ASPR TRACIE Technical Assistance Request

Request Receipt Date (by ASPR TRACIE): 1 March 2021
Response Date: 10 March 2021
Type of TA Request: Complex

Request:

ASPR TRACIE received a request for information on clinical presentation, disease progression, and related information from clinicians in the field treating COVID-19 patients after the acute phase of the virus has passed, frequently referred to as "COVID long haulers."

Response:

- COVID-19, like other infections, can leave lingering effects for patients long after they have recovered from the acute phase of the illness, even if they only had mild symptoms.
- COVID-19 post-illness syndrome presents differently from other post-illness syndromes previously identified, although research from the previous Severe Acute Respiratory Syndrome (SARS) epidemic suggests that significant percentages of those patients had lasting problems with fatigue, depression, and lung function as well.
- The potentially unique nature of the ongoing effects from COVID-19 infection requires comprehensive long-term patient management to address a diverse set of symptoms.
- Many long-term symptoms of COVID-19 are directly related to the effects of hospitalization and damage to the lungs and other organs with resulting fatigue and shortness of breath that may persist for months. Over 30% of hospitalized patients in one study had significant residual symptoms two months after discharge and over 60% had symptoms at 6 months in another study.
- Less well understood and characterized are persistent fatigue, neurologic, and inflammatory changes, and other symptoms that persist after milder illness and affect approximately 10% of patients.
- NIH recently announced a new initiative to study "Long COVID," which they have named Post-Acute Sequelae of SARS-CoV-2 infection (PASC).
- NIAID has speculated that PASC is similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).
- In the February 16, 2021 Project ECHO COVID-19 Clinical Rounds series, clinicians discussed long-term COVID-19 care, post-discharge and establishing clinic models for follow-up care.

COVID-19 can leave survivors with symptoms related to organ or systemic damage, to include:

- **Heart** – lasting damage to heart muscle, myocardial inflammation, ventricular dysfunction
- **Lungs** – long term damage and scarring to tiny air sacs (alveoli)
- **Brain** – strokes, seizures, Guillain-Barre syndrome, increased risk of Parkinson's and Alzheimer's, sleep dysregulation, altered cognition, memory impairment, olfactory and gustatory dysfunction (smell and taste)
- **Kidneys** – acute kidney injury and delayed effects on renal function

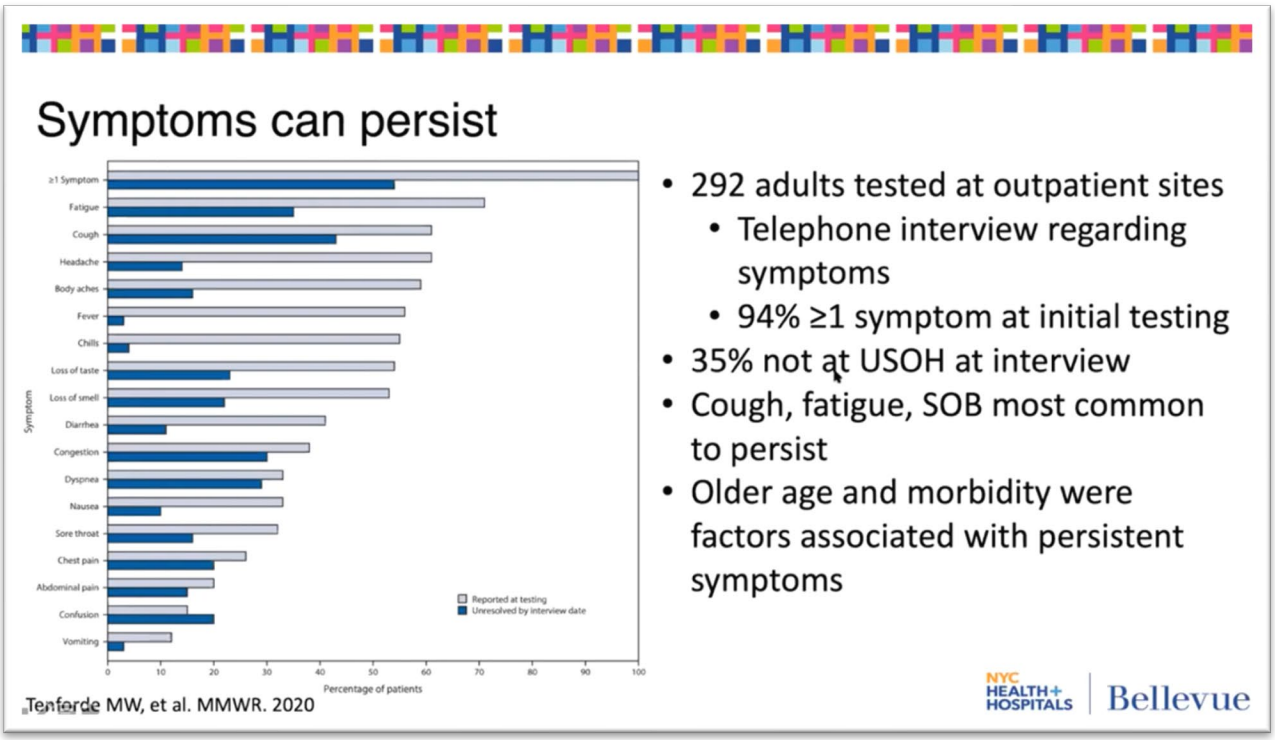
The most common long-term symptoms include:

- Fatigue
- Shortness of breath
- Cough
- Joint pain
- Chest pain
- Muscle pain or headache
- Fast or pounding heartbeat
- Loss of smell or taste
- Memory, concentration or sleep problems
- Rash or hair loss
- Blood clots and blood vessel problems
- Mood disruption – depression, anxiety
- Difficulty sleeping
- Difficulty concentrating
- Inability to exercise
- Rash
- Alopecia

A study of non-hospitalized patients with long-term symptoms revealed that the severity of the acute phase does not necessarily corollate with the number, severity, and persistence of ongoing symptoms.

- In one study, 35% of outpatient COVID-19 patients still did not feel back to themselves by the second check-up.
- The most common persisting symptoms were cough, shortness of breath, or fatigue.
- Morbidity factors and older age made it more common to continue to experience symptoms, however, long-term symptoms occurred in every age group.

Figure 1. Bellevue Perspective of Ongoing Symptoms.



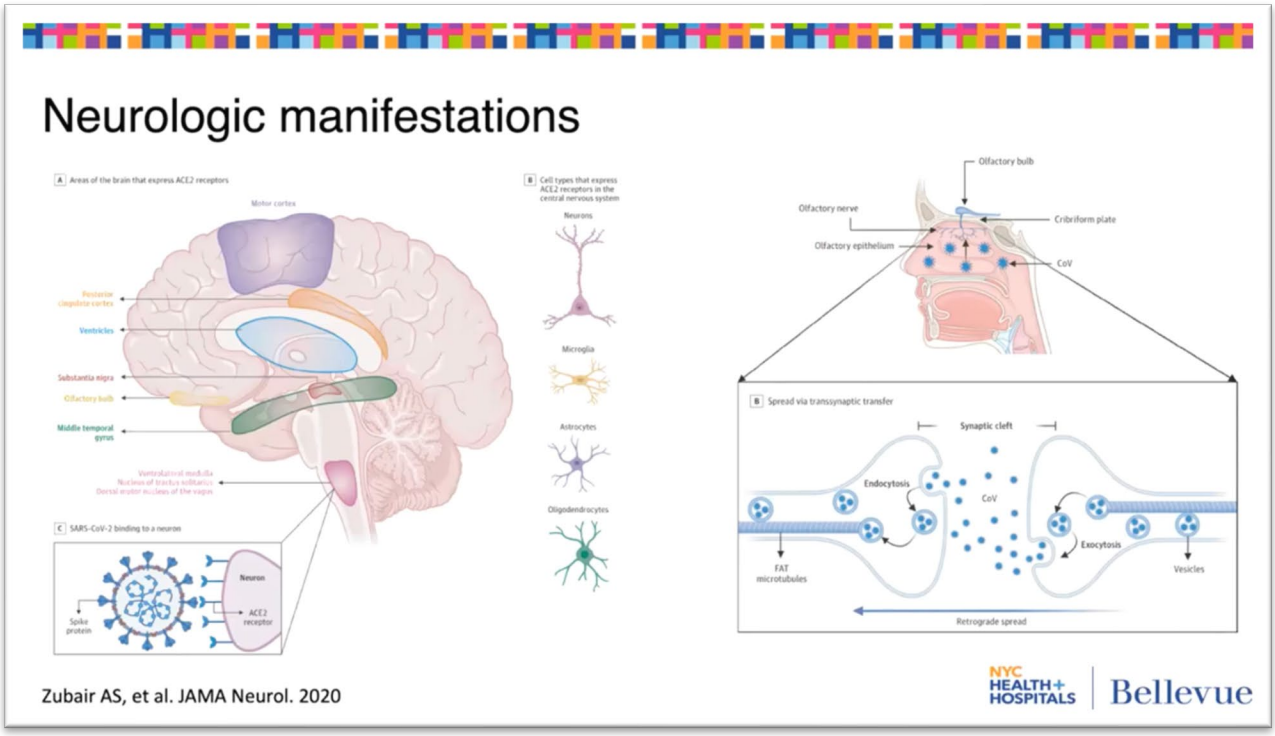
This slide from Bellevue's (NY) presentation during Project ECHO COVID-19 clinical rounds, dated 12/8/2020, illustrates ongoing symptoms which can occur in COVID-19 patients after they have recovered from the acute phase of the illness. It also notes that cough, fatigue, shortness of breath are the most common symptoms to continue. Among 292 patients who were diagnosed and remained outpatients, 94% had more than one symptom at initial testing, and 35% did not feel well at the time of their interview. Older age and co-existing conditions were factors, but ongoing symptoms were observed and reported in every age group.

Review of Systems

Neurologic

- Most common persisting neurologic symptoms are headache, inability to smell or taste, and cognitive changes ("brain fog").
- COVID-19 can infect the brain. New evidence shows the spike protein on the COVID-19 virus can attach to ACE2 receptors. Depending on which route the virus infects determines on the associated symptoms. COVID-19 can use several routes of infection to reach the central nervous system. Also, megakaryocyte clumps have been found on post-mortem examination, which is unexpected and may contribute to the unique neuropathologies.

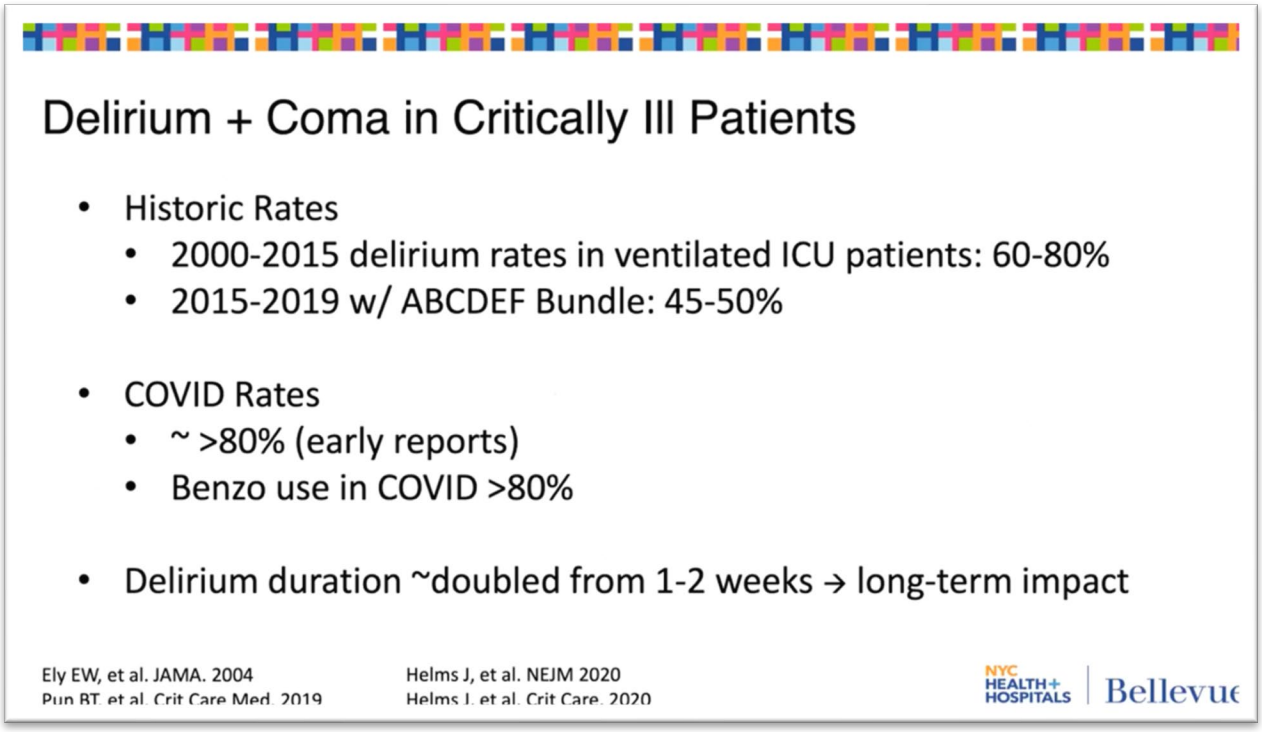
Figure 2. Bellevue Perspective on COVID's Effect on Neurological Systems.



This slide from Bellevue's (NY) presentation during Project ECHO COVID-19 clinical rounds, dated 12/8/2020 illustrates the different routes by which COVID-19 can infect the neurological system and pathways to invade the central nervous system.

- Delirium and coma in ICU patients on a ventilator occur in between 60-80% of patients treated in the ICU. This can lead to prolonged hospitalization and continued symptoms after discharge.
- COVID-19 requires heavy sedation and the use of more benzodiazepines, which can delay weaning off ventilators, prolonging the need for the sedation.
- Long-term use and high doses of benzodiazepines can result in dependence and withdrawal symptoms that can be problematic long after hospital discharge.

Figure 3. Bellevue Perspective on Delirium and Coma in Patients Intubated in the Intensive Care Unit (ICU).



This slide from Bellevue's (NY) presentation during Project ECHO COVID-19 clinical rounds, dated 12/8/2020 illustrates the statistics of improvement in reducing delirium in patients intubated within the (ICU). Due to requirements of intubation for COVID-19 patients, clinicians have documented a return to delirium rates seen prior to the introduction of the ABCDEF bundle[1] due to required high dosage of benzodiazepines to achieve the appropriate level of sedation.

Cardiovascular

- Potential long-term cardiovascular effects may include:
  - heart failure
  - life-threatening arrhythmias
  - sudden cardiac death
  - impaired myocardial flow reserve from microvascular injury
  - coronary artery and aorta aneurysm formation
  - hypertension
  - labile heart rate and blood pressure responses to activity
  - accelerated atherosclerosis
  - both venous and arterial thromboembolic disease
  - myocarditis
  - other signs and symptoms

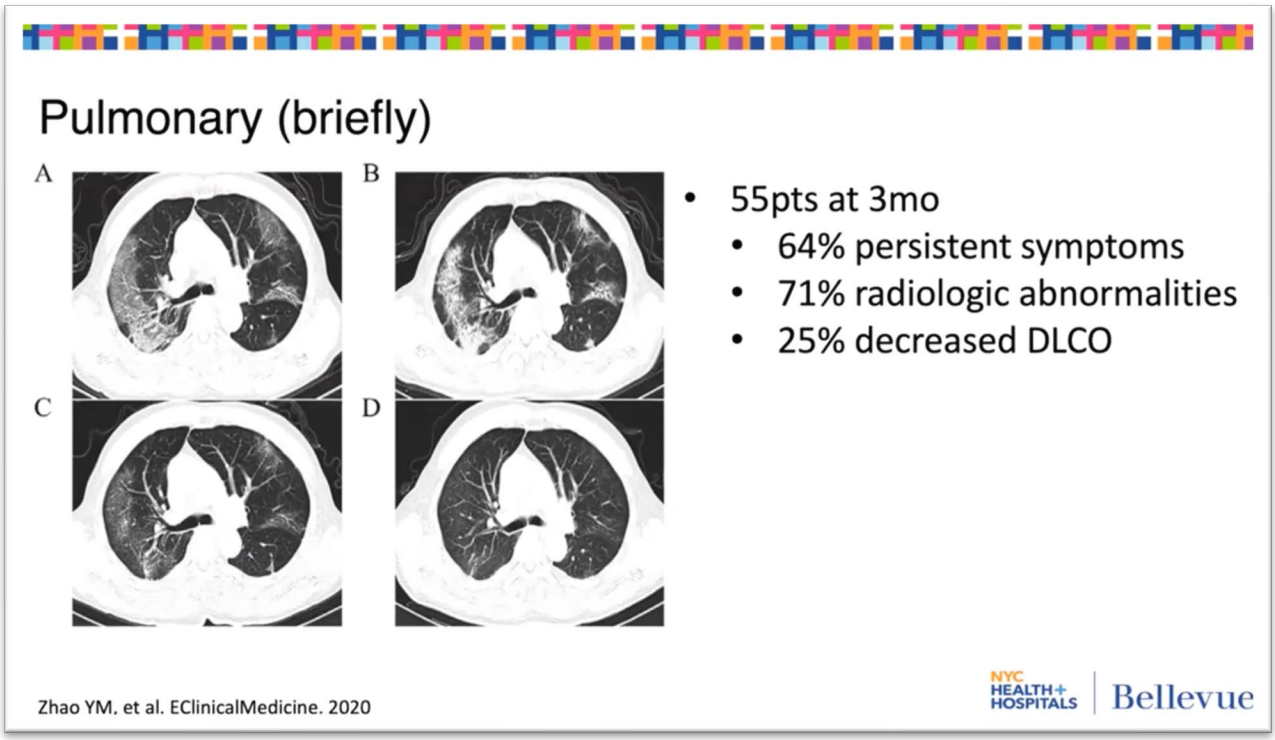
[1] The ABCDEF bundle includes these steps: Assess, Prevent, and Manage Pain; Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT); Choice of analgesia and sedation; Delirium: Assess, Prevent, and Manage; Early mobility and Exercise; and Family engagement and empowerment.

- At 71 days after diagnosis, a cardiac MRI (cMRI) examined the cardiovascular system of COVID-19 patients. Seventy-eight percent (78%) showed cardiac involvement. Sixty percent (60%) showed myocardial inflammation. However, the clinical significance of this is unknown.
- In one study of outpatient athletes, the majority without symptoms, 46% showed myocarditis or prior myocardial injury 53 days into recovery. This finding has not been replicated in other studies.

Pulmonary

- COVID infections can cause long-term pulmonary symptoms, including:
  - cough
  - shortness of breath and fevers
  - respiratory failure
  - pulmonary hypertension
- Individuals may experience overall worsening of lung conditions, such as:
  - asthma
  - chronic obstructive pulmonary disease (COPD)
  - interstitial lung disease
- In a study from China examined patients at three months after diagnosis, 64% had persistent pulmonary symptoms, 71% had radiologic abnormalities, and 25% had decreased diffusing capacity for carbon monoxide (DLCO).
- A recent study out of Belgium looking at critical status and lung function of severe patients 10 weeks after severe COVID-19 infection found that 54% survivors of severe COVID showed abnormal lung function measured by PFTs 10 weeks after disease presentation. People who were critically ill had more dysfunction. It was not statistically linked to persistently abnormal imaging, labs, or residual symptoms.

Figure 4. Bellevue Perspective on Systemic Pulmonary Long-term Symptoms



This slide from Bellevue's (NY) presentation during Project ECHO COVID-19 clinical rounds, dated 12/8/2020 illustrates three-month imaging from a Chinese study on the pulmonary system.

Mental Health

- COVID-19 may precipitate or exacerbate psychiatric symptoms. It is unclear the degree to which the illness is directly linked.
- One literature review noted substantial increases in anxiety and depression, substance use, loneliness, domestic violence and child abuse.

Long Term Patient Needs

The panelists from Project ECHO COVID-19 clinical rounds, dated 12/8/2020 listed numerous services and products that patients will likely require after recovery, including:

- Monitoring for cardiac, neurologic, pulmonary, renal, and psychiatric symptoms that require further workup
- Monitoring of cardiopulmonary performance for those with known impairment
- Medications including supportive pulmonary therapies, anticoagulation therapies
- Physical therapy
- Psychological support and access to professional resources

- Chronic oxygen therapy will be necessary for those patients who continue to have low blood oxygen levels on room air.
- Connection to a clinic can ensure patients have access to all the clinical services to continue to support their recovery.

Long-Term Systemic Needs

In anticipation of the ongoing long-term treatment of COVID survivors, the panelists of the Project ECHO COVID-19 clinical rounds, dated 12/8/2020 identified several ongoing challenges to providing services to long-term patients as well as some opportunities to mitigate these challenges, such as:

- Inadequate bandwidth to care for complicated post-COVID-19 patients in a clinic setting in addition to all other duties
- The need for coordination between caregivers to provide cohesive case management for those with multi-modal disease
- Enthusiasm wanes when caregivers do not see immediate results (e.g., someone recovering or symptoms improving with therapies) which may require dedicated clinic personnel, personnel rotation, or other strategies to ensure their commitment and energy is focused on these patients and not divided among various tasks or responsibilities.

Opportunities to Improve Long-Term Patient Management

- Provide access to specialized COVID clinics which provide a "one stop shop" to see clinicians and professionals who are working as a team to provide comprehensive care to COVID survivors (Project ECHO COVID-19 clinical rounds, dated 12/8/2020)
- Telemedicine can help in remote areas or to replace some visits, but it does not replace the experience of in-person care (Project ECHO COVID-19 clinical rounds, dated 12/8/2020)

Sources

- Anticipating the long-term cardiovascular effects of COVID-19
- As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts
- Cardiac Involvement After Recovering From COVID-19—Reply
- Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection
- Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults
- Clinical Status and Lung Function 10 weeks after severe SARS-CoV-2 infection
- COVID-19 (coronavirus): Long Term Effects
- Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit
- Follow-up of adults with non-critical COVID-19 two months after symptoms' onset

- Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery
- Late Sequelae of COVID-19
- Long-Term Effects of COVID-19
- Management of post-acute covid-19 in primary care
- Mental Health UK. Managing your mental health during the coronavirus outbreak
- Neurologic Features in Severe SARS-CoV-2 Infection
- Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019
- Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?
- Persistent Symptoms In Patients After Acute COVID-19
- Pharmacological treatment of delirium in the intensive care unit
- Post-Acute COVID-19 Syndrome
- Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19
- Project ECHO, Clinical Rounds, 12/8/2020, Video.
- Short- and Long-term Lung Damage from COVID-19
- Sixty-Day Outcomes Among Patients Hospitalized With COVID-19
- Social Media and Emergency Preparedness in Response to Novel Coronavirus
- The Mental Health Consequences of COVID-19 and Physical Distancing: The Need for Prevention and Early Intervention
- The Tragedy of the Post-COVID "long haulers"
- Toward understanding the 2019 Coronavirus and its impact on the heart