrative medicine research, nutrition, and global health among others. She currently leads an NIH funded clinical research training program focused on training the next generation of integrative medicine researchers. Dr. Zwickey also teaches nationally and internationally.

LS (Liz Sutherland): Would you please explain what post-COVID syndrome is?

HZ (Heather Zwickey): This is an excellent question because it turns out post-COVID syndrome has several variations. Post-COVID syndrome refers to any long-term symptoms that remain when the infection is over. There's a less severe form of Post-COVID syndrome that involves chronic depression and fatigue, which seems to affect around 30% of people who have had COVID. But there's also a more severe form that affects about 10% of people who were infected. The more severe form manifests as difficulty breathing; joint pain; chest pain; and brain, memory, and sleep issues. Some people also have ongoing loss of taste and smell. Data suggest that 70% of people who have had COVID have some sort of long-term symptoms, which they don't necessarily report because they aren't debilitating.

LS: Are there any known common factors among people who suffer from post-COVID syndrome or that seem to determine whether it's the more severe or less severe form?

HZ: There doesn’t seem to be. To date, we have not seen a gender difference. It is more common in adults over

50, but data from the UK indicate that 26% of people in their twenties and 30% of people in their thirties are suffering from post-COVID syndrome, suggesting that age is not necessarily a factor. You might think that people who experienced severe COVID symptoms are more likely to have more severe post-COVID syndrome. But again, we see shortness of breath, chest tightness, joint pain, and muscle aches in people who had asymptomatic infection. So, it doesn't have a strong link to whether you had an asymptomatic or severe case of COVID. However, we do know that individuals with underlying health conditions, particularly cardiopulmonary issues and hypertension or diabetes and obesity are more likely to have the more severe form of post-COVID syndrome.

LS: Is there any connection between the severity of intervention that a person received for COVID infection and long-term sequelae?

HZ: It's not unusual to see longer term effects from some of the treatments. If a person was placed on a respirator, they are far more likely to get long-term sequelae, both physical and psychological. Psychological sequelae such as depression, anxiety, and even pain are commonly caused by proinflammatory cytokines. Intubation itself causes inflammation, and it takes a long time for that inflammation to heal. The issue is, if it’s similar to other coronaviruses like SARS and MERS, these post-COVID syndromes could end up lasting a very long time.

LS: Given that previous coronavirus like SARS and MERS affected a much smaller number of people, what can we learn from them regarding post-COVID syndrome?

HZ: They did affect a much smaller population, but we do know that 40% of people in Hong Kong who survived SARS experienced chronic fatigue for three to four years following their infection. This was not something that had an impact for only a couple of months. Those SARS survivors actually met the criteria for chronic fatigue syndrome. We may see the same thing with this SARS-COV-2 virus. We just don't know yet.

LS: Is it known how soon after the initial COVID infection resolves that sequelae show up?

HZ: It's variable. For some people, it happens the next day. For other people, it shows up a month later out of the blue. Those people often think they have been reinfected because the symptoms are so similar: shortness of breath, tightness in the chest, fatigue, and chills, but they do not test positive for the COVID virus.

LS: It's not uncommon for viral infections to have lingering sequelae. Is post-COVID syndrome different because of the severity and variety of ongoing symptoms?

HZ: Yes, the severity and variety, but also the frequency. For example, flu, Epstein–Barr, Ebola, and some other viruses cause long-term sequelae in some individuals, but those viruses don't have that effect in 30% to 70% of the individuals they infect.

LS: Is there a correlation between the damage caused when the virus initially attacks and the subsequent symptoms of post-COVID syndrome?

HZ: Potentially. At least for the lung symptoms. We know a severe inflammatory response happens in the lungs, which leads to a variety of downstream effects like thrombotic microangiopathy and oxygen deprivation. In some people, even people who only had mild COVID symptoms, it's thought that organ damage in the lungs, heart, brain, or kidneys causes the phenomenon of silent hypoxia, hypoxia that people don't even realize they are experiencing. That organ damage contributes to the inflammatory response, which manifests as part of the post-COVID syndrome.

LS: Some percentage of people who had severe COVID infection make autoantibodies to their own immune system. Is there something unique about the SARS-COV-2 virus that triggers this, or could it potentially happen with any viral infection in susceptible people?

HZ: We know that infections are a common trigger of autoimmune disease. People will often show up with autoantibodies post any infection if they are predisposed. If they have cells that have escaped immunological tolerance and can be activated by a bystander effect mechanism, then any infection can trigger an autoimmune reaction. It's not unique to SARS-COV-2. What is unique is that we're measuring it, because we're measuring everything in these folks right now.

LS: How closely would you recommend that doctors monitor their patients after they've had COVID-19 infection?

HZ: This is a really interesting question right now because your immune system is designed to try to shut down those autoimmune reactions. If you have enough TGF-beta production in your gut, those autoimmune reactions will be self-limited. They'll show up, but within a month, they'll be gone. On the other hand, for people who do not have enough TGF-beta and who are unable to resolve a specific immune response, this could lead to long-term autoimmune disease. We are in a unique situation where all of a sudden we have these predictive autoantibodies showing up. In some cases, predictive autoantibodies appear 10 to 15 years prior to the development of autoimmune disease. Some people will ultimately resolve and never go on to develop autoimmune disorders. I'm sure these patients will be followed, but the question is should everybody be followed, because anyone potentially could be at risk for autoimmunity post-SARS-CoV-2.

LS: And there's no way currently to test for any markers of who is likely to be more susceptible?

HZ: No, unfortunately the way that we test for these things is literally to look at each autoantibody for each autoimmune disease. It would be incredibly expensive to do that for the 15 million people who have so far been infected.

LS: I'm taking from what you're saying that one of the ways to promote TGF-beta production is to have a healthy gut microbiome. Is that correct?

HZ: Very true. Healthy microbiome, vitamin D, and vitamin A are our TGF-beta promoters. We now have an incredible opportunity to focus on what promotes the health of the microbiome, because it is critical to the health of patients surviving COVID-19.

LS: Would it be dangerous to give a COVID vaccine to somebody who had post-COVID syndrome or who might be on their way to developing it?

HZ: That's a great question. The current recommendation is that even people who have had COVID should get a vaccine, because we don't know how long-lived their immunity is from the infection. But if somebody is sick with post-COVID syndrome, I'm not a physician, but I think it's very rational to not give them a vaccine at that period of time. We know that the current vaccines from Moderna and Pfizer are stimulating a very strong immune response. Stimulating a strong immune response in somebody who already has an inflammatory reaction is only going to make them feel worse.

LS: Regarding the methodology of the vaccine trials, at least the Pfizer and Moderna trials, a participant is tested for COVID infection only if they show symptoms. This would potentially leave a number of people who have asymptomatic infections, which we know is not uncommon, unaccounted for. Doesn’t this mean that declarations about vaccine efficacy are potentially inaccurate?

HZ: You're absolutely right. We are not accounting for people with asymptomatic infections. The way they're determining who has an infection post-vaccination is who shows up with symptoms and goes on to be tested. If you have an asymptomatic case, hopefully the vaccination will reduce the severity and length of infection, that's what it’s designed to do, but it will not make it so that you cannot transmit the virus.

LS: Perhaps accounting for the impact of asymptomatic infections is one of many more pieces of data that will be clarified once the vaccines are available in the real world?

HZ: True. And that's common for vaccine studies. Another thing that's common for vaccine studies that may not be clear to people is that we usually can't tell the rate of adverse events until we have a huge number of people who've been vaccinated. The fact that we're seeing very low adverse event rates right now is not unusual. Most vaccines have an adverse event rate of less than 1%. When hundreds of thousands of people are vaccinated, then we start seeing more adverse events. We don't see a lot of adverse events when we're doing trials with 25,000 and 40,000 participants.

LS: In addition, children and pregnant women are excluded from these trials, so any impact of vaccinating those populations isn't known yet.

HZ: That's true.

LS: I'd intended to ask if you had a choice of the Pfizer, Moderna, or Oxford-AstraZeneca vaccine, which one you'd choose for yourself, but unfortunately, problems have recently come to light with the Oxford-AstraZeneca study. In any case, I'll just throw that question out to you: Do you feel like you have enough information at this point to say which one of these vaccines you'd opt for?

HZ: The published data from Pfizer show that their vaccine induces a T-cell response, as well as interferon gamma production. This is what you need to fight an infection. I know everybody talks about antibodies, but antibodies are short lived. The IgG antibodies that we're seeing post-infection should go away in six weeks to eight weeks. That's normal. The half-life of IgG is 23 days, so 46 days later, it's gone. You need T cells for long-term immunity. So far, only data from the Pfizer trial shows a T-cell response. Neither the Moderna or AstraZeneca trials have reported a T-cell response.
The AstraZeneca vaccine uses the same adenovirus strategy that was used in the nineties in an attempt to develop HIV vaccines. Using the adenovirus vector for HIV caused problems. The adenovirus started targeting different tissues, because of course it's a virus, so it can mutate. I like the AstraZeneca vaccine because it doesn't have additives. Using a live viral vaccine means you don't have to add preservatives. By contrast, the Moderna and Pfizer vaccines use lipid nanoparticles for their adjuvant. This is why people are experiencing pain and a strong inflammatory response post vaccination. This happened in the placebo group as well, indicating it's not due to the mRNA, but the lipid nanoparticle adjuvant.
I'd prefer not to use a lipid nanoparticle adjuvant, but given the situation right now, if I were making a decision today, I would probably go for the Pfizer vaccine. Six months from now, that could change. I think there will be more vaccines on the market, and we will know more about long-term immunity and potential vaccine sequelae. We're in month three of a two-year trial for the Pfizer vaccine and month two for the Moderna vaccine. We just don't know what the results are going to be yet.

LS: Before we go, is there anything you would like to add about post-COVID syndrome or the vaccines on the horizon?
HZ: Regarding COVID infection in general, there is new data showing it can cause male sterility. I bring this up because I know there are a number of people who advocate for the path of developing natural immunity or herd immunity to COVID. But because of our vulnerable populations, because of post-COVID syndrome, because we don't yet know the long-term effects of autoimmune disease induced by this virus, and because of the new data about male sterility, I don't support the philosophy of let's just let everybody get COVID.
LS: That's a very important clarification to make. Dr. Zwickey, thank you so much for your time and for this highly informative interview.

ADDENDUM

Dr. Zwickey wishes to clarify a statement made in this interview. Because some COVID patients may actually have too much TGF-beta, she advises physicians to think in terms of **balancing cytokines** rather than

promoting TGF-beta. Vitamin D, in fact, is important for cytokine balance.

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