We have underestimated and misunderstood COVID-19 since it first appeared

As we learn more, it's clear that COVID-19 can be more than just a respiratory disease. It's joined the ranks of other “great imitators” -- diseases that can look like almost any condition.

COVID-19: What to Know if You Have a Heart Condition
Though COVID-19 mainly affects the lungs, the virus can make it harder for your heart to function as it should

ABOUT

It can be a gastrointestinal disease causing primarily diarrhea and abdominal pain. It can cause symptoms that may be confused with a cold or the flu. It can cause pinkeye, a runny nose, loss of taste and smell, muscle aches, fatigue, diarrhea, loss of appetite, nausea and vomiting, whole-body rashes, and areas of swelling and redness in just a few spots.

In a more severe disease, doctors have also reported people having heart rhythm problems, heart failure, kidney damage, confusion, headaches, seizures, Guillain-Barre syndrome, and fainting spells, along with new sugar control problems.

It's not just a fever and coughing, leading to shortness of breath, like everyone thought at first.
This makes it incredibly difficult to diagnose and even harder to treat.

“This is a disease progression we have never seen for any infection that I can think of, and I’ve been doing this for a couple of decades,” says Joseph Vinetz, MD, an infectious disease specialist at Yale School of Medicine.

How It Invades

When viral particles land in our eyes, nose, or mouth, “spike proteins” on the virus connect with a specific receptor, known as ACE2, on the surface of our cells, allowing entry. ACE2 receptors make a great target because they are found in organs throughout our bodies. Once the virus enters, it turns the cell into a factory, making millions and millions of copies of itself -- which can then be breathed or coughed out to infect others.

In order to evade early detection, the coronavirus uses multiple tools to prevent the infected cells from calling out for help. The virus snips off distress signal proteins that cells make when they are under attack. It also destroys antiviral commands inside the infected cell. This gives the virus much more time to make copies of itself and infect surrounding areas before it is identified as an invader. This is part of the reason why the virus spreads before immune responses, like fever, begin.

Direct Attack

Many with mild or no symptoms are able to fend off the virus before it gets worse. These people may have symptoms only in the upper airway, at the site where they were first infected. But when someone’s body can’t destroy the virus at its entry point, viral particles march deeper into the body. The virus seems to take a few paths from there, either setting up camp in the lungs, fighting its way into the digestive tract, or doing some combination of both.

“There’s clearly a respiratory syndrome, and that’s why some people end up in the hospital. Some people get a gastrointestinal illness with diarrhea, maybe some abdominal pain, which may or may not be associated with a respiratory illness,” says Vinetz.

Once the virus is deeply embedded in the body, it begins to cause more severe disease. This is where a direct attack on other organs that have ACE2 receptors can occur, including heart muscle, kidneys, blood vessels, the liver, and potentially the central nervous system. This may be one reason for the vast array of symptoms COVID-19 can cause.

“It’s highly unlikely that any other organs can be affected through direct invasion without severe disease,” Vinetz adds.

The brain and nerves may also fall prey to direct attack. Kenneth Tyler, MD, chair of the Department of Neurology at the University of Colorado School of Medicine, cautions that direct central nervous system (CNS) attack is still being worked out at this time.

There are many routes a virus could take to invade the CNS. One somewhat disputed view is that the loss of smell could indicate that the nerve responsible for smell is infected and can carry the virus into the CNS, including the brain. “This can be shown to occur in experimental models with non-human coronaviruses and is a potential route of invasion for some other viruses. However, there is no evidence to date establishing that this actually occurs with SARS-CoV-2,” the official name of the virus that causes COVID-19.

Early findings, including those from autopsy and biopsy reports, show that viral particles can be found not only in the nasal passages and throat, but also in tears, stool, the kidneys, liver, pancreas, and heart. One case report found evidence of viral particles in the fluid around the brain in a patient with meningitis.

COVID-19 is proving to be far more dangerous to far more parts of the body than previously believed.
Collateral Damage That Kills

Severe damage to the lungs may be one trigger that activates and overstimulates the immune system through a barrage of signaling chemicals, known as cytokines.

The flood of these chemicals can set off what is referred to as a "cytokine storm." This is a complex interplay of chemicals that can cause blood pressure to drop, attract more killer immune and inflammatory cells, and lead to even more injury within the lungs, heart, kidneys, and brain. Some researchers say cytokine storms may be the cause of sudden decompensation, leading to critical illness in COVID-19 patients.

The Relationship Between COVID-19 and Diabetes

Uncontrolled blood sugar can make it harder to fight off infection. Here’s what you should know about diabetes and COVID-19

at high rates even when patients are on blood thinners for clot prevention. In one study from the Netherlands, 31% of patients hospitalized with COVID-19 got clots while on blood thinners.

Cuker says that “new studies validate what we have all been seeing with our eyes, which is that ‘boy, it seems that these patients are clotting a lot.’ … And it could be that the rate of thrombotic events are even higher than we truly recognize.” Though the reason for the clotting is still not clear, it seems to be playing a much larger role in death than previously understood.

Beyond the collateral damage from cytokine storms and clotting, other things like low blood pressure that comes from a severe illness, low oxygen levels, ventilator use, and drug treatments themselves can all harm organs throughout the body, including the heart, kidneys, liver, brain, and other organs.

Double-Edged Sword

Even though researchers are learning more each day about the virus and how and where it attacks the body, treatment geared toward these targets also pose significant problems. Many drugs come with a risk of destroying the delicate balance that allows the body to help fight the disease or to manage inflammation.

The ACE2 receptor that the virus uses to enter cells is a key player in lowering inflammation and reducing blood pressure. Targeting or blocking this receptor as a treatment strategy to prevent viral entry into cells may actually worsen blood pressure, increase the risk of heart failure and kidney injury, and increase inflammation that may worsen lung injury.

Drugs that target the immune response to lower the risk of a cytokine storm may also tamp down the immune response, making it hard to kill off the virus over the long run.

Using medicines to prevent clotting may end up causing severe bleeding. Cuker points out that “we don’t have a good read on bleeding … we have limited evidence about the clotting risk … we have zero evidence on bleeding...
risk in these patients, and it's a real priority to understand this risk, especially because one of our strategies to treat the clotting is stepping up intensity of anti-coagulation.

Timing is likely to be key in treatment strategies. For example, patients may need a drug to boost the immune system early on in the disease, and then one to tamp it down if the disease progresses and cytokine markers begin to rise.

**Just the Tip of the Iceberg**

Cuker says that what we know about clotting and almost everything else when it comes to COVID-19 “is just the tip of the iceberg.”

Sanober Amin, MD, PhD, a dermatologist in Texas, agrees. She’s been tracking the wide variety of skin findings that dermatologists across the world have been noting on social media.

She recently posted images on social media that show the wide variety of skin findings she has been seeing and hearing about. Her post received a massive response. Amin says that “dermatologists from around the world, from Turkey to France to Canada to the U.S., are sharing information about rashes that they’ve observed in people with COVID-19.”

Some rashes seem to be consistent with what’s called a viral exanthema, which is a term for a general rash that can happen with almost any virus. But, Amin says, “some skin findings are more consistent with superficial clotting in blood vessels close to the skin.”

This is what some have started to call “COVID toes,” also called pernio. Dermatologists are seeing more cases of these small clots in toes and fingers, especially in children.

It’s hard to know which skin conditions are related to COVID-19 because a lot of people without “typical” symptoms are not being tested, Amin says. Researchers will still need to work out which symptoms may be caused by the virus and which may just be unrelated early findings.

**Unanswered Questions**

For now, much of the information we have about the symptoms of COVID-19 come from hospitalized patients who are very sick by the time they seek care and may not be able to share information about the early signs and symptoms they may have had.

**Best Practices for COVID-19**

About

Because of the lag in testing in the U.S., we still don’t know the full extent of what mild and moderate versions of the disease look like, or what effects the disease has on people who have many symptoms but aren’t quite sick enough to be hospitalized.

One open question is what the long-term effects may be for survivors. What does life look like after being on a ventilator or suddenly needing dialysis? Will we see decreases in heart, lung, and kidney function that is long-lasting and permanent, or will patients eventually recover?

We also don’t know how people will clear infections. If the new coronavirus ends up being an acute infection, like other coronaviruses, most recovered people should develop at least a short-term immunity. It’s also possible that the virus may persist as a latent infection, like chickenpox, lying dormant in the body, only to re-emerge periodically as shingles does, or become a chronic infection, like hepatitis B, living within the body for a sustained period of time, causing long-term damage.

“It’s definitely going to be an acute infection ... there’s no way it’s going to be latent or chronic, no way ... I think so... we’ll see,” Vinetz says.