

Covid-19 Long-Term Sequelae are Unknown

By M. Alexander Otto
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The take-home message from a growing number of recent COVID-19 case reports is that the infection might be far more than a respiratory disease.

Although a cause-and-effect relationship is unknown, people with the virus have presented with or developed heart disease, acute liver injury, ongoing GI issues, skin manifestations, neurologic damage, and other problems, especially among sicker people.

For example, French physicians described an association with encephalopathy, agitation, confusion, and cortico-spinal tract signs among 58 people hospitalized with acute respiratory distress (N Engl J Med. 2020 Apr 15. doi: 10.1056/NEJMc2008597).

In particular, Yale New Haven (Conn.) Hospital is dealing with unexpected complications up close. Almost half of the beds there are occupied by COVID-19 patients. Over 100 people are in the ICU, and almost 70 intubated. Of the more than 750 COVID admissions so far, only about 350 have been discharged. "Even in a bad flu season, you never see something like this; it's just unheard of," said Harlan Krumholz, MD, a Yale cardiologist and professor of medicine helping lead the efforts there.

Kidney Injuries Prominent

"When they get to the ICU, we are seeing lots of people with acute kidney injuries; lots of people developing endocrine problems; people having blood sugar control issues, coagulation issues, blood clots. We are just waking up to the wide range of ways this virus can affect people. Our ignorance is profound," Dr. Krumholz said, but physicians "recognize that this thing has the capability of attacking almost every single organ system, and it may or may not present with respiratory symptoms."

It's a similar story at Mt. Sinai South Nassau, a hospital in Oceanside, N.Y. "We've seen a lot of renal injury in people having complications, a lot of acute dialysis," but it's unclear how much is caused by the virus and how much is simply because people are so sick, said Aaron Glatt, MD, infectious disease professor and chair of medicine at the hospital.

However, he said things are looking brighter than at Yale.

"We are not seeing the same level of increase in cases that we had previously, and we are starting to see extubations and discharges. We've treated a number of patients with plasma therapy, and hopefully that will be of benefit. We've seen some response to" the immunosuppressive "tocilizumab [Actemra], and a lot of response to very good respiratory therapy. I think we are starting to flatten the curve," Dr. Glatt said.

"Look for tricky symptoms"

The growing awareness of COVID's protean manifestations is evident in Medscape's Consult forum, an online community where physicians and medical students share information and seek advice; there have been over 200 COVID-19 cases and questions since January.

Early on, traffic was mostly about typical pulmonary presentations, but lately it's shifted to non-respiratory involvement. Physicians want to know if what they are seeing is related to the virus, and if other people are seeing the same things.

There's a case on Consult of a 37-year-old man with stomach pain, vomiting, and diarrhea, but no respiratory symptoms and a positive COVID test. A chest CT incidental to his abdominal scan revealed significant bilateral lung involvement.

A 69-year-old woman with a history of laparotomy and new-onset intestinal sub-occlusion had only adhesions on a subsequent exploratory laparotomy, and was doing okay otherwise. She suddenly went into respiratory failure with progressive bradycardia and died 3 days later. Aspiration pneumonia, pulmonary embolism, and MI had been ruled out. "The pattern of cardiovascular failure was in favor of myocarditis, but we don't have any other clue," the physician said after describing a second similar case.

Another doctor on the forum reported elevated cardiac enzymes without coronary artery obstruction in a positive patient who went into shock, with an ejection fraction of 40% and markedly increased heart wall thickness, but no lung involvement. There are also two cases of idiopathic thrombocytopenia without fever {or} hypoxia.

An Italian gastroenterologist said: "Look for tricky symptoms." Expand "patient history, asking about the sudden occurrence of dysgeusia and/or

anosmia. These symptoms have become my guiding diagnostic light” in Verona. “Most patients become nauseated, [and] the taste of any food is unbearable. When I find these symptoms by history, the patient is COVID positive 100%.”

aotto@mledge.com

“Make sure that they didn't die in vain”

There was interest in those and other reports on Consult, and comments from physicians who have theories, but no certain answers about what is, and is not, caused by the virus. Direct viral attack is likely a part of it, said Stanley Perlman, MD, PhD, a professor of microbiology and immunology at the University of Iowa, Iowa City.

The ACE2 receptor the virus uses to enter cells is common in many organs, plus there were extra-pulmonary manifestations with severe acute respiratory syndrome (SARS), another pandemic caused by a zoonotic coronavirus almost 20 years ago. At least with SARS, “many organs were infected when examined at autopsy,” he said.

The body’s inflammatory response is almost certainly also in play. Progressive deangements in inflammatory markers C-reactive protein—D-dimer, ferritin correlate—with worse prognosis, and “the cytokine storm that occurs in these patients can lead to a degree of encephalopathy, myocarditis, liver impairment, and kidney impairment; multi-organ dysfunction, in other words,” said William Shaffner, MD, a professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center, Nashville, Tenn.

But in some cases, the virus might simply be a bystander to an unrelated disease process; in others, the experimental treatments being used might cause problems. Indeed, cardiology groups recently warned of torsade de pointes—a dangerously abnormal heart rhythm—with hydroxychloroquine and azithromycin.

“We think it’s some combination.” but don’t really know, Dr. Krumholz said. In the meantime, “we are forced to treat patients by instinct and first principles,” and long-term sequelae are unknown. “We don’t want to be in this position for long.”

To that end, he said, “this is the time for us all to hold hands and be together because we need to learn rapidly from each other. Our job is both to care for the people in front of us and make sure that they didn’t die in vain, that the experience they had is funneled into a larger set of data to make sure the next person is better off.”