

National Institute of Allergy and Infectious Diseases Virtual Workshop on Post-Acute Sequelae of COVID-19

Thursday, December 3, 2020, 10:00 am-4:30 pm ET and

Friday, December 4, 10:30 am-2:30 pm ET

Meeting Information

The National Institute of Allergy and Infectious Diseases hosted a virtual Workshop on the Post-Acute Sequelae of COVID-19 on December 3 and 4, 2020. The purpose of the workshop was to summarize existing knowledge on post-acute manifestations of COVID-19 and to identify key knowledge gaps.

Top Line Takeaways

- The post-acute sequelae of COVID-19 (“long-COVID”) cause a wide range of gastrointestinal, cardiovascular, dermatologic/ mucocutaneous, respiratory, musculoskeletal, and neurological issues. Indirect health problems that stem from this include depression, anxiety, post-traumatic stress disorder, etc.
- COVID-19 hospitalizations and infections are getting worse. As the nation heads into the winter and infections increase, the number of Americans with long-COVID will increase.
- Some providers are setting up clinics or divisions to specifically treat long-COVID. This includes the John Hopkins Post-Acute COVID-19 Team Clinic and Dr. Jorge Vasquez’s clinic at the Zuckerberg San Francisco General Hospital. These offices use a multidisciplinary approach to treat both physical and mental issues.

- Long-COVID leads to substantial levels of depression and anxiety, which can be further compounded by economic-insecurity due to medical costs and the inability to return to work.
- There is a negative stigma that is associated with COVID-19, which can extend to survivors' families, friends, and colleagues.
- There was widespread agreement on a range of symptoms characterizing long-COVID, but also broad agreement that the medical community does not yet know all of the long-term effects. Further clinical investigations are needed. Many of the presentations in the workshop highlighted research that relied on case studies, rather than large sources of data.
- There are research barriers for long-COVID and the corresponding treatments. COVID-19 attacks many parts of the body, meaning that it is difficult to trace a long-term issue to a single cause or general cause.
- Initial studies show that people at a higher risk of long-COVID are women and persons with a higher body mass index (BMI).
- Existing COVID-19 treatments are very novel, so the wealth of data from traditional vaccines (i.e. DNA vaccines or non-mRNA vaccines) do not carry over to assessing how mRNA vaccines would work against comparative diseases.

Speakers

- **Dr. Anthony Fauci**, Director of the National Institute of Allergy and Infectious Diseases
- **Dr. John Brooks**, Chief Medical Officer of the Centers for Disease Control and Prevention
- **Dr. Ann Parker**, Assistant Professor of Pulmonary and Critical Care Medicine and Co-Founder and Co-Director of John Hopkins Post-Acute COVID-19 Team Clinic
- **Dr. Jorge Vasquez**, Division of Experimental Medicine and Division of Pulmonary and Critical Care of University of California San Francisco
- **Dr. Janet Diaz**, Lead for the Clinical Management Response for COVID 19 at the World Health Organization Emergencies Programme

- **Dr. Sipho Dlamini**, Doctor of Infectious Disease and HIV Medicine at the Groote Schuur Hospital University of Cape Town
 - **Dr. Peter Piot**, Director of the London School of Hygiene and Tropical Medicine
 - **Dr. Ignacio Sanz**, Chief of Rheumatology and Director of the Lowance Center for Human Immunology at Emory University
 - **Dr. Shane Crotty**, Lo Jolla Institute for Immunology at the University of California San Diego School of Medicine Department of Medicine, Division of Infectious Disease and Global Public Health
 - **Dr. Stanley Perlman**, Professor of Microbiology and Immunology and a Professor of Pediatrics at Perlman University of Iowa
 - **Dr. Kanta Subbarao**, Director at the World Health Organization Collaborating Center for Reference and Research on Influenza and Department of Microbiology and Immunology
 - **Dr. Avi Nath**, National Institute of Neurological Disorders and Stroke
 - **Dr. Wendy Post**, Johns Hopkins Medicine
 - **Dr. Terri Hough**, Oregon Health & Science University
 - **Dr. Hashem El-Serag**, Baylor College of Medicine
 - **Dr. Judith James**, Oklahoma Medical Research Foundation
 - **Dr. Peter Rowe**, Johns Hopkins Medicine
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Post-Acute COVID-19: Clinical Observations

Director Anthony Fauci:

- COVID-19 hospitalizations and infections are getting worse. He expects a post-Thanksgiving surge to become apparent in the coming weeks. Christmas travel will likely lead to another surge.

Dr. John Brooks:

- Coronavirus is a single-stranded RNA virus that causes a variety of lethal disease in a large variety of mammals and birds. The illness is usually respiratory or enteric (relating to or occurring in the intestines).
- There are many strains of Coronavirus, with SARS-CoV-2 being one of the most severe. SARS-CoV-2 spreads so quickly because it can become infectious before people show symptoms.
- Anosmia (loss of the ability to detect one or more smells) and/or dysgeusia (distortion of the sense of taste) are very common symptoms. These may be longer-term but relatively minor compared to much more serious long-term effects.
- Long-term issues can include gastrointestinal, cardiovascular, dermatologic/mucocutaneous, respiratory, musculoskeletal, and even neurological issues.

Dr. Ann Parker:

- COVID-19 can cause impairments in physical function, cognition, and mental health.
- Physical function: myopathy, respiratory issues, etc.
- Cognition: prolonged delirium and fatigue.
- Mental health: grief over lost loved ones, fear, social isolation due to infection.
- The John Hopkins Post-Acute COVID-19 Team (PACT) Clinic is building a multi-disciplinary team to treat all aspects of long-COVID.
- Studies by John Hopkins show that more than half of patients studied are showing substantial mental health impairments, both intensive care unit (ICU) and non-ICU survivors, separate from or in addition to neurological damage.

Dr. Joshua Vasquez:

- Dr. Vasquez reviewed an individual with virologically suppressed human immunodeficiency virus (HIV) who was infected with COVID-19. This patient suffered from many common long-COVID issues. One unique complication was severely reduced gas-exchange (DLCO).

- His clinic, which is in the Zuckerberg San Francisco General Hospital, has developed a multi-disciplinary care model that focuses on pulmonary treatment, respiratory therapy, and psychiatric help.
- Long-COVID leads to substantial levels of depression and anxiety, which can be further compounded by economic-insecurity due to medical costs and the inability to return to work.

Dr. Janet Diaz:

- Providers need to better understand:
 - What long-COVID is (and create a working definition if possible);
 - What the possible range of health issues can be; and
 - Possible treatments.
- Post-intensive care syndrome (PICS), which is a general range of health problems that remain after critical illness that are present when a patient returns home after an ICU stay, is a serious issue for COVID-19 patients who end up in the ICU.
- It is unclear what percent of patients develop prolonged symptoms and/or complications. There needs to be global research into this to see if there are differences in different regions of the world.
- The World Health Organization (WHO) is setting up a global database to track this information. The WHO has also set up a standardized form for collecting long-COVID data, which is called the “Rapid core case report form (CRF).” An example can be found [here](#).

Dr. Peter Piot:

- Dr. Peter Piot was infected with COVID-19 and has recovered. He used his own experience as a case study. He is 71 and had no pre-existing conditions. His experience:
 - Started with a fever, splitting headache, brain fog, and diarrhea.
 - It escalated to extreme fatigue and low oxygen saturation. His fatigue remained for 3-4 months after infection.
 - To date (around 7 months after infection) he has fully recovered, except that he needs to sleep more.

- People at a higher risk of long-COVID include women and persons with a higher BMI.

Presenter Comments:

- There is a negative stigma that is associated with COVID-19, similar (albeit not as severe) to the stigma associated with HIV/AIDS.
- Friends and family may avoid contact with someone who has recovered from COVID. Social isolation can extend to health care workers.
- Some people who get infected might be shamed by others for being irresponsible and getting infected.
- Coworkers and employers may become upset with workers who have long-COVID fatigue.

Public Comments:

- There is not enough long-COVID research being done. The [Patient-Led Research](#) is a team of researchers who are also COVID patients. A small percentage of people experience vision loss, hearing loss, heightened allergy experience, and changes in sensitivity to medications. This group supports using the term “long-COVID” in naming this condition.
- Patients are struggling in getting their provider to believe that they have long-term COVID-19 issues. For example, some patients have had long-COVID mental issues written off as something else, such as Attention Deficit Hyperactivity Disorder (ADHD).

Viral Pathogenic Features and Host Immune Response

Dr. Ignacio Sanz:

- There is an elevated level of auto-antibodies in some patients who experience severe disease.

Dr. Stanley Perlman:

- Discussed the pathogenic features of COVID-19 and manifestations of extrapulmonary infection. His presentation looked at diseases similar to COVID-19 where more literature exists. For Severe Acute Respiratory Syndrome (SARS), neurological and psychiatric sequelae have been reported in some studies. It is unclear why SARS and COVID-19 manifest so differently. They are similar in sequence and use the same receptor, so they should manifest similarly.

Dr. Kanta Subbarao:

- Options for studying COVID-19 infection and its consequences include:
 - Intact animals (largely mice); and
 - Stem cell derived human tissues, including adult tissue, pluripotent stem cells, and embryonic stem cells.
- Studies in mice have shown that COVID-19 causes long-term lung tissue damage. There is also some evidence of cell death and microhemorrhages (small focal intracerebral hemorrhages) in the cerebellum and brain stem.

Comments:

- It is plausible that kids have a stronger T-Cell count (cells that maintain immune homeostasis in humans over decades but can also be responsible for inflammatory or autoimmune disease response) which is why they are less likely to show symptoms.
- The cytokine storm (an immune response where the body starts to attack its own cells and tissues rather than just fighting off the virus, and is a relatively common COVID-19 reaction) is likely a part of the reason why there is so much damage to the body.
- The delayed T-Cell response may cause by lymphocytopenia (lymphocytopenia is an abnormally low number of lymphocytes, a type of white blood cell that helps fight viruses).

Post-Acute COVID-19 Perspectives

Dr. Avi Nath on Neurological, Psychiatric, and Neuromuscular Sequelae

- All human coronaviruses cause neurological damage. Cerebral complications of COVID-19 include:
 - Anosmia (loss of smell)
 - Encephalopathy (diffuse disease of the brain that alters brain function or structure)
 - Stroke
 - Meningitis/encephalitis (brain inflammation)
 - Seizures
 - Leukoencephalopathy (disorders of brain white matter)
 - Acute disseminated encephalomyelitis (brain and spinal cord inflammation)
 - Acute necrotizing hemorrhagic encephalitis (bleeding and tissue death in the brain)
 - Limbic encephalitis (autoimmune conditions characterized by inflammation)
 - Multisystem inflammatory syndrome (Kawasaki's disease)
 - Myalgic encephalomyelitis/chronic fatigue syndrome, and
 - Dysautonomia (dysfunction of the autonomic nervous system, which can affect the heart, bladder, and intestines, and blood vessels).
- Dr. Nath discussed three of the above COVID-19 complications in more depth.
 - Encephalopathy: One study found patients who experienced encephalopathy due to contracting COVID-19 had a hospital stay which was 3 times as long as other patients. One third of hospitalized patients had an altered mental status and two-thirds were unable to manage activities of daily living upon discharge. Encephalopathy onset was independent of the severity of respiratory disease. Encephalopathy was more common in older patients, though neurological symptoms are generally more common in young patients

- Anosmia: Data is currently unclear whether the virus can enter through the olfactory pathway. Case reports have seen a pattern of frontal lobe involvement which suggests viral transmission from olfactory pathways. One study looked into mapping a pathway in mice to assess whether the virus could travel from the nose to the brainstem (which controls respiration). However, there is currently no evidence of an olfactory transmission pathway with COVID-19. If it does happen, there is a concern for Ondine's curse (central hypoventilation system) resulting in a build-up of CO₂, which can result in death
- Encephalitis: There have been multiple types of encephalitis seen in COVID-19 patients including:
 - Viral encephalitis
 - Acute disseminated encephalomyelitis (brain and spinal cord inflammation)
 - Acute necrotizing hemorrhagic encephalitis (bleeding and tissue death in the brain)
- During the post-acute phase of COVID-19, there are several common nervous system symptoms. Fatigue is the most common symptom, followed by memory and concentration loss, headache, and insomnia.
- One study also compared psychiatric symptoms, anxiety disorders, and insomnia in patients with COVID-19 versus influenza and found that mental disorders are much more common in COVID-19 patients.
- The above post-acute conditions are also present in patients with long-COVID. However, before providers designate a condition or symptom as long-COVID, they should first assess whether the symptoms result from:
 - Other comorbidities
 - Residual damage from acute infection
 - Persistent or restricted viral replications
 - Persistent immune activation, or
 - Unknown cause
- Several major unanswered questions remain:
 - Whether the virus targets immune cells in the central nervous system?

- What is the mechanism of viral spread to the brain?
- What is the proper characterization of types of post-COVID neurological sequelae?
- What are the types of intervention studies which should be done?

Dr. Wendy Post on Cardiovascular Sequelae

- We do not know all the long-term effects of COVID-19 and need more clinical investigations.
- Much of the initial concern for long-COVID patients stems from cardiac MRI study results (German and Wuhan studies).
- These studies led to concern for cardiac risk for college athletes. Cardiovascular Magnetic Resonance (CMR) results have led to discussions for appropriate tests and return to play conditions
- Postural Orthostatic Tachycardia, or POTs (a condition characterized by too little blood returning to the heart when moving from a lying down to a standing up position) is another long-COVID concern.
- There are also multiple studies describing high incidents of troponin elevations, which represent myocardial necrosis.
- Additionally, patients with COVID-19 have experienced endothelial dysfunction and thrombosis. COVID-19 infects endothelial cells (blood vessels) through binding to the ACE2 receptor which results in a downregulation of ACE2. Activated endothelial cells release cytokines which can lead to inflammation, vasoconstriction, and thrombosis.
 - Of the 3,334 consecutively hospitalized COVID-19 patients at NYU, 29% of ICU patients had a thrombotic event and 12% of the 2,505 non-ICU patients had a thrombotic event.

Dr. Terri Hough on Pulmonary Sequelae

- COVID-19 targets the respiratory systems. During the initial infection, host airway cells are infected:
 - During early COVID-19, patients have an infection and inflammation of bronchial and alveolar epithelium and capillary endothelium,

- During progressed, or later COVID-19, patients experience:
 - A loss of the epithelial-endothelial barrier integrity.
 - Inflammatory infiltrates in interstitial and alveolar spaces.
 - Edema fluid accumulated with hyaline membrane formation.
 - Microthrombosis of pulmonary capillaries.
 - And possible development of pulmonary emboli (blood clot).
- Many individuals have asymptomatic infections and mild illness is most common. Only 5-10% of infections lead to hospitalization. Of those hospitalized:
 - Most patients are hypoxemic (have a low level of oxygen in the blood)
 - 24-36% receive ICU care
 - 12-24% receive mechanical ventilation
- Acute Respiratory Distress Syndrome (ARDS) is common and is a serious lung condition that causes low blood oxygen due to lung damage and fluid retention. A cough and labored breathing are also common COVID-19 sequelae.
- Respiratory failure is often prolonged. In the early days of combatting the virus, only a third of patients survived and were liberated from a ventilator in 14 days.
- A meta-analysis of 148 early studies, including 24,410 adults, described the top 5 presenting symptoms:
 - Fever (78%)
 - Cough (57%)
 - Fatigue (31%)
 - Hyposmia (25%)
 - Dyspnea (23%) (labored breathing)
- Chest imaging is abnormal in most infected patients.
- Researchers have noted several persistent abnormalities in hospitalized patients:
 - Spirometry shows mild air flow obstruction in 10% of patients, which is not associated with COVID-19 severity.
 - Total lung capacity is mildly reduced in 10-20% of hospitalized patients versus 4% of patients recovering in outpatient settings.

- Diffusing capacity is mildly to moderately reduced in 55% of severe and critically ill patients, 33% of hospitalized/less sick patients, and not reduced in patients recovering in an outpatient setting.
- A reduction in ground glass opacities is seen in all hospitalized patients (with a residual abnormality seen in 91% of patients). However, 93% of chest x-rays are normal in patients recovering in an outpatient setting
- Long-COVID presents a lot like post-sepsis and post-intensive care syndrome, so there is a need to dissect it and distinguish it from those diagnosis. Additionally, how to define the length of time an individual continues to present with symptoms before diagnosing long-COVID is an area of needed discussion. Some data refers to long-COVID as starting after four weeks; however, there are still patients on ventilators at the four-week mark who have not transitioned to the post-acute COVID-19 phase where long-COVID becomes apparent.
- There is limited data at this time and many questions remain, including:
 - What are risk factors for protracted symptoms?
 - What acute care factors/treatments modify the course of recovery?

Dr. Hashem El-Serag on Renal, Gastrointestinal (GI), and Metabolic Sequelae

- Providers are seeing high rates of acute kidney injury, thrombotic microangiopathy (damage including clots in capillaries and arterioles), and focal glomerulosclerosis (kidney disorder exemplified by scar tissue that forms in some of the glomeruli in the kidneys).
- There is evidence that SARS-CoV-2 directly infects the kidney.
- Among hospitalized patients, several GI/Liver manifestations are common, including:
 - Diarrhea (7.7%)
 - Nausea/vomiting (7.8%)
 - Abdominal pain (3.6%)

- Patients with elevated aspartate aminotransferase (AST) (an enzyme released into blood when liver or muscle cells are damaged) (15.%)
- Patients with elevated alanine transaminase (ALT) (an enzyme that increases in blood when the liver is damaged) (15%)
- Patients with elevated T. Bilirubin (a yellow/orange pigment) (16.7%)
- Viral shedding (viral replication) in stool which continues after respiratory samples are no longer positive
- Literature has also “exploded” to assess the relationship between COVID-19 and metabolic disease, primarily diabetes. After cardiovascular conditions, diabetes is one of the main indicators of increased COVID-19 mortality.
- There are several key unknowns related to COVID-19 and its effects:
 - What is the relevance of continued viral replication in the stool after negative viral respiratory samples?
 - What are the intermediate and long-term changes in gut permeability and gut microbiomes/dysbiosis (imbalance of the intestinal microbiota)?
 - What are the long-term impacts of gut microbiome related diseases (inflammatory bowel disease, irritable bowel syndrome, non-alcoholic fatty liver disease)?
 - What does the longitudinal follow-up of COVID-19 patients show?
 - Whether to incorporate COVID-related testing/assays in existing disease specific cohorts or case-control studies?
 - Whether tissue biobanks and/or patient registries aid in addressing these questions?

Dr. Judith James on Immunologic and Rheumatologic Sequelae

- Providers have seen several post-acute COVID-19 rheumatologic and immunologic conditions, which include:
 - Multi-system Inflammatory Syndrome in adults (MIS-A)

- Anti-phospholipid antibody syndrome (disorders that occur if the body's immune system makes antibodies that attack and damage tissues or cells)
- Vasculitis (inflammation of blood vessels)
- Prolonged fatigue, malaise, myalgias (muscle aches), and arthalgias (joint pain), often with a positive ANA (post-COVID fibromyalgia or Type 2 lupus-like disease)
- Prolonged lymphopenia (when the blood is missing white blood cells)
- Autoantibody positivity
- Dr. James addressed several of these conditions in more detail.
 - Multi-system Inflammatory Syndrome in adults (MIS-A):
 - The weekly COVID-19 Morbidity and Mortality Report (MMWR) for October 9, 2020 reported that 27 patients, nearly all African American or Hispanic, had MIS-A.
 - There are five criteria used for linking MIS-A with COVID-19:
 - Severe illness requiring hospitalization in a person older than 21
 - Positive COVID-19 test
 - Severe dysfunction of one or more extrapulmonary organ systems
 - Laboratory evidence of severe inflammation
 - Absence of severe respiratory illness
 - About half of the 27 reported patients had a prior respiratory disease. Nearly all of the patients had cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms, without severe respiratory illness. Renal, skin, and eye inflammation symptoms were also seen.
 - Treatment for MIS-A usually includes Intravenous immunoglobulin (IVIG) inhibitors and Janus Kinase (JAK) inhibitors. However, the pathogenic mechanisms related to COVID-19 are not yet understood.

- Vasculopathy and Vasculitis (disease/inflammation of blood vessels) can occur in the central nervous system, kidney, aorta, arteries, GI track, skin, and other organs either with the initial COVID-19 infection or later. This can also occur concurrently with thrombosis and can be life threatening.
- Postthrombotic Antiphospholipid Antibodies (when the immune system mistakenly creates antibodies which make it more likely for blood to clot) were recently detected in patients with COVID-19. A significant percentage of patients with COVID-19 (30-50%) are at least transiently positive for it.
- Post-COVID fatigue, malaise, myalgias (muscle aches), and arthralgias (joint pain) can last for months after COVID-19 onset. Combined symptoms resemble patients with fibromyalgia (such as profound myalgia, trouble thinking or remembering, myalgias, arthralgias, headaches, shortness of breath, chest wall pain). Some patients also have positive ANA and lingering lymphopenia, which is similar to lupus.

Dr. Peter Rowe on Pediatric Sequelae

- Providers are seeing long-COVID in children.
- Case reports and systematic reviews suggest children can experience long-COVID similar to adults and with similar symptoms (such as fatigue, dyspnea, palpitations, headache, brain fog, etc.).
- However, there is no consistent ascertainment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) features.

Summary of Breakout Sessions on Day #2

Breakout Session 1: Neurological/Psychiatric/Neuromuscular Sequelae

- Around 70% of long-COVID sufferers have long-term fatigue.
- The prevalence of specific neurological issues for long-COVID include:

- Encephalopathy: 3-32%
- Acute ischemia: 1-4%
- Intracranial hemorrhage: 0.2-1%
- Neuropsychiatric disorders (mental disorders attributable to diseases of the nervous system): 5-40%
- Neurogenic respiratory failure: unclear
- Dysautonomia (a condition in which the autonomic nervous system does not work properly, which may affect the functioning of the heart, bladder, intestines, sweat glands, pupils, and blood vessels): unclear
- Skeletal muscle injury: 5-20%

Breakout Session 2: Cardiovascular Sequelae

- As it relates to long-COVID, there is a severe lack of information. More studies need to be done.
- It is unclear what the most effective diagnostic imaging test is.
- Asymptomatic and premorbid conditions are missing from the studies that are being conducted.
- There is a need for myocardial assessments for various populations.
- Researchers need to do a better job differentiating patients with acute respiratory distress syndrome (ARDS) and those with less severe disease.

Breakout Session 3: Pulmonary Sequelae

- The severity of illness does not necessarily equal the severity of sequelae. This makes research difficult because many people who get infected with mild COVID-19 (and later develop long-COVID) do not go to the hospital and/or their doctor.
- Dyspnea (shortness of breath) that is unexplained by exams, imaging, and pulmonary function tests can still be extremely debilitating.
- Even when a patient has dyspnea that can be explained by some diagnostic, there are still issues because people might get dyspnea for many different reasons. Doctors might need to conduct multiple diagnostic tests to figure out the source of the dyspnea, and this can lead to a higher

chance of misdiagnosis and therefore a higher chance of using the incorrect treatment.

Breakout Session 4: Renal/GI/Metabolic Sequelae

- A very common long-COVID complication is long-term diarrhea. Around 19% of patients experience regular diarrhea even 6 months after initial infection, sometimes up to 5 times a day. Some people also experience hemorrhoids and/or have blood in their stool.
- Many patients are also experiencing acid-reflux symptoms.
- COVID-19 can cause job loss, fear, depression, etc. Long-COVID can exacerbate this. Some people cope by eating more food and/or drinking excess alcohol. This causes further damage to the GI tract.
- Long-term impact on the brain-gut axis include:
 - Irritable bowel syndrome; and
 - Functional dyspepsia (indigestion).
- Long-term impact on the gut microbiome include:
 - Inflammatory bowel disease;
 - Irritable bowel syndrome;
 - Non-alcoholic fatty liver disease; and
 - Clostridium difficile colitis (an infection that results from the disruption of normal healthy bacteria in the colon).

Breakout Session 5: Immunologic/Rheumatologic Sequelae

- There needs to be more data on how various COVID-19 vaccines work on persons with immune disorders.
- Need to determine:
 - Whether there should there be a different risk assessment for persons with immune disorders?
 - What would constitute a reasonable assessment of safety for these populations?
 - How long after a vaccine approval would complications become apparent?

- The vaccine candidates currently seeking EUA approval are mRNA based, which is a new vaccine platform. Therefore, older data might not be useful.

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