

Good afternoon. I'm Commander Ibad Khan, and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Risk Communication Branch at The Centers for Disease Control and Prevention. I would like to welcome you to today's COCA Call, Treating Long COVID: Clinician Experience with Post-Acute COVID-19 Care.

Free continuing education is offered for this webinar. Instructions on how to earn continuing education will be provided at the end of the call.

In compliance with continuing education requirements, CDC, our planners, our presenters, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planners have reviewed content to ensure there is no bias. This presentation will not include any discussion of the unlabeled use of a product or a product under investigational use. CDC did not accept commercial support for this continuing education activity.

At the conclusion of this session, participants will be able to accomplish the following: Identify signs and symptoms of long COVID which occur after the acute phase of SARS-CoV-2 infection, identify potential multidisciplinary teams for patient care, describe common challenges to post-acute COVID-19 care, and finally, describe examples of patient-centered, interdisciplinary, post-acute COVID-19 care.

All participants joining us today are in listen only mode. After the presentation, there will be a Q and A session. You may submit questions at any time during today's presentations, and to ask a question using Zoom, click the Q and A button at the bottom of your screen, then type your question in the Q and A box. The video recording of this COCA call will be posted on COCA's webpage and available to view on demand shortly after the call ends. If you're a patient, please refer your questions to your healthcare provider.

And, for those who may have media questions, please contact CDC media relations at (404) 639-3286 or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA Call. We are pleased to have with us Lieutenant Commander Alfonso Hernandez-Romieu who's part of CDC's COVID-19 Response on the Clinical Team, Late Sequelae Unit. Our second presenter is Dr. Jennifer Possick, who's an Associate Professor in the Pulmonary, Critical Care and Sleep Medicine Section as part of the Department of Internal Medicine at Yale University School of Medicine, and our third presenter is Dr. Allison Navis, who's an Assistant Professor in the Division of Neuroinfectious Diseases, as part of the Icahn School of Medicine at Mount Sinai. I would now like to turn it over to Lieutenant Commander Hernandez-Romieu. Please proceed.

All right. Can everyone hear me?

Yes, sir. We can.

Okay. Great. So, good afternoon, everyone. My name is Alfonso Hernandez. I'm the infectious disease physician and epidemic intelligence service officer working with the COVID-19 Late

Sequelae Unit. So, I'll be giving a brief introduction to long COVID where we hear from our two wonderful speakers on their clinical experience managing patients at post-acute COVID clinics. Next slide.

So, as reports of long term COVID-19 symptoms emerged, the need for scientific research about long COVID has intensified. I'm sure you've seen reports like some of the ones shown on this slide describing patients with ongoing and sometimes debilitating symptoms many months after acute SARS-CoV-2 infection. The published medical literature by comparison is still scanned, but is growing rapidly. In both the medical literature and press use a wide variety of means to describe this issue, and we've heard the need for standardized terminology and definitions. Next slide.

However, long COVID may overlap with other complications of acute COVID-19 illness, making it hard to define because the spectrum of COVID-19 severity varies, it can be hard to differentiate between the long term effects specific to SARS-CoV-2 infection from those that occur in other illnesses. For example, people hospitalized for severe COVID-19 may develop a range of long term consequences from acute illness, such as nosocomial infections and deconditioning, especially those who have been in the intensive care unit. In addition, critical illness in general can lead to long term complications, commonly referred to as the post ICU syndrome.

SARS-CoV-2 infection can also lead to specific complications like stroke, Guillain-Barre Syndrome, and multisystem Inflammatory disorder which can cause prolonged symptoms and disability. Now, this Venn diagram is just an example of a framework for thinking about these long term effects, and more work is needed to further define them. The CDC is collaborating with the National Institutes of Health, the World Health Organization, among others to define and understand long COVID. So, with this framework in mind, I'll introduce some of the scientific work that has been done around long COVID. Next slide.

So, based on information available so far, persons with long COVID often present reporting persistent severe fatigue, headaches, and brain fog which is defined as mild subjective cognitive impairment, approximately four weeks after acute illness, and reports from clinicians have highlighted that long COVID may be independent of acute illness severity. Next slide.

The most comprehensive longitudinal data is from a recently published Chinese cohort. Among 1,733 patients, 3/4 of patients hospitalized with COVID-19 have at least one ongoing symptom six months after their acute illness, with 63% endorsing fatigue and muscle weakness, 26% sleeping difficulties or dyspnea, and 23% anxiety or depression. Next slide.

In that same study, one in five patients who did not require supplemental oxygen during their hospitalization had decreased lung function at six months, with decreased lung function defined as below normal six minute walk test depicted on the left or impaired gas exchange with the diffusion capacity for carbon monoxide less than 80% predicted on the right. The proportions of patients with decreased lung function increased in proportion to the severity of acute disease. Next slide.

And, prolonged symptoms are common in patients with mild COVID-19 disease not requiring hospitalization. In three studies that focused on people who were not hospitalized for COVID-19 in a post-acute COVID clinic in France, and telephone surveys of patients in the Faroe Islands in Switzerland, anywhere from 35% to 54% of patients had persistent symptoms after two to four months. Half to 3/4 of patients attending the post-acute COVID clinic in France endorsed new symptoms not initially present or symptoms that reappeared after initial resolution. In addition, 9% of patients in the Faroe Islands study reported persistent severe symptoms at four months. Next slide.

Now, another important finding among patients attending the post-acute COVID clinic in France was that more than 1/4 developed new neurological signs and symptoms after their acute COVID-19 illness. These included but were not limited to cognitive dysfunction, balanced disorders, paresthesia, and swallowing and speech disorders. Next slide.

So, to summarize, first, new or prolonged symptoms may occur beyond four to six months among patients with COVID-19, regardless of severity of acute SARS-CoV-2 infection. Second, in addition to respiratory symptoms, initial reports highlight the high prevalence of fatigue and muscle weakness, sleeping difficulties, depression and anxiety, and neurological symptoms. Now, the studies I presented are limited by the absence of measures of pre-COVID functioning and health in the patients they evaluated, so incorporating pre-COVID health status in future studies may improve our estimates of symptom frequency in organ dysfunction. Third, it is important for providers evaluating patients to perform baseline and serial comprehensive reviews of systems and physical exams to detect new or recurrent manifestations in patients with possible long COVID and improve its medical management.

Our speakers on this call will share their experience with diagnostic testing and treatment of patients, and finally, there's still a lot we do not understand. We must remember that empathy towards and validation of patients suffering from long COVID is essential. Next slide.

Now, before we move on to our guest speakers, I want to highlight that CDC is involved in a multi-pronged approach to understand and characterize long COVID through cohort studies, administrative data and chart reviews, and clinician engagement among others. We have information on our website for clinicians and the general public as shown on the two links on the right part of the slide.

And, I have added some resources and the main references used for this presentation at the end of the slides. And, that is it. Thank you for your attention. And, I think so now we'll move on to Jennifer Possick. I think we need to advance a couple more slides.

Thank you, Alfonso. So, my name is Jennifer Possick, and I thank you for the invitation to be part of this panel today. So, as a pulmonologist, I'm going to admit up front that my glasses have a very specific lens that come from a pulmonary and critical care background. As you'd expect, the clinic at our center has focused on patients with persistent respiratory symptoms and investigating the potential long term pulmonary sequelae from COVID-19, but this is embedded in the larger context of generally trying to help these survivors return to health in partnership with other subspecialists and multidisciplinary partners. Next slide.

So, my objectives today over the next several minutes, I'll review our current understanding of post-COVID-19 respiratory systems and sequelae. I'll explain how prior experience informed our initial approach to post-COVID pulmonary assessment. I'll share our framework for evaluating these patients in the context of a pulmonary specialty clinic, and discuss how our initial observation are shaping the next steps we take. Next slide.

So, this is a typical patient. I met him last summer. He's a 50 year old man who was previously fit and very active. He was admitted with COVID-19 in May 2020 and developed hypoxemic respiratory failure. He required high flow nasal cannula but did not require intubation. He was hospitalized for a few weeks and spent a few weeks more at short term rehab.

Once home, he was thankfully able to wean off of supplemental oxygen in about a week or two. Our initial visit together was in the summer of 2020. At that point, he was better but still very symptomatic. The CAT scan pictured above was performed at the time of his initial outpatient pulmonary consultation and shows persistent ground glass infiltrates as well as mild fibrosis, but it was improved from the imaging performed during his acute hospitalization. Pulmonary function tests at that time showed severe restriction and diffusion impairments but normal oxygen saturation both at rest and when walking.

He had another short term follow up scan a few months thereafter that showed clearance of the ground glass infiltrates. He did not receive any additional systemic corticosteroids. And, that that point, he had really minimal residual fibrosis on his scan, and his pulmonary function tests had shown improvement. However, though his symptoms had definitely improved from time of discharge, he still had dyspnea and fatigue that were both limiting his return to work and hobbies. He also, at that point in the fall, began to disclose issues with memory and concentration impairment and worsening of anxiety and depression. Next slide.

So, as already discussed, post-COVID symptoms are very common. As shown here, the majority of hospitalized patients report persistent symptoms one month out, and as we now see in longer than that. Most people have multiple symptoms simultaneously. In our experience, as referenced earlier, the dominate symptoms may actually shift over time as you follow people longitudinally.

Though the symptom complexes vary from person to person, dyspnea, fatigue, and exertional intolerance are among the most common reported and are significant obstacles to resuming usual activities. The previously discussed Lancet study indicates that a quarter of people will continue to report dyspnea in particular six months post infection. Though most of the data published has focused on individuals who required hospitalization, the limited studies of people with more mild acute illness indicate the potential for post-COVID symptomatology that is nearly indistinguishable from those with more severe disease. And, this has been our anecdotal experience as well. Next slide.

So, in addition to appreciating the high burden of post acute phase respiratory symptoms among the survivors, early on in the pandemic, the concern arose in the pulmonary community about the potential for post-COVID pulmonary fibrosis. And, this is in part because amongst the SARS 2003 outbreak survivors, approximately 5% or less of those individuals developed persistent interstitial changes. This has been described as well in survivors of MERS and also among

patients with all cause ARDS. In COVID-19, persistent imaging abnormalities appear to be more common in patients with more severe disease which is not surprising. But, notably, more recent data, as referenced earlier, indicates that impairment in pulmonary function tests such as diffusion capacity and in functional testing such as six minute walk, impairments can be observed in those who did not have hypoxemia as a feature of their acute illness as well.

So, here I have images from a study that compared profiles of about 80 patients that had similar initial radiographic burden of disease but subsequently diverged in terms of short term radiographic and clinical recovery. The survivors who had persistent interstitial lung disease, which was about half in this cohort. Though it should be noted that this was just two months post acute illness, seemed to be associated with a signature of sustained inflammation which was loosely defined and included the serum markers like CRP, LDH, leukocytosis, and even elevated D-dimer. The sustained inflammation was seen not only in the acute phase of their disease but also post acute as well. There is some correlation observed with older age male gender and underlying comorbidity burden, but risk factors, potential interventions, long term prognosis is not at all known. Next slide.

So, though our prior SARS experience would hopefully suggest that potential post-COVID-19 pulmonary fibrosis would be restricted to a minority of patients, this is not yet known with COVID-19. These patients are a primary focus of a pulmonary subspecialty clinic like ours because our aim is to identify those cases early and intervene with pulmonary rehab, supportive care, and potentially disease modifying interventions with close followup. Though, treatment options are still at the exploratory phase. In addition, it's worth noting that there are other separate objective pulmonary sequelae that have been observed that weren't specific that are being monitoring like pulmonary emboli, with or without right heart strain and also acquired hemidiaphragm paralysis.

Pulmonologists are well prepared to manage those sorts of known entities with known pathways. However, again, the dominant pattern emerging, both anecdotally and in the literature seems to be a subset of patients with persistent, sometimes debilitating symptoms, including dyspnea and exertional intolerance despite the normalization of pulmonary function tests and thoracic imaging in the months following their acute illness. Though, for pulmonologists, dyspnea of unknown origin is a common referral and the ideal evaluation, treatment, understanding of risk factors, etiology, and prognosis for these specific patients in the wake of COVID-19 remains uncertain. So, it's a challenging issue that requires further investigation that will undoubtedly span multiple different specialties. Next slide.

In our opinion, pulmonary recovery from COVID-19 should be appropriately framed both in a multidimensional context, and it should be viewed over a longer time span. The survivors of other coronaviruses like SARS and MERS showed sustained reduction in physical function, quantified by measures like the six minute walk test, but in other dimensions as well, and most importantly in health related quality of life overall. Though this is a respiratory disease, this was driven by the respiratory symptoms in part but not exclusively. So, shown above is a mixed cohort of SARS and MERS survivors over a six months time period. And, you can see that though improvements were observed in the first six months, in many dimensions, people

experience multidimensional impacts on their life similar to or more pronounced than those who had other chronic health conditions.

Similar findings have been observed in the post-ARDS population as well. So, at one year, most initially observed pulmonary function tests or imaging abnormalities greatly improve or even resolve, but many patients will still demonstrate impairments in physical or cognitive or psychological function, what was previously referenced as post-ICU syndrome. This is even more pronounced after more complicated hospitalizations or for those who required advanced interventions, things like neuromuscular blockade, heavy sedation, high dose corticosteroids which notably some COVID-19 patients also receive. At five years, the same ARDS survivors can demonstrate persistent impairments in physical function and commonly report respiratory symptoms out of proportion to objective data. So, it's extremely important to bear these past lessons about a subjective/objective mismatch in mind when evaluating and counseling COVID-19 survivors with persistent symptoms and limitations. Next slide.

All this past and present experience factored into how we originally designed our clinic model and how we continue to modify it. In addition, there's a situational overlay that bears discussion when developing clinical models for post-COVID care. So, institutionally, this means integrating infection control considerations and adapting to resource strain associated with response to an ongoing pandemic. For a person, this includes issues like isolation from usual social supports, potential stigmatization, financial hardship, and the psychosocial strain of the numerous unknowns associated with this new illness whose story is unfolding in real time. Next slide.

So, I apologize for this extremely busy figure. This was our original clinic model launched in the spring, early summer of 2020 and recently published in Chest. But, to summarize the key points, the foundation of our clinic model is an in-clinic collaboration with physical therapy, respiratory therapy, pulmonology, and social work. We evaluate patients who have either been hospitalized with COVID-19 or who have respiratory symptoms persisting more than six weeks, regardless of disease severity.

A significant proportion of our patients were never hospitalized. Many are healthcare workers or essential workers. Though we utilize telehealth during the first surge, we've mainly transitioned away from that and are predominately relying on in-person evaluations with previsit triage guiding associated testing up front. Not all of our patients get pulmonary function testing. Most get repeat chest imaging, and some get selected lab work.

PT evaluation includes the six minute walk test, some basic strength testing, the sit to stand evaluation, and a dowel test. Our current patient PRO is the Promise Global Health Survey, but many were considered and would be applicable to this population. Visits for patients can be extremely long, and this is an ongoing focus for us as we revise our model. Beyond our in-clinic collaboration with PTRT and social work, we have ad hoc, arms length collaboration with multiple subspecialists, predominately neurology and cardiology. Enrollment of our initial 230 patients into a registry database has begun, and we have just started invasive CPAP or cardiopulmonary exercise testing for those with persistent, unexplained dyspnea and otherwise negative cardio and pulmonary workup in hopes of learning more. Next slide.

So, observations that are driving our next iteration. First is that imaging has been most helpful in those with abnormal pulmonary function tests or prior abnormal imaging. People with normal PFTs may not need repeat imaging at all. From a physical therapy perspective, most of our patients have benefited subjectively from some sort of structured program, whether that's at home, in rehab, or in pulmonary rehab.

But, the ideal rehab strategy for post-COVID remains unclear. Our current recommendations are following along with the recent ERS and ATS consensus statement recommending low to moderate exercise in early phases of recovery rather than high intensity. Social work has proven essential. In our geographic area, mental health resources are difficult to access. Wait times can be significant, and social work has helped to bridge this gap and address other important issues such as financial hardship, bereavement, and care barriers.

We did not anticipate how common neurocognitive symptoms would be in the patients that we saw, and so what started as a purely collaborative model with neurology evolved into the need for an independent neurology post-COVID program at our institution that launched at the end of 2020. Finally, you know, the subjective objectiveness vaccine in SARS and MERS is, again, being seen in this population, and I think that's to be expected. We are working hard to avoid over testing our patients, and we'll be analyzing our existing database to determine which elements of assessment seem the most helpful both to our patient's diagnosis and to their care plan. On balance, our earliest patients continue to slowly and steadily improve. So, for most but not all, supportive interventions may be the biggest yield, but it's important to identify those with even low frequency complications that need specific therapy, like interstitial lung disease. Next slide.

I'd just like to thank the CDC for this opportunity and also my home institutions of the Yale School of Medicine and Yale-New Haven Hospital. To my partners in the Section of Pulmonary and Critical Care and particularly in the Winchester Chest Clinic post-COVID-19 recovery program and our collaborators across both institutions and at other institutions as well. That's all for me, and I will hand things over to Dr. Allison Navis.

And, Dr. Navis, you might be muted. You might want to unmute your line. We will give Dr. Navis just a moment to unmute herself.

Hello. Sorry. Can you hear me now?

Yes, Dr. Navis. I can hear you. Thank you.

Okay. So sorry about that for technical issues. So, my name's Allison Navis. I'm the lead clinical neurologist at Mount Sinai Hospital in our Post-COVID Center, and we can just dive right in. I have a lot to go over today. So, next slide.

So, I wanted to kind of give an evolution or sort of a timeline of how, what we've been dealing with and how that's changed our approach to workup and management. So, for myself, in April 2020, I'm based in New York City, I was redeployed to serve as a medicine attending on a inpatient COVID service when we were getting hit really hard here. And then, after that, in May,

I served as a neurology consult attending and focused more on sort of the neurological symptoms we were seeing in the COVID patients who were admitted, including encephalopathies, stroke, ADEM, and Guillain-Barre Syndrome. I started in the Post-COVID Center in June, shortly after that, and I think when I started, we expected, you know, I did not expect neurology to be one of the top referrals, and I thought we would be seeing more of the hospitalized patients with moderate to severe COVID and sort of following the neurological symptoms that they had had.

But, in reality, we quickly realized that neurology was a top referral, along with pulmonology and cardiology. That the majority of patients had not been hospitalized or what have what we might call mild COVID, and that we were seeing a broad range of neurological symptoms in addition to non-neurological symptoms. Next slide.

So, initially, this brought up some concern for possibly a widespread neurological process. We know that the ACE2 receptor which COVID binds to to enter cells is not widely expressed in the brain, although it is expressed in the vasculature, and we have limited data on the neurological impact of COVID, but there have been some autopsy studies of patients who died of acute COVID that did show inflammatory changes in the brain.

There's been some evidence that COVID can affect the brain, but that seems to be very rare and less common than the inflammatory changes. But, based on, you know, the patients we were seeing initially in the Post-COVID Center, I started to be concerned that maybe COVID was more neurotropic than we had expected. And, I also want to keep in mind that, you know, we see a broad range of symptoms in post-COVID, but more, the more objective neurological syndromes like mononeuropathies, brachial plexopathies. Those are not what we see primarily there. So, I'm going to be discussing the other symptoms. Next slide.

So, an example of a post-COVID patient, a 42-year-old woman who was. [Inaudible Comment].

Dr. Navis, we seem to have lost you on the phone line again. Dr. Navis?

Can you hear me now?

I can hear you, yes. Thank you. Go ahead, Dr. Navis. You can proceed.

Dr. Navis, you might have muted yourself again. If you can hear me, Dr. Navis, can you unmute yourself, please?

Hello.

Hi, Dr. Navis, can you hear me?

Hi, yes. I'm so sorry. I keep getting logged out. Okay, I'll jump back into this. So, in addition to the cognitive issues that the patient was experiencing, she was continuing to work, although had to cut back her hours and was struggling with the work that she had to do.

She also noted physical fatigue that worsened with exercise. She had a tingling sensation throughout her body, but it was worse in her hands, and she also had heart rate elevations, palpitations, and shortness of breath. Next slide.

So, brain fog is one of the most common neurological symptoms that we're seeing. Brain fog is a symptom. It is not a diagnosis, and it means many different things to different people. Oftentimes, it's a combination of short term memory issues, concentration, or sort of word finding speech difficulty. There doesn't seem to be any clear correlation with the severity of COVID infection, age, or risk factors, meaning that we're seeing a lot of patients who had mild COVID, were not hospitalized. We're seeing a lot of younger patients and patients who were previously healthy. The symptoms often fluctuate, so patients will say they have good days where they feel like their normal self and bad days, and the fluctuations often correlate with worsening of other symptoms like fatigue or dysautonomia.

The impacts on life varies. So, some patients are able to continue working. It might be a little bit more challenging, but they haven't had to stop working. Whereas, others are out on disability. We're also seeing a lot of sleep changes, many patients with difficulty falling asleep or waking up frequently throughout the night, and we're also seeing a lot of mood symptoms, so many patients expressing depression, anxiety, or PTSD-like symptoms. Next.

So, initially, my approach to workup was quite broad. I did blood work for contributing reversible causes, neuroimaging, neuropsychological testing, EEGs if there was concern for seizure activity, EMGs for paresthesias if concern for neuropathy, and in rare instances, lumbar puncture. Next slide.

I think there's, oh, I think the slides are out of order, actually. So, this should have been two slides ago. In addition to the brain fog, we're also seeing these other symptoms as well. So, headaches are probably the second most common symptoms that we're seeing. They can, oftentimes they're described in different ways. They might be migraine sounding or a tension headache sounding, but they, many patients will say that it's sort of this constant pressure like sensation.

Maybe not too painful but then fluctuates in severity. And, many patients don't have a history of headaches, and now they do complain of frequent headaches, and others who have a history of migraines might know worsening of frequency and severity. We're also seeing paresthesia. So, a lot of patients complaining of tingling or numbness, sometimes burning sensation. It can be focal. It can be throughout the entire body, and sometimes alternating in locations, and more often, patients will say that it's a little bit worse distally in their extremities.

And then, the dysautonomia we're seeing. So, and objectively seeing fluctuating heart rates and blood pressures and subjectively patients complaining of lightheadedness, palpitations, and GI disturbances. And, as mentioned previously, most patients when they're coming in, they have multiple chief complaints. It's very rare someone comes in with just brain fog and they feel fine otherwise. Usually, there's multiple things going on. Next slide.

So, sorry. This is a little bit out of order. This should have been after the one previously.

But, after, our approach to workup, what we started finding with these patients was that, you know, most of the workup was coming back essentially normal. Neuroimaging I'll talk about in a second, but no widespread signs of damage. Neuropsych testing has been variable. We're really not seeing seizures in these patients and even the data and acute infection in hospitals, there's really not an increase in seizures. EMGs have been negative for neuropathy, but we'll talk about why that might be, and then when lumbar punctures are done, we're really not seeing major concerning changes there. Next slide.

So, in terms of neuroimaging, you know, we're really not seeing large, inflammatory, or infectious lesions. We're not seeing signs of what looks like encephalitis. We're not even really seeing many strokes. So, there was concern that, you know, maybe patients were having lacunar strokes and that could be contributing to some of these symptoms, but that's not common.

Now, when I say we're not really seeing anything, you know, concerning on the MRIs, that doesn't mean they all look perfect. We can see what's called white matter changes or microvascular ischemic changes. This is a very common image finding, regardless of COVID. As neurologists, you know, we oftentimes don't even think much about it. Most patients, especially as someone gets older or if they have high blood pressure, diabetes, even migraines come predisposed to white matter changes.

And, mild to moderate white matter changes can look like the first two pictures here. So, little periventricular changes, maybe some subvertical dots. We usually don't think of these as clinically significant, and they're not very concerning. If someone has severe changes, as shown in that picture on the right, that can be clinically significant, but we're really not seeing severe changes like that in these MRIs. And, I do think that we need to be a little cautious in attributing these image findings to COVID.

It's possible, since COVID can affect the vasculature. It could cause some white matter changes, but because they are so common, unless you have an MRI of someone right before they got COVID and after and it shows a change in the white matter, you really can't sort of draw that correlation. Next slide.

So, in terms of the cognitive test findings, we're seeing sort of a lot of things across the board. So, in younger patients, and that's usually like people in their 20s, 30s, maybe 40s, the results have oftentimes been within normal limits.

So, we're really not seeing, you know, major changes there, and that doesn't mean that, you know, they aren't experiencing cognitive changes, but if someone is especially, you know, high functioning at baseline, they can still have a decrease in their scores on cognitive changes that's, or on cognitive testing that's normal but might be a decrease for them. Some people we might see some issues with attention. It's possible that if they had, like, a mild ADD previously that that can be exacerbated. But, the results have been very reassuring for the younger patients. Now, for older patients, we are seeing some deficits, and it really varies in the areas we see them in.

So, it can be a memory, attention, processing speed, executive function. But, we're don't seeing a clear pattern, so I also work with patients with HIV, and we know that HIV can cause a

dementia, and that has sort of a very clear pattern that we tend to see. And, that's not what we're seeing here so far, at least, anecdotally. But, we are seeing changes, and again, this is a snapshot in time. So, we don't know what the cognitive test results were before, and they might improve with time.

But, there is a question of if COVID is causing these cognitive changes or especially if someone's older, maybe in their 60s or 70s, could there have been a little bit of underlying cognitive impairment prior to COVID that really got exacerbated or unmasked. The reports also comment on contributing factors and mood is something that they often comment on. So, again, we're seeing a lot of depression, anxiety, and PTSD, and that can absolutely worsen cognitive symptoms. Sleep, again, being another important factor in cognition. And, fatigue as well.

So, some patients, you know, they're extremely fatigued, and if you're feeling very rundown, you're not going to score as well on a cognitive testing, and so that could also be a contributor. But, I think it's important to highlight that brain fog does not equal dementia. Dementia is a neurological diagnosis, and brain fog is a symptom. But, we are seeing a lot of reassuring cognitive test results. That doesn't mean that these changes are not present and affecting these patients, but you know, we're not seeing patients who were previously high functioning coming in with dementia. Next slide.

So, what else might be occurring once we start getting these results back? How did our understanding evolve? Next slide.

So, could there be damage to the central nervous system? Possibly or absolutely. You know, we really don't know. There's no evidence to really support this on a large scale or refute it.

I think it's unlikely that there's widespread infection in the brain. There could be some inflammation. There could be a role of the vasculature playing into this, but we really don't know. Could the peripheral nervous system be affected? It absolutely could. It's much more vulnerable to systemic insult.

So, it's not protected by the blood/brain barrier. So, any inflammatory or metabolic changes can cause neuropathies, and we are seeing the presence of a small fiber neuropathy on some of our patients, and so that could explain some of the symptoms as well as dysautonomia and tingling. Other possibilities, so we started looking into, you know, whether a lot of these patients are having, like, a POTS-like syndrome or hyperadrenergic POTS due to excessive catecholamines, and then we started looking more into whether this is more of an MECFS-like process. Next slide.

So, I'm not going to go into all the specifics of small fiber neuropathy, POTS, and MECFS, but I wanted to like highlight the main symptoms that we usually associate with these syndromes, and you can see here that there is a lot of overlap between them.

So, brain fog is a common complaint in POTS and MECFS. You can get paresthesias, dysautonomia, fatigue, and so, you know, whether these are all independent syndromes or on a

continuum, you know, it's hard to say. But, this does show the sort of similarity between the patient symptoms that we're seeing and these other syndromes. Next slide.

So, the current approach to workup and management has evolved since then. Next slide.

And, this is how I've been approaching things. So, in terms of history, and I think it's very important to get an idea of all the symptoms that patients are experiencing and their correlation, and if multiple symptoms are present, does it fit into one of these other sort of broader diagnoses? I like to assess the severity of COVID, and if there were complications, I might be a little bit more keen to do a workup for those patients if they're extremely sick and hospitalized in the ICU. Older patients, patients with vascular risk factors or immunosuppression, I might do a little bit more of a workup on. Impact on sort of ability to work or daily living is important.

So, patients who do have those really good days, it's a little bit reassuring, more reassuring than patients who are, you know, completely disabled by these symptoms. As a neurologist, focal neurological deficits or symptoms are always something that we keep an eye out for and workup, and then I try and assess sleep and mood as well. Next slide.

So, what I've been doing, and this is not part of any sort of standard algorithm. This has been my approach is I check blood work on everyone. So, I get a TSH, vitamin B12 and vitamin D on all the patients. If there is severe cognitive deterioration or concern for dementia, I'll do sort of the broader cognitive workup, checking HIV, RPR, thiamine, and folate, and I'll check on hemoglobin A1c if there's concern for neuropathy. In terms of imaging, you know, ideally an MRI of the brain or a CAT scan of the head. I tend to push for imaging in anyone who had moderate to severe COVID, anyone who's over the age of 50 years old, anyone with medical comorbidities. So, vascular risk factors, immunosuppression.

Again, those patients who had a large impact on their work or ADLs, and then neurological deficits or focal deficits. And then, oftentimes, I'll consider holding images on the patients who had less severe COVID who are younger, otherwise healthy. And then, again, have those fluctuating symptoms. It's not that I never get imaging. You know, sometimes it's appropriate to still check, but I do think that it's probably safe to hold on imaging or not jump to imaging in those patients.

And, the neuropsychological testing has been quite helpful. It can be very reassuring for patients to see that, you know, they do not have dementia, that they're still scoring quite well. If it does show deficits, it can help, you know, highlighting other contributing factors, and sometimes, it can, you know, provide an approach to working with those deficits. So, it might show, for example, an issue with auditory memory versus visual memory. And so, they, you can work with patients to provide them tricks if they need to remember something, to maybe, you know, write it down and visualize it instead of just hearing it. Next slide.

EEGs, I don't tend to get too often, but if there is any concern for seizure activity, if there's episodes of altered consciousness, I would consider getting it. I'm really not getting any lumbar punctures unless there's very severe cognitive deterioration or other concerning neurological deficits. At the EMGs, again, they have been normal for most patients, and EMGs are normal in

small fiber neuropathy. They're not sensitive enough to pick up on those changes in the little nerve endings.

So, if you do want to confirm a small fiber neuropathy, a skin biopsy is needed. It can be helpful in giving you a diagnosis there, but it really doesn't change the overall management. So, oftentimes, you know, I'll discuss that with patients, but I won't push for it. And then, if you are concerned for POTS or some autonomic neuropathy, you know, autonomic function testing can be helpful. But, again, a lot of this stuff, it's appropriate, I think, to just treat symptomatically, and you don't necessarily need to jump to diagnostic testing.

And, I think it's overall okay to do a small focused workup. Again, we've done extensive workups, and they haven't really shown any actionable items, anything that would have changed our overall management. So, if resources are limited or if there is financial constraints, I think it's fine to just do a very focused workup. And then, you can always go back and do more testing if anything evolves or new symptoms develop down the road. Next slide.

So, in terms of sort of treatment, it's really symptomatic and supportive, and I know there's a lot of information on this slide. But, for brain fog, you know, we don't have treatments for cognitive changes, unfortunately. So, it's really addressing any abnormalities in blood work that could be contributing, addressing those other contributing factors like sleep and mood which I'll talk about in a second. If attention is a major issue, you know, medications that can help with attention might be needed. We do have a cognitive rehab here which has been extremely helpful, although I know that's not a resource that's available everywhere.

But, if it is available, it's something to consider. In terms of the dysautonomia, we've been recommending that everyone increase their hydration to two to three liters of water a day, increasing salt intake, or at the very least maintaining, not avoiding salt, electrolytes, and compression stockings. If there's a sympathetic nervous system, you know, component or excessive catecholamines, you're seeing, you know, tachycardia, palpitations, meditation and breathwork can be quite helpful in sort of quieting the sympathetic nervous system down. For POTS, you consider adding in midodrine or fludrocortisone or if they're, you know, getting hypotensive, for the hyperadrenergic POTS, a beta-blocker can be quite helpful. For the small fiber neuropathy, it's addressing any other abnormalities that could be contributing, and we've had patients who develop diabetes after having COVID.

So, it's important to still work those up. And then, it's really just symptomatic treatment. So, you know, gabapentin, pregabalin, your tricyclics, duloxetine to try and ameliorate the symptoms. And then, addressing dysautonomia if it's present. And, in terms of the fatigue, I am not an MECFS doctor, and that could be a whole lecture on its own, but the one thing I do want to highlight that we have been telling all of our patients is, you know, in terms of exercise or exertion to really limit it and to do sort of a pacing of exercise.

So, very low impact, short duration, with gradual increases. Don't do anything that causes you to feel worse afterwards or causes a post exertional malaise. And, we've really sort of moved away from this idea of, you know, reconditioning people. Next slide.

Other critical factors. So, sleep is extremely important. First and foremost is always addressing sleep hygiene, so making sure they go to bed at the same time. You know, no phones or TVs in bed. If that doesn't work, you know, sleep aids can be very helpful. I usually go with melatonin or valerian root first, and then you can kind of escalate from there if needed.

If there's paresthesias or headaches also present, then sometimes gabapentin or amitriptyline or a tricyclic can be helpful, and I think it's important to also assess for sleep apnea. And then, I just want to highlight the importance of mental health aspects. I think it's extremely important to address those, to not be dismissive of them, but also not, you know, attribute everything to it. A lot of patients do have depression and anxiety that's secondary to these ongoing symptoms, and I think that's extremely understandable. However, we do know that depression, anxiety, and PTSD can affect cognition and other symptoms, and that is something we can act on, and hopefully, improve those symptoms. I do not start antidepressants for depression, but if someone has some concurrent paresthesias or headaches, things like duloxetine or venlafaxine can be very helpful for that. They also can be activating so they can help a little bit with the fatigue component as well. Next slide.

So, in conclusion, again, apologies for the technical issues today, but we're seeing a lot of different neurological symptoms in these patients, and I hopefully highlighted that I think it's important to get a broad history to try and see if there's a larger diagnosis that might emerge instead of getting too much tunnel vision on one specific symptom. So far, the diagnostic workup has not really shown much, and I think that's reassuring, but you know, I think it's okay to do less of a workup and then you can always add on later if needed and not over interpret things like imaging.

I think it's important to stress that we do not have medications to cure neurological damage, so a lot of the treatment is going to be symptomatic and supportive, and the multidisciplinary approach is really critical. I could not do all this by myself. The [inaudible] department, PMNR department, pulmonology, cardiology, and we have an MECFS expert that works with us. They have all been absolutely critical. And, while we don't know what's causing these symptoms, they are very real for patients, and we are seeing patients get better.

I think it's important to reassure them of that while still supporting them in their journey. Thank you.

Thank you very much. Presenters, I want to thank you for providing our audience with such useful information. We will now go into a Q and A session. Please remember you may submit questions through the webinar system by clicking the Q and A button at the bottom of your screen and then typing your question.

Our first question asks, "In your clinical experience, do the pulmonary pathological changes occur simultaneously with neurologic changes, or are they parallel events, or does one usually follow the other?"

This is Jennifer Possick. I would say that one of the hallmarks of caring for people with this condition is the heterogeneity. So, people, of course, who present to us are presenting primarily

because of respiratory symptoms, and the people who have had both, who have experienced both neurologic and respiratory symptoms, regardless of order or time, of course. You know, we talked a lot with those people to try and understand. And, certainly in some cases they seem to be concomitant, and in some cases, there may be some sequentiality to it, but what patients have revealed to me, too, is that it's very difficult for them to track the presence or absence of a symptom when they're experiencing so many at once.

And so, if initially shortness of breath is really the most limiting and frightening symptom, then that's the one they focus on and perhaps report the most. As that, perhaps improves, then other more subtle symptoms become more evident. And, I don't know that I believe that it's because they are occurring later, but maybe the appreciation of them is emerging later, if that makes sense.

Thank you very much. Our next question asks, "Can the presenters please share from their experience the prevalence and characteristics of long COVID in children and adolescents?"

This is Allison. I'll just say that I don't think I can give the prevalence since I don't see children, but we're definitely seeing similar symptoms. I do think it is sort of the long COVID symptoms are present in the pediatric population. I have received emails from pediatricians sort of asking about the neurological workup and treatment for them. But, I, unfortunately, I can't give a prevalence.

Hi, and this is Alfonso from the CDC, and yeah, I think that is a really crucial question. We are actively gathering data on the issue, and we can't really give a prevalence. I don't even think we could give a prevalence for adults at this point. But, we are actively looking into this.

Thank you very much. Our next question asks, "Have you seen any association in long COVID with any pre-existing conditions or any underlying medical conditions that patients had prior to developing COVID?"

This is Allison. I'll say on the neurological side, there doesn't seem to be any correlation. We have very, a lot of patients who are young, previously healthy, and if anything, I think that's been the more noticeable thing is that we're not seeing patients, you know, with prior vascular risk factors and, you know, things that could be more concerning for strokes or other changes in the central nervous system. But, the many patients were previously healthy.

This is Jennifer. I would echo that. I think we don't really know yet. It's like, you know, we're still very much in the exploratory phase, but you know, speaking purely from the standpoint of a practice that cares for a lot of people with a lot of different types of chronic pulmonary disease, nothing has really, clearly emerged anecdotally and we have had people within the practice with a variety of chronic pulmonary diseases who have contracted COVID and recovered, and even amongst them, the outcome is very variable. So, I think there's still just very much more to learn.

Thank you. Our next question asks, "Do you see a decrease in incidents of long COVID symptom or syndrome in patients that have been treated with remdesivir and/or monoclonal antibodies, or is that not the case?"

This is Jennifer. Again, I don't think we know the answer to that question. I think, you know, the aim of people who are trying to create registries and studies of patients experiencing these symptoms is in part to understand questions like that. You know, we are gathering data on treatment histories amongst people that we see in our program and hope to know more as time goes on.

Thank you. Next question asks, "Have you observed long COVID symptoms in patients that are, that were COVID positive but otherwise asymptomatic?".

This is Allison. Yes. I have. I think that is definitely a smaller percentage of patients, but I've definitely had patients come in who were antibody positive, never had any clinical illness and coming in with various sort of similar neurological symptoms, paresthesias, fatigue, cognitive changes. So, it does seem to be possible, but at least anecdotally seems to be a smaller percentage.

Thank you. And, we have time for one more question, and it's sort of a two-parter. The question asks, "What kind of post-COVID follow up do you recommend in light of your clinical experience with long COVID, and what are some recommendations specific to cardiopulmonary rehab for patients for increasing their functional?"

This is Jennifer. I think that there's no single model for that, and I think one of the challenges given the scope of the pandemic and the number, sheer number of people affected is marshalling enough boots on the ground resources to see people and address these issues. And, you know, quite frankly, we see people much more frequently than our original model outlined, and because we aren't able to see as many of them as frequently as they need in the clinic, we do a lot of communication with them outside of the format of a formal clinic visit in collaboration with other people. I think that, you know, as I said in my talk, I think the optimal strategy for rehab for people who have experienced COVID-19 is not as, is not a known entity, and I think that because post-COVID symptoms are not a single entity either, there are likely to be many different kinds of rehab that are needed for patients with different symptom complexes and clinical courses. And, that's why the collaboration across all these different disciplines is so important to quickly build a body of knowledge and construct a plan from there.

Thank you very much. At this point, I want to thank everyone for joining us today with a special thank you to our presenters, CDC's Lieutenant Commander Hernandez-Romieu and our guest speakers Dr. Possick from Yale and Dr. Navis from Mount Sinai. All continuing education for COCA calls are issued online through the CDC Training and Continuing Education Online System at <https://tceols.cdc.gov>. Those who participate in today's COCA call and wish to receive continuing education, please complete the online evaluation by March 1, 2021 with the course code WC2922-012821. That access code is COCA012821. Those who will participate in the on demand activity and wish to receive continuing education should complete the online evaluation between March 2, 2021 and March 2, 2023 and use course code WD2922-012821. The access code is COCA012821.

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Again, thank you for joining us for today's call, and have a great day.