Transcription: Long COVID and PI

Emma Mertens: Alright, everyone. It is seven PM eastern, so we're gonna go ahead and get started. Good evening, and welcome. Thank you for joining us as we continue the immune deficiency foundations twenty twenty six education series. Our featured speaker for this evening is Dr.
Manish Butte, who joins us to discuss primary immunodeficiency and long COVID-nineteen. My name is Emma Mertens, and I'm the Program Manager for Education here at the Immune Deficiency Foundation. On behalf of the organization, we thank you for tuning into this virtual event. Throughout this series, guest speakers will provide a deep dive into clinically advanced topics from the world of PI. If time permits, the session will be followed by a Q and A with our presenter.
In offering these programs, we aim to engage and empower the PI community through education. During portions of tonight's talk, we will offer audience polls. When a question pops up in your screen, you may submit a response by clicking one of the presented options. As always, closed captioning is available. This webinar is made possible by our wonderful sponsors.
It is due to their partnership and contributions that we can offer programs like this for the PI community. Please join me in thanking our sponsors. Before we get started, a brief disclaimer. Please remember the information shared during this meeting is not intended to be a substitute for medical advice, diagnosis, or treatment. We are here today as a trusted source and friend to provide you with information.
Always seek the advice of your physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice or delay seeking it based on information presented during an educational event. Alright. We're going to kick things off by asking you to answer a quick question using our Zoom polling feature. We'll give it about thirty seconds for everyone to answer, and then we're gonna ask the same question after Dr.
Butte's talk and we'll see how your knowledge has changed. Alright. We have a good mix of answers in the in the mix here. Alright. And with that, I'm so pleased to introduce our speaker for this evening.
Manish Butte is an Indab professor of Pediatrics and Division Chief of Immunology, Allergy and Rheumatology at UCLA. He sees both pediatric and adult patients living with rare immune deficiencies through the UCLA immunology and immunodeficiency clinic. Through his lab, researchers work to better understand the immune system and improve treatments for immune dysregulation, autoimmunity, and cancer. Welcome and thank you for joining us, Dr. Butte.

Dr. Butte: Thanks Emma, and thanks everyone for joining. I'm Manish, as Emma said, and I'm really happy to be here. I've been unfortunately gotten the rest for twenty hours a couple weeks ago, and I am still getting over it. And I know many of you in the audience know exactly what this is like. This is like it's not common for me to have a post viral asthma, but I hear I am.

And so, please bear with me if I have to cough once in a while. I I apologize. I I I think whatever I had is it wasn't fluid, well, it wasn't COVID, it wasn't RSV, but it was a doozy. And and so I hope those of you at home don't don't get this one. So I'm gonna open up my slides here and get started here.

So all of you should be able to see my slides. And I'm going to talk about Long COVID today, a topic that I know was much more interesting to all of us a few years ago, but continues to have a lot of interest for our audience with primary unit deficiencies. And continues to make the news as people suffer with long COVID. Now years after the original pandemic, we're still seeing patients with this and still struggling to understand how we can treat it effectively. So are there no relevant disclosures related to long COVID?

I don't wanna work on long COVID right now in my lab or with any funding or conflicts. Gonna start by giving you the take home points. I think this is potentially a complicated topic. I'm gonna try to make this really as simple as possible that because I do think we've learned a lot about long COVID and the immune system over the last few years. I'm gonna try to give you those key take home points, so you really leave this talk understanding something about long COVID.

Lung COVID means that you have at least sixty days of symptoms, and it has to be so sixty days after the COVID infection, and it has to last for at least three months. This is typically much more than three months or two months, but actually a year to a year and a half of symptoms. The average is fifteen months based on surveys. So people who do get this long consequence of colitis, are not getting over that quickly. It takes over a year in some cases. Now, as I'll show you the statistics, the frequency of the symptoms goes down and down and down. So, most people have resolved solved their long COVID symptoms by the time you get to a year and a half, that's of course really good news. One of the major risk factors we've learned about who gets long COVID and the severity of long COVID is the severity of the original COVID infection itself. Those who have bad COVID infection and have been a hospital with oxygen in the ICU, etcetera, those patients tend to have more serious long term consequences as well. So probably the most important risk factor is the severity of COVID infection.

We don't know how many people have long COVID. Surprisingly, the overlap of symptoms and the nonspecific symptoms is makes it really hard to nail down who has long COVID. But The estimates based on surveys is that about one out of every twenty people is suffering from some degree of post COVID, post acute infection symptoms for months or

years after the infection. One thing we do know is that females have more symptoms and mails that I'm gonna show you that have some data to support that in a little bit. The most common symptoms that people complain about in the long COVID are fatigue, cognitive problems, including brain fog, and then exercise intolerance, the inability to do hard work or go for walks or exercise because they'll they they collabs with fatigue.
In in some ways, this overlaps a lot with MECFS. The symptoms of long COVID are often grouped. These are not just as scattering, but oftentimes you'll find pairs or common clusters of symptoms. For example, there are clusters of cardiac and kidney symptoms, respiratory, sleep, and anxiety symptoms. And some of these anxiety symptoms can overlap into depression.
Musculoskeletal and neurologic symptoms, and that can be everything from weakness or paresthesias, pain, and in the neurologic, including brain fog. And then the last cluster is digestive and respiratory. So you'll see respiratory, for example, in two different clusters, respiratory symptoms after COVID are common. This is because a lot of the inflammation occurred in the lungs, in the original infection. We now have a really good idea as to what's the cause of long COVID.
This is a big break through. Of course, this had been an unknown for many years. And there are still many unknowns. I don't wanna oversimplify that message here. But one of the major ideas that has come from the research has has has borne out now in many studies that it is an injury to the blood vessels and the activation of a system called complement that leads to clotting problems and that cascade that site goal of blood vessel injury, complement activation and clotting problems is likely to be the underlying cause for why different organs like the lungs, like the gut, like the brain, like the kidneys, like heart, why these different organs have consequences in in in injury.
Because there's so many parts of the body that are affected by long COVID, we focus right now treatments based on the symptoms, which parts of the body are affected and how to manage them. I'm gonna go over each of the sort of organs and some of the treatments that people are pursuing right now. And I'll talk to you a little bit about some of the clinical trials that are going on to try to treat as well, for treatments as well. Okay. So these are all the take home points.
Hopefully, if you just tune out now or you gotta start working on dinner or something, you'll have to take gotten the key the key message that I wanna share with you.

Emma Mertens: Doctor Butte, before I'm so sorry. Before you launch into this next slide, are you are you able turn up your volume at all. We're we're getting a couple folks saying that they're having a hard time hearing.

Dr. Butte: Yeah. It's because I'm a

Emma Mertens: I know. I know. If if if if this is the best you can do, that's totally okay. I just want that.

Dr. Butte: I'm gonna go to microphone. I'm gonna my input by having now. Is that better?

Emma Mertens: That's that's great. Thank you, Dr. Vue. Okay. Sorry about that.
And I

Dr. Butte: can yeah. I maxed it out now in Zoom. Okay.

Emma Mertens: You're great. Thank you.

Dr. Butte: Yeah. Okay. So long COVID is has a lot of consequences, unfortunately, this is not a mild disorder. Those who do suffer from long COVID, eighty five percent of them report a decreased quality of life. That is a huge number.
Over half of them have cognitive impairments that affect their ability to work or have, you know, read, enjoy cognitive activities. When that's impaired, everything gets impaired. Many of them are describing difficulties with breathing and lung function. That can impact exercise, that can impact work as well. Many of them have abnormal chest CTs because their lungs continue to show inflammation, and some of them have cardiac problems, including arrhythmias, So I picked some of the higher numbers from these from these surveys because these are this is just trying to help people remember that the impact of Oncovid is really significant.
These are big, big numbers. So again, one of the key points that we've learned is that those who've had the more severe acute infections go on to having the more severe chronic infections, especially in the lungs and especially in the brain. Okay. So who goes on to developing wrong COVID? Obviously, not not everybody does.
Only a portion of people get COVID go on having the long term consequences. How do we know who's gonna get it? Don't have an answer. There's no formula for this, but we do know some of the risk factors that increase the risk of developing this long term consequence. One of the risk factors is female sex.
Another is having comorbidities like diabetes and obesity. These tend to make the original COVID infection worse, but also along COVID. The variance of COVID seemed to have different risks. The ones that were early in the in the COVID pandemic especially the original Wuhan stream, Alpha, Gamma, those original ones that came in the first year and then delta, which came the year after that in twenty twenty one, those seem to have much more long COVID than Omicron, which came in twenty twenty two, and right around Thanksgiving of twenty twenty two, and swept the world in January of twenty twenty three, and now has been the dominant strains since twenty twenty three. The Omicron strains have much less long COVID.

Canning COVID more than once seems to increase the risks of long COVID, especially again if the infections themselves are not mild. If they're mild, very symptomatic infections, it's less consequential. Older people have worse long COVID than young people. As I'll show you, some of the women who developed long COVID report to their providers that they that many of the symptoms overlapped with periods of perimenopause. Lower socioeconomic status might have to do with access to care, and then there are some folks who have genetic risk factors associated with long COVID.

Gonna talk about those a little bit. I know this is this audience has some interest in genetics because we know that genetic mutations cause a lot of the problems with primary immunodeficiencies. And so some of these genes can overlap and be of interest. In the end, you have to add up all these portions of risk, and it creates a probability of developing the longer consequences of COVID. So the first risk factor that I mentioned was female sex. And across the board, whether you're talking about skin symptoms, GI, cardiovascular, respiratory, brain dysfunction, muscular skeletal. Across all the symptoms, females will report more frequency of long COVID symptoms than males. And this has been carried out through many studies over the years. Now it's important to note that the females who do report the symptoms are not the younger ones. So below forty is much less likely to develop long COVID, than above forty.

And in fact, again, many of the women reported these symptoms as being overlapping with the development of perimenopause symptoms. Another real factor was developing severe COVID during pregnancy. We do know that that was a very unique and troubling group of patients who developed severe COVID during pregnancy. Many of them will go on to having consequences of long COVID. Okay, another risk factor that I mentioned was the different strains of COVID.

We know that COVID itself is a highly mutating virus. It goes through changes, as it passes through people, and of course, through the animal hosts like that's where it originated. And as it goes through different strains, we have found over the years that it has become milder. The spread of COVID is milder and the clinical consequences of infection have gotten milder over the us three years, especially. The original strain or Wuhan strain of COVID had a much higher rate of both severe infection and death, and long COVID, up to ten percent of people were developing long COVID after the Wuhan strain.

Eight or nine percent were developing after Delta. Delta was a strain that occurred again the year after months of twenty twenty one. But in twenty twenty two, end of twenty twenty two, early twenty twenty three, Omicron arose as the dominant strain. All the strains we've had in twenty twenty three twenty twenty four, twenty twenty five, and presently circulating in the world, they're all based on the old macron backbone mutations, and those have a lower incidence of long COVID. One other thing that we've learned and again this work was published just recently in the New England Journal Medicine is that those who got

vaccinated to the delta strain in the twenty twenty one vaccines, the Omecon strains in the twenty twenty three, twenty twenty four, twenty twenty five vaccines all of those folks who got vaccinated had less severe infection, less hospitalization, but also less long COVID. And it cuts the risk of long COVID by roughly half. So this is a very important point that we try to emphasize this to the Lake public as to get vaccinated because we don't want people to develop long COVID. We also don't want people to spread the infection to those with immunodeficiencies who have our higher risk of getting more serious complications. So as I mentioned, the symptoms of local COVID are across the whole body, but they're not random, they're not sporadic, they tend to happen in clusters, and these clusters tend to follow some patterns. These patterns are not universal.

They are not locked in that everyone has to have the same kind of symptoms every time as we know. But what we do see is that in the first three months, oftentimes there are some GI symptoms that dominate for appetite and diarrhea. Tend to dominate. This is thought to be associated with the idea that COVID not only infects the lungs, but can also infect the GI tract. I don't know if many of you remember, but in early on during COVID, the first clusters of children who were published with COVID actually GI symptoms more than respiratory symptoms.

And we know that the receptors that the virus likes to attach to and enter into the body through are found in the lungs and also in the gut. So anyway, some of these earlier long COVID and chronic symptoms tend to be in the gut. There's also some respiratory symptoms, of course, and low grade fevers. Moving through the first year of symptoms, the symptoms spread all over, including some of the fatigue, fainting, so syncope, that can occur due to cardiac. Problems like arrhythmias and palpitations.

Strokes can develop muscle aches, chronic muscle aches, and fatigue, and then some of the respiratory symptoms and cardio respiratory symptoms, cough and sweating and fever. During the end of the first years where some of the more dominant neuropsychiatric symptoms developed, including difficulty sleeping, and then trouble with disorientation and brain fog. And those become more dominant than into the first year where brain fog of memory loss and exercise intolerance tend to dominate, and some of those earlier symptoms are less less dominant. Now, when you try to catalog all the symptoms of COVID, you'll find that really every system in the body can be affected. I've tried to group these based on different parts of the body and the physiology underneath.

But remember that these symptoms all can overlap in any one individual. So some of the brain and cognitive symptoms are are grouped at the top here. Persistent fevers and fatigue. Brain fog is a very dominant one. But also headaches and dizziness.

Some folks have ringing in the ears, some people have blurred vision. So these are sensory changes and changes in in case and smell. So changes in that in the in the sensation and then changes in alertness, awakeness are are some of the brain symptoms. In the lungs

and heart, you can have arrhythmias, as I mentioned, or you can have chronic cough. And then some folks develop autoantibodies or injury to the regulation of the of the of the of the systems of the body so they can have what's called dysautonomia.
Their blood pressure or their heart rate can go up or down. Sometimes these are these patients were grouped into what's called pots. There are symptoms that affect the deeper organs, so lungs and kidney, and many of these are related to clotting. You're gonna hear the word clotting a lot in the next thirty minutes or so because, again, this is one of the dominant theories that we have as to what causes long COVID. So these clots, deep vein clots, which are larger clots, or small micro clots in the brain and sorry, in the lungs and kidney can lead to injury in the kidney in in in these organs.
And then there's endocrine disorders that arise, including diabetes, there was a significant uptake in both Type one and Type two diabetes after COVID, and then some folks developed thyroid endocrine autoimmunity. Now, the CDC surveyed the development of long COVID and published this finding in twenty twenty three. Subsequent studies from around the world have echoed this result. I like this result because it really captures the exponential decrease in symptoms. That occur over the first year.
So there are a lot of people who have symptoms during COVID or within the first three months to COVID, but they fall off very rapidly by three months, only half, and then by six months third, and then again, down by a third, and then down by third. So the the rate of expense of decrease every three months is very fast. At the end, though, when you're talking about one year to fifteen months, this decrease starts to level off and you end up with a number that again we don't know the prevalence but we think it's somewhere around five percent one out of every twenty people has some long ongoing symptoms even beyond a year and a half. The good news is for those who are six months in or nine months in, there is a lot of hope to see a diminishment in those symptoms over the next upcoming months.
Now, put this slide in, you know, because this was how we used to approach long COVID a few years ago.
There was a lot of arrows that start with infection and end with long COVID and trying to trace all the different things that happened to our body during infection and after infection to try to map out this maze and how to figure out what the physiological problems are that go from here to here was a puzzle. And we've learned a lot along the way this this particular path from infection, acute infection to long COVID, we've been able to narrow some of these options because of scientific research. For example, we don't believe autoimmunity is a major cause of long COVID anymore. I'm gonna show you the slide to tell you more about that. We also don't believe that the virus is persisting or reactivating as a cause of long COVID.
This is not to say that it's zero chance of that, but this is less likely to be the theory. Instead, what we believe is that the blood vessels themselves are inflamed, are injured, and that

injury to the blood vessels is what causes the lung and COVID eventually. So, I appreciate that they're still, and I hope you appreciate their So many unknowns about what goes wrong in our body in long and term infections, but we have some good ideas now as to what causes lung covenants. Okay. So the first thing I mentioned is no autoimmunity.
Or or autoimmunity is not likely to be the dominant cause of long COVID. There were for years folks trying to gather antibodies from patients with long COVID and test if those are triggering some of the symptoms. And A group of Yale has published … Akiko Iwasaki group has published now multiple papers in in very reputable journals that have been replicated by other groups that now support the idea that there are no individual autoantibodies that are found in long COVID patients as compared with patients who are healthy or patients who have just acute COVID. Really, this study in twenty twenty three put this theory to bed. And I think this is important to be able to say what we think is likely or not unlikely.
Anyway, so I think autoimmunity is a was always something in the back of our minds as something that might have been triggered by COVID, but we don't think this is the cause of long COVID. The next theory that I think we've been able to put to bed is viral persistence. The idea that COVID is lasting in our body for years and years and years and triggering these symptoms is now less likely to be an important theory. Why is that? Because when you go surveilling patients who are immune competent, people have normal immune systems, we really don't find much COVID in their bodies.
And and this is with people who have the who have gone probidding in different tissues in the body. As I mentioned, there are some studies to support the idea that COVID can persist in the gut. The lungs tend to be cleared and sterilized of COVID within ten days to two weeks in most immunocompanyan people. The gut can show some longer persistence of the virus for a few more weeks, but in general, it doesn't last for that long in our bodies. We clear this infection pretty quickly.
Other evidence to support why we don't think persistence of the virus is the cause of long COVID, is that there have been now clinical trials where people have given medicines that eliminate the virus and have not seen improvement in long COVID. Paxlovid, for example, conducted a clinical trial, treating patients for a long period to try to eliminate their long COVID and they did not have a clinical benefit. Another reason to believe that viral persistence doesn't isn't the cause of long COVID, is that patients have received vaccines to boost their T cell responses against the virus and have not seen a significant clearance of the long COVID symptoms. About a quarter, the patient's got better after this vaccine has been given as a treatment now of long COVID. Patients already have the immune responses to COVID kind of booster T cell responses to COVID to see if they can clear long COVID and the results are mixed.
So this is unlikely to be a benefit to try to clear it because it's probably not persisting. The last is immunoglobulin treatments and we're going to talk about immunoglobulin

treatments as into the clinical trials. Unfortunately, these trials are not very high quality, but I'll show you what's out there so you get an idea. But unfortunately, the message is that even with immunoglobulin treatments There is no evidence for the idea that you can clear a virus that's persisting and could treat long COVID. Now with all of this being said about immunocompanyin people, the most of the people who have long COVID are immune competent.

We should remember that those of of you out there who have or maybe with a deficiency can have persistent infection and especially those patients with T cell defects. We know that T cells are needed to clear this virus. Antibodies can be a shield to prevent the virus from coming in antibodies can prevent the virus from spreading throughout the lungs, but they're not needed to clear the infection. You need T cells to clear the infection and patients who have genetic disorders of T cells And I have we're getting some here, like, those who have skid or hypochromophic skid, combined immune deficiencies, bone or bone marrow transplant patients, oftentimes, will have weaker T cell function and can have persistent COVID infection. That means more than five days, more than ten days, more than twenty days.

There are publications of patients with T cell defects who've had months and even years of COVID infection. That is not common. Okay. That's not what most people in the community you're having. It's not what anybody in the community is having.

It's only those these rare genetic immune disorders of T cells. This is one of the reasons why we do recommend patients get treatment for COVID. Especially those who have primary immunodeficiencies. Medicines like paxel that would work incredibly well to clear the infection, and are recommended. Okay.

Now I'm going to get to the cause of long coated. And this slide is a little complicated. I'm gonna try to make it simple on the next slide, but I wanna give those of you a chance who like pictures and to see things, a chance to see it in pictures, and then have a chance to see it in words because all of us learn in different ways. The virus itself triggers a lot of the immuneers ounces during the first days, hours, and weeks of infection, and then it's cleared. But what we've learned is that the viral infection activates the blood vessels.

So this figure is showing the inside of a blood vessel and the virus triggering the the activation of the wall of the blood vessel. The wall of this blood vessel has cells, they're called endothelia, and these cells become reactivated. This is the cause that we think of long COVID. That this activation of the blood vessels attracts a protein called complement. And complement then assembles itself into a set of proteins and this set of proteins normally is a protection for us.

It normally helps us fight bacterial infections. That's what complement is in our blood for. It attacks bacteria and kills bacteria. But when the blood vessels become inflamed in this way, The complement instead of attacking a bacteria can attack our own blood vessels,

and that creates injury to these same endothelial cells. That injury to the endothelial cells attracts clots.
And these clots can be in the form of platelets, and they can be in the form of clotting proteins in our blood clotting factors that they're called. And together, these clots form aggregates, and the aggregates, and the clots come back and activate the blood vessels. So this is a loop and this feedback loop that involves the injury to the blood vessels, the activation of complement, the activation of clotting, and the injury to the blood vessels again is likely to be the cause, the underlying cause of long COVID. Now, I'm gonna show you it in words, again, because some people learn in different ways. So, and I'm gonna try to explain it again.
The lining of the blood vessels that line, different parts of our body, especially our lungs, get damaged during COVID. The virus itself doesn't necessarily spread to our body or infect these blood vessels, but the injury to the blood vessels is occurring because of inflammation that's made in the lungs or due to low oxygen levels, of course, that's one of the injuries in the lungs due to the COVID infection itself. This is why we believe that the severity of the original acute COVID infection leads to long COVID. Because if you have low oxygen levels and you're in the hospital and you need supplemental oxygen or intubation in order to survive, the injury to the blood vessels is severe because of that low oxygen level. There's also a lot of inflammation that develops in these patients who are very sick.
And then inflammation, especially interferons and other factors that I won't go into here, cause injury to the blood vessel cells. Once those lining of the blood vessels become injured, and that injury is is chronic, even though the infection itself may be over, the blood vessels themselves don't heal that quickly. They start to attract complement. Now remember, complement is a set of proteins that defend us from infections. But in this case, it's abarently activated in the blood vessels, and it ingers the blood vessels further.
And that attracts more complement and ingers the blood vessels further. And so you have one of the feedback loops here. When the blood vessels are injured, they attract clots. And those clots, again, can be micro clots. They can be macro clots.
We heard about deep venous thrombosis, for example, big vein clots, but this can also be micro clots throughout the circulation. And those micro clots themselves when the assemble on the blood vessels lead to more complement activation and more clotting. So you end up with a second feedback loop. And these feedback loops injuring the blood vessels, injuring the blood vessels, injuring the blood vessels, it is the underlying cause of long COVID. When it hits different organs in the body, throughout the body, you can end up with different symptoms.
And that's why the lungs and some people are affected, the heart and some people are affected, etcetera. The size of the blood vessels seems to have matters. Micro blood vessels, little capillaries versus larger blood vessels. And that's why sometimes you see

patterns, the kidneys, and the heart because they have similar sized blood vessels. A paper recently published in the journal looked at this mechanism in the brain.
It's not just though deep organs, but also in the brain, and they found that activated platelets, attracting clotting factors will lead to injuries to the blood vessels, and they're they call these micro thromboses. That's sounds like a technical term, but these are micro clots in the brain. And that leads to this blood vessel injury complement and activation and inflammation. Now in the brain, the inflammation can spread beyond the blood vessels, go into the actual organ itself and affect the function of the neurons in the brain. That could be the cause of fatigue, that could be the cause of disorientation, that could be the cause of brain fog, is inflammation that spreads beyond the clots inside the blood vessels.
Of course, the clots themselves in the blood vessels cut off oxygen. And if you're talking micro little capillaries and the amount of oxygen that can come through those capillaries becomes blocked off with little micro clots. We know that that's an injurious in the second way to the brain and to other organs. But cutting off how much oxygen these organs can get. Okay.
So I hope everyone at the end of that can really appreciate why we think the acuity of the original infection, the low oxygen levels and the inflammation that arise from original infection lead to this blood vessel injury and lead the long COVID throughout the body. So we've come to learn more about the risks I mentioned, some of the risks earlier, including female sex and severity of infection. There are some genetic risks that have been identified related to long COVID. I know some of you are interested in genetics again because the causes of your underlying parameters of deficiencies are genetic variants that affect your B cells and T cells and neutrophils and other white blood cells. A gene that was recently published in Nature Genetics called FOX P4 seems to be regulating the regeneration of the blood vessels in the lungs.
And so this really fits in with what I've been talking about for the last few minutes. Then if if the regeneration of these blood vessels is slow, then the injury takes longer to heal and you can accumulate more of this feedback loops and get more and more cascades of injury. So regeneration of these tissues is very different than the original fire. The fire may burn, and the fire may put out, and the tissues then have to take time to regenerate. Other genes that have been identified related to risk of long COVID are related to blood clotting.
Again, this fits into what I was just talking about a few minutes ago that the blood clotting cascade that begins in these injured blood vessels leads to injury. And so when there are genes that cause an increase in blood clotting mutations, then that causes a more severe long COVID. One last set of genes that have been identified, and this probably is obvious to all of you, but those who have genetic causes that cause more severe COVID will have a more severe risk of long COVID. We have identified those in an international effort. As being related to what's called type one interferon signaling.

I'm not going to go into all those details now. I know many of you heard me talk about type one interferons during early twenty twenty one and twenty twenty two when we were first learning about these, I gave some talks for IDF than others. To try to help educate the community about interferon. And in interferon pathways, either auto antibodies in interferon pathways or mutations in interferon pathways seem to be one of the major risk factors for severe COVID. That of course adds up to more with severe risk factors that are evolving long COVID as well.

Okay. So let's now migrate to talk about treatment. And then as Emma mentioned, there'll be plenty of time for questions. There have been a handful of studies where people tried to use immunoglobulin to try to treat long and COVID. Unfortunately, the studies that have been published so far are really weak, and I don't think they are conclusive at all. Unfortunately. I wish there were high quality studies looking at intravenous immunoglobulin in a proper blinded placebo controlled fashion. Unfortunately, that was not done. So this is one study that you can look up published in twenty twenty two. Where six patients were treated with IVIG, many of these patients were already on IG, although we don't know why. The patients who did get IVIG did report a lower set of symptoms, including some of the loss of taste, listlessness, insomnia, brain fog, etcetera. A second study was published in twenty twenty three. Again, looking at a handful of patients with open label treatment And the only thing we know is that this study reported significant to remarkable benefit. Again, this is not a very well controlled study, and there weren't enough subjects really to be able to define what how the benefit worked to benefit it or not. There is a group at the NIH that has posted that they would be interested in studying IVIG in PASK, also called post acute squamous long COVID, or long COVID.

They're looking for neurological effects. This is a study sponsored by derological Institute in NIH. And this study, to my knowledge, is ongoing. They were using a high dose IVIg strategy. So many of you get immunoglobulin where you'll get half a gram to a gram per kilogram per month.

This is using double that. This is using a total of two grams per kilogram, and this is a lot. This is what we use typically at these kinds of doses to control autoimmunity. And for example, Kawasaki disease and other autoimmune diseases will use IVIg at these kinds of high doses. This is way above the replacement doses that most patients with the PI will be receiving.

We don't have the outcomes from this study yet. Some folks have started to look at treating the clots. Remember I mentioned the clots are part of this cascade that leads to the ongoing blood vessel injury, and some folks have started to look at treatments related to clots. And that can include antibodies that block fibrin, fibrinanalytics that dissolve clots and other medicines. A group in the UK that's sponsored by the entire NIH has now published a study called heal COVID where they used a anti clotting medicine, a cot

busting medicine called apixaban .
They did not look at long COVID symptoms yet. They have not published that, but what they did look at was in the first year after giving apixaban . That they did not reduce the rate of readmission to the hospital or severe consequences like death. So the short term consequences in terms of admissions and hospitalizations wasn't improved by using this clot busting medicine. And again, we don't know whether long term consequences like long COVID are improved.
There are still no studies to my knowledge where people are looking at clot busting medicines or clot dissolving prevention medicines and long COVID. Okay. So let's talk about these different organs and the different treatments as we come to the end here. So some people have end organ tissue injury and especially the heart and lungs. Some of the ways that doctors have worked up, these tests are some of the tests you'll see in the middle here.
Many of you may have already undergone some of these tests like pulmonary function tests or echocardiograms for other reasons. These are the kinds of tests that may help inform how much injury there is to the heart and lungs. The treatments that are being recommended for injury to heart and lungs include rehab, cardiac and pulmonary rehab. And time, time heals the many of these injuries in the heart and lungs. And again, some folks are trying anti fibrotic agents to try to reduce the scarring in the lungs.
There are some folks with injury to the blood vessels. As mentioned, this is one of the major causes of long COVID. And people are studying those injuries to the blood vessels, especially for example, in the brain, the kidney and other organs where MRI works really well to study blood flow. They're doing forms of MRI imaging. You can look at the blood vessels in the back of the eye by using by doing a retinal examination.
Tiny blood vessels back there give information to an ophthalmology just about a blood flow. And different kinds of scans measuring blood flow are being done. When blood flow is injured, these kinds of treatments are being attempted. Again, because they're not recommended treatments, they're not one size fits all. I just have collected here some of the ones that doctors all over are trying to reduce injury to blood vessels and improve blood flow.
Drugs for example that relax the blood vessels like calcium channel blockers may be able to improve blood flow. The neuropathy symptoms are really diverse. I mentioned some of them are related to autonomic dysfunction. Sometimes gathered under the term pots. And the tests for pots include things like tilt the table and standing tests where heart rate and blood pressure can be measured in different positions to see if there's a dysregulation of heart rate and blood pressure.
Medicines that are being used for pots you may be familiar with include medicines like midodrine and fludrocortisone. GI symptoms are, as I mentioned, common in the first year

of symptoms, and there can be some dysmotility in constipation that are long term consequences. The way people study that in patients is by doing motility studies. This can be barium swallow. Those are imaging capsule microscopy studies looking to see how the transit of the gut is affected, and they could be done by biopsies, colonoscopies and synchodoscopies.

The treatments that are being done in include in some cases medicines that can help increase the movement in the gut. These are sometimes prescription medicines or over the counter medicines, and they can help improve the movement to reduce things like constipation. And then, again, back to the brain, some of the imaging studies like a functional MRI or diffusion weighted MRI can reveal whether they're parts of the brain that have been affected by low blood flow and low oxygen. This can look like a stroke. This can look like scarring.

This can look like injury to the brain to an MRI. Some folks undergo those final taps in order to look for inflammation. Some people undergo neurocognitive testing to see if things like brain fog or word recall problems are affected. Psychiatric testing can also be done to look for anxiety and depression. Treatments are really diverse, of course, and often involve rehab.

Whether that's neuroplasticity and interventions. And some folks around the world are using direct stimulation of the brain to see if they can improve some of these outcomes. Okay. So let's skip to the take home points. Please get vaccinated even if you're antibody deficient.

We know from many studies that T cells benefit from the vaccines, and T cells are needed to clear the infection. Antibodies are a good shield. T cells are needed to clean up all the virus from your body. So please get vaccinated even if you're antibody deficient. T cells will benefit and please encourage those around you who will have help immune systems to get vaccinated so this infection doesn't spread.

Remember also the commercial immunoglobulin products, all of them, are obtained from folks whose plasma contains protective antibodies. Almost everybody has been vaccinated or has had COVID themselves. And their antibodies, which results in commercial immunoglobulin products, has for those protective antibodies in it.

Treatments are really focused on organ by organ. You saw that over the last five or six slides.

We know how that the original inflammation and infection can be gone, but the long term consequences of regenerating and recovering these organs can be slow. And so rehab tends to be a major way of improving function progressively. The studies that have been done with immunoglobulin have been really poor quality, and I do not suggest that high dose IVIG at this point is a recommendation for long COVID. There is one study that is tantalizing out there looking at complement. I've mentioned now that complement that we

think an endothelial actuation complement is one of the major drivers of long COVID, and a group has been sponsored by farming to run a trial using theRC1 inhibitor called ruconest. This clinical trial was published on clinicaltrials dot gov, but and what was completed, but we don't have published results yet. So we're excited to see what the outcomes of that study might be. I am hopeful that by blocking complement that one can improve long COVID. Besides C1 inhibitor, there are many commercially available complement inhibitors out there. These are all prescription drugs.

They have serious consequences because they create immune compromised. They affect complement, and complement is one of our major defenses. So we can't use these medicines willy nilly. They have to be used in clinical trials and highly observed in careful settings because you may create risk while trying to create benefit. And that ethical balance has to be met in the form of really careful study.

I would love to see a complement inhibitor studied in long COVID, those of you out there who have some poll, please encourage it. I think this is a promising area for research. And And to end with research, I want to just mention that my labs research and a lot of the labs that I know that work on the immune system are funded by the NIH and by the National Institute of Allergy, Immunology, Infectious Diseases and I had. NIAID is so important to all of us. And the funding for from NIAID and for in other institutes at the NIH is low.

It has been cut. And we're very hopeful that NIH funding will be protected by Congress But right now, their numbers are not great. And I really want to encourage all of you out there who are interested in immune system to understand that the NIH and sponsors a lot of us studied immune system. This is where our knowledge comes from. It's from public dollars. Going to researchers and improving knowledge. I would really encourage all of you to reach out to your, you know, to folks, if you have any say, to your congresspeople, etcetera, and encourage them to support congress encourage them to support the NIH. This is something that I think a a lot of us believe in and are very hopeful for them. Okay. That comes to the end of my slides.

I think I've given at least fifteen minutes for all of us to be able to ask questions. So and my voice is a lot first so far. So let's let's see where the questions take us.

Emma Mertens: Wonderful. Thank you so much, Dr. Butte. That was super interesting and enlightening, and I know we're gonna have some great questions here for the q and a. And thank you for for going along with the volume change.

We had a bunch of people chime in up. I can hear much better so Thank you so much. Alright. Getting started with Q and A, if everyone can just make note of the ground rules, we just shared in the chat. If you could go by those.

I would greatly appreciate it. Alright, Dr. But how are people affected if they have had COVID numerous times. Is it the type of thing where with each subsequent infection, it's

going to be worse, it's going to be lighter? And what does the what happens to the potential damage over the course of more frequent infections?

Dr. Butte: Yeah. The more infections, the higher the risk of long COVID, and it really has more with the severity of each infection than just the number. If you have one severe infection, it can be enough to push that inflammation and that cascade of blood vessel injury into long COVID. If you have a series of severe infections, it's going to be worse. On the other hand, people have very mild infections, may not have that as much of a risk.
So if you want to think about it, think about the severity, the more important than the number, but certainly if you have more of them and they're severe, it definitely adds up.
Howard

Emma Mertens: Bauchner: Sure, thank you so much. All right. So I know you talked on in during your presentation that there have been a couple studies that have not been super conclusive. We have the one coming hopefully soon from farming that we're hoping has some more results to share. But if I iG therapy does end up being a treatment option, does that mean that people who are already on iG therapy because of PI or another condition will they be less likely to get long COVID?
Or based on, you know, the little bit that we do know from the trials that have been completed, would they need that additional dose of IG therapy to receive any sort of benefit?

Dr. Butte: Yeah. Great question. Again, I don't believe that IgG therapy has borne out a benefit for long COVID. The ones that are trying to study it at in that neurological institute are using high dose IVIg. So you have to answer your question.
Again, most people who are getting immunoglobulin replacement therapy aren't getting high dose. High dose is two or three times as much as replacement dosing in some cases more. And so, yeah, that this is a very different thing to get high dose, IVIG. And to get replacement dose IG. And that's one of the reasons why it has to be done in a clinical trial setting because it does add more risks to get high dose IVIg.
But yeah, we don't actually have evidence high dose IVIg will benefit.

Emma Mertens: Thank you, Dr. Butte. Alright, next question. So I know you mentioned the importance of vaccination against long COVID. What other things that can folks in our community do to protect themselves from long COVID?

Dr. Butte: Yeah. Great question. So in twenty twenty one and in twenty twenty two, there were long acting antibodies. They wanted to under the name Evushield, many of you that have gotten Evushield back then. Evushield was a great idea.
The idea of creating a monoclonal antibody that lasts in the blood for six months and

shields us from COVID was an amazing idea and worked really well. Many of our PI patients at UCLA got an episode also patients with solid organ transplants and other risk factors for developing severe COVID got heavy shield. And it seemed to work. It kept people out of the hospital. It kept people who did get COVID, kept their COVID to be very mild.
And so we were really encouraged by those long acting protective antibodies like heavy shield. There are not a confluence of every shell right now for omicron, for the current omicron strains. But when the drug companies do get them out, I do encourage people to get them because it does provide I'd you know, a really nice protection in addition to vaccination. Beyond vaccination and every shelled or the equivalent to whatever the next version of will be called, we we know that there are certain defenses that you can take to protect yourself from COVID. You know, COVID can be spread in a airborne fashion and so staying away from people who are sick and staying and wearing a mask if you're going to be around people who are sick is a is a good defense.
The kinds of masks that are really protective are N95 masks. Not the surgical masks that you could put your fingers underneath. Those tend to not be as protective as the ones that feel against your face and that move in and out with each one of your breaths. That's a sign that all the air that you're breathing is going through the mask and not around the mask. It's a very simple test you can do to tell whether your mask is really shielding you in filtering the air or not.
If you are wearing one of those masks, especially in indoor settings, especially in indoor crowded settings, especially in indoor crowded settings where people are coughing and you don't know everyone around, Those are the ways that you protect yourself from from exposure. This is a community acquired infection. Our community knows how to protect themselves from community acquired infections. There's a lot of common sense here that we learned and yet to keep practicing it. I got my first COVID infection going into an indoor soccer stadium game with twenty two thousand people, and and I got COVID from that. That was obvious. But, you know, so you know how to protect yourself from this. This. We haven't learned all the key lessons on how to protect ourselves from this. Now for those of you who have to go to work in crowded settings, you know, we've tried to recommend people have enough airflow in the workplace so that the risk factors of viruses aren't building up in the air.
It's very hard to measure airflow and we don't have great measurements for this, but we do know that if there are a lot of people in the room, a lot of people talking in the room that it needs to have more airflow and if on the other hand if the rooms are larger and have fewer people in them, then they can have less airflow. So beyond that, there's no, like, a numerical way of saying this room has enough airflow or not. But those that's the other sort of important way of reducing risk.

Emma Mertens: Or who get vaccinated and kinda stick to the basics that we all learned about back in twenty twenty. You can keep those going. Mhmm. If that makes you more comfortable. Alright.
Thank you, Dr. Butte. Alright. Next question. We had a couple of folks mentioning a study that had been conducted that looked at viral persistence in tissue and whether this persistence may be driving immunodeficiency or immune exhaustion, for example, impacting the T cells or the NK cells.
What are your thoughts on that?

Dr. Butte: Yeah. Right. Again, viral persistence is real for those who have T cell defects. We know many, many papers and of course the science is kind of obvious in this regard. T cells are needed to clear the infection.
Those who have weak T cell function or numbers have a higher risk of not clearing the infection. That can last then in different tissues for months or years or at least months months have been published. So yes, it's definitely possible that the immune to the T cells are weaker, that the the coronavirus can persist. That those weak T cells are not then becoming exhausted. They themselves were weak and allowed.
The the virus to persist. T cell exhaustion is something separate. T cell exhaustion occurs in people with healthy immune systems. My T cells, for example, can undergo exhaustion. T cell exhaustion has to do with persistence of antigen over the course of a few days to weeks, not years or months, and it leads to t cells to go into a mode where making more and more inflammation isn't productive, and so they go into a less and less productive mode.
So I think it's important not to put the chicken and egg problem here. T cell defects lead to viral persistence, and viral persistence doesn't occur in patients who have intact T cell function. In other viruses like hepatitis, herpesviruses, HIV, where the virus isn't easily cleared, those are the cases where you can end up with T cell exhaustion, even folks with healthy immune systems. So I know these concepts all sound like they're overlapping, but they are separate.

Emma Mertens: Thank you. Alright. Next question. You mentioned blood clots during your talk, and someone wanted to clarify if clotting is an issue, am I protected from developing said issue if I'm already on blood thinners?

Dr. Butte: Yeah, that was the purpose of that study that was done in England to try to see if putting patients on blood thinners are protected from developing long COVID. They weren't protected from rehospitalization, or admission to the hospital, those patients who had severe COVID injury, and then went on blood centers didn't get better. We don't know if it protects from long COVID yet. There's no published results on that yet.

Emma Mertens: Thank you, Dr. Butte. Alright, I know you also mentioned pots in your talk a couple of times. This individual wants to know if you have some symptoms of pots prior to getting COVID, does getting sick make the pots worse And will they stay at that elevated level? Or will they dissipate once COVID backs down?

Dr. Butte: I'm sorry. One more time does that? Pots

Emma Mertens: So if they have if they have pots before they get COVID, then they get COVID, will the pots get worse? Or will it kind of chill out and and go back to how it was prior?

Dr. Butte: Yeah. Unfortunately, there's no no good answer for that. For some people, the pots is driven by auto antibodies. And auto antibodies, we know, can flare during infections. People make more antibodies as a defense from infections, and that can include auto antibodies.
We know a lot of autoimmunity comes worse with flares after infections. And as the infections sit down and the B cells reset, those auto antibodies can go down again too. So flares of autoimmunity are something that folks with autoimmunity to understand. And if the pots is bigger and by autoimmunity, then yes, they can flare and then get better again.
Now in Long COVID, the idea that there is endothelial injury leading to to the pots because of dysregulation of the blood vessels, not necessarily due to autoimmunity.
That's a that's a different theory causing the the dysfunction, causing the the pots. And in those cases, it's not going to be flares of autoimmunity, but it may be more persistent.

Emma Mertens: Okay. Thank you. Alright. Here's a good question I think we can all benefit from. How do I find someone to diagnose or treat my long COVID symptoms?

Dr. Butte: Great question. Some of the big academic medical centers have started long COVID clinics recently, and it has one. And it's being run by a multitude of doctors. Who are brought in based on different specialties that are needed. It can be a primary care clinic that is the sort of the home, but bringing in another specialist in order to coordinate that kind of care.
So big economic centers are trying to run long COVID clinics. To try to study these patients, to try to bring interventional trials into place, and then also just to make sure that the patients get all the right specialists. So often times, you'll have to go to an academic center or to find a long COVID clinic.

Emma Mertens: Troy, thank you, Dr. Butte. And then kind of a spin off of that question. So how do I get people to understand that the symptoms I have, particularly major fatigue is related to COVID. They think I'm just being

Dr. Butte: Oh, god. Yeah. I really feel free. And and and it's because fatigue is such a nonspecific symptom that people don't really understand how to really link the symptom of fatigue. To the infection.
There's it can get very difficult. You know, what we have to do is, you know, go to specialists who have seen cases of of of long COVID and it could be a neurologist. It could be a clinic. That allows them to be able to examine you, look at your history prior to COVID and after COVID and be able to say, you know, we think this is a consequence, this is long COVID. Unfortunately, it's not like this fatigue is different from that fatigue.
In some way that is absolutely diagnostic of the long COVID. We just don't have those kinds of tests.

Megan Messick: So one that I think will nicely wrap us up and then I know you have to hop off Yeah. Is just related to those research that you mentioned, How do we go about for those in the audience who are interested in participating in future clinical trials, finding out additional information and being participants?

Dr. Butte: Yeah, great question. All clinical trials in the United States are required to be posted onto a government website called clinicaltrial dot gov. And you can go to clinicaltrials dot gov and type in in the search box, long COVID. You will see every single study that has been sponsored in America, in long COVID. The ones that have completed, the ones that got started and never stopped, the ones that never really got started, everything is in clinicaltrials dot gov.
That website is an amazing resource. You can find studies that are recruiting And you can see if they're recording your view. You can find studies that are being contemplated and not yet recruiting. All of them are in there. And again, that's required by law.
So it's a really great resource for people to learn about clinical trial, not just in long COVID, in cancer, in every area of clinical trial research in America, that website is a single source of everything. And so I do encourage people who are interested in that more cutting edge kind of looking for treatments and looking for clinics and for the answers. To go to clinicaltrials dot gov because it is a resource that, you know, works actually quite well right now.

Emma Mertens: Awesome. Thank you so much, Dr. Butte. I know you have to run. So we'll go ahead and wrap up the Q and A portion. And for those who are still joining us, I'll have a couple of closing remarks, but thank you so much, Dr.
Butte for joining us this evening. This was so informative, and I know a topic that was really important for a lot of folks as they're navigating board.

Dr. Butte: You're welcome. I I I I don't get to see the questions. I hope most of the questions got answered. I know there's a every time that I've given I talk about in Vancouver, there's so

much interest in it and a lot of people, you know, are looking for answers. It is such a confusing topic.
I hope I was able to make some of it clear about the underlying mechanisms. And hopefully you can find, you know, some nearby doctors that large medical centers, academic centers near you who can, you know, offer that interdisciplinary care that's needed for this disorder. This is not a, you know, one pill or one doctor kind of solution. This is gonna require a lot of coordinated care, but it's out there. There are, you know, our clinics are out there, help trying to help people, and hopefully, you'll be able to marshal those resources locally for yourselves.
Sorry. My voice is going.

Megan Messick: No. Your your voice held out for so long or so long. You too.

Dr. Butte: Alright. Have a good evening. Bye.

Megan Messick: Yes. Thank you. For our friends who are still online, my name is Megan Masik. I've been your tech support behind the scenes. And in Emma's absence, I'm gonna share a couple of more resources that I'll also include in the chat to close this out for the evening.
The first is that primary immune dot org is your go to website for additional resources, upcoming events, and more. All materials are free to access print or have mail directly to you. And if we did not get to your question tonight, you can ask our IDF program. A team member will personally connect with you through our Ask IDF platform to tackle your questions and direct you to appropriate resources. You're also able to take the immune deficiency foundation on the road with our engaging podcast series.
You can find programs like bold conversations, undiagnosed in chronic twenties by searching for the immune deficiency foundation podcast. We also do have a YouTube channel, and that's where you'll be able to find our recordings from our digital education events, and tonight's program will be available in the coming weeks. I also want to share too that our conference is slowly approaching here quicker every day. I hope you guys will join us in San Antonio, Texas as we convene for the largest gathering of individuals affected by PI in the world. I'll also be including the conference website and the chat for you guys to register.
But before we go, I heartfelt thank you to all of our amazing volunteers and supporters who make programs like this possible If tonight's presentation resonate with you, we hope you'll consider supporting future programming. Your donation at any level helps us continue building community and delivering meaningful content. So thank you so much. And thank you everyone for joining. I'm gonna drop some of those links in the chat and we'll see you

guys here for our next webinar in the coming months.
Take care.