

Medical News & Perspectives

Researchers Tie Severe Immunosuppression to Chronic COVID-19 and Virus Variants

Jennifer Abbasi

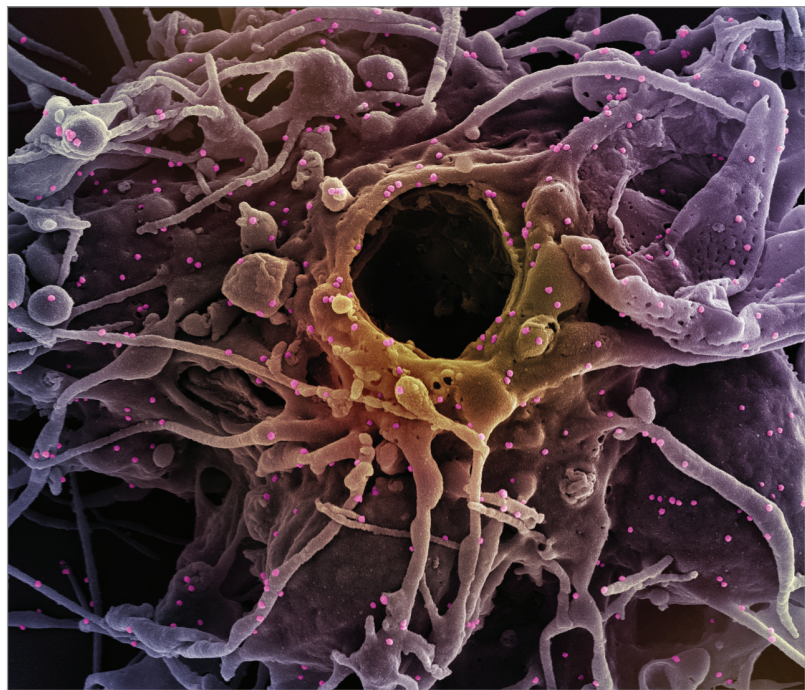
Last summer, a UK man in his 70s was admitted to Addenbrooke's Hospital in Cambridge with COVID-19 pneumonia. He hadn't been able to shake his illness since testing positive for SARS-CoV-2 more than a month earlier. Despite interventions including multiple rounds of the antiviral remdesivir and convalescent plasma, he died in the hospital's intensive care unit about 9 weeks after his arrival.

Throughout his hospitalization, the patient continued to test positive with a high viral load. This, along with his worsening illness, indicated that he was battling an ongoing infection with live, replicating virus for more than 100 days.

His body wasn't equipped for the task. Back in 2012 he had been diagnosed with marginal B-cell lymphoma. The blood cancer, along with the treatment he received for it, had wiped out his B and T cells—both arms of his adaptive immune response—leaving him severely immunocompromised.

University of Cambridge clinical microbiology professor Ravindra K. Gupta, MD, PhD, who consults part-time on infectious disease cases at Addenbrooke's, was involved in the patient's care. Gupta and colleagues analyzed the man's SARS-CoV-2 genomic sequences, which they had collected over 23 time points, starting with the first positive nasopharyngeal swab. Their findings, published in *Nature* in February, showed the virus evolving and adapting to treatment over the 3-month-long infection. The patient was likely contagious all along, Gupta said in an interview, although there's no evidence that the virus was transmitted to others.

A number of case studies like this one now demonstrate that some patients with severely weakened immune systems can take months to clear the novel coronavirus, if they ever do. These patients are potentially contagious for much longer than average. Compounding that, their prolonged infections and suboptimal therapies can provide the time and the evolutionary pressure for variants to emerge. The fear is that



A cell is infected with the SARS-CoV-2 B.1.1.7 variant (pink particles).

these changes could produce a more transmissible virus, like the B.1.1.7 variant of concern, or that the resulting variants could resist therapies or vaccines, as is potentially true with B.1.351 and P.1.

"I think we need to wise up that there is this group that could sustain transmission and generate new variants to the virus," John Mellors, MD, chief of the infectious diseases division at the University of Pittsburgh and the University of Pittsburgh Medical Center (UPMC), said in an interview.

Mellors and Gupta are among the virologists who believe that the SARS-CoV-2 variants of concern circling the globe first arose in immunocompromised hosts. "There's no other explanation for how this is happening," Gupta said. "It's the product of chronic infection."

Physicians are now grappling with how best to treat COVID-19 in severely immunosuppressed patients without encouraging treatment-resistant variants to emerge.

They're also working out how long to isolate these patients and how to determine when it's safe to lift the precautions.

Diverse Presentations

Exactly who falls under the category of severely immunosuppressed is still an open question. "The challenge we and other centers are now facing is how to define who these patients are," Ghady Haidar, MD, a transplant infectious disease physician at UPMC, said in an email.

Certain conditions, including some hematological malignancies and rare congenital disorders, can substantially impair the immune system, according to University of California, San Diego, infectious disease specialist Saima Aslam, MD. The myriad immunosuppressive therapies for immune-mediated diseases, cancer, and transplants can cause transient or chronic immunodeficiencies for millions of patients. Aslam and others cited rituximab, a B cell-depleting

agent used in certain blood cancers and a range of autoimmune disorders, as one such medication on their radar. A recent [study](#) in *Gut* potentially implicates infliximab, a biologic used to treat inflammatory bowel disease, as another.

Case reports of prolonged infectious SARS-CoV-2 shedding describe patients with [lymphoma](#), leukemia, and [myeloma](#), as well as [individuals](#) with allogeneic hematopoietic stem cell transplants, chimeric antigen receptor T-cell (CAR-T) therapy, and the autoimmune disorder [severe antiphospholipid syndrome](#). One [article](#) reported long-term infectiousness among 3 patients, 1 with untreated HIV, 1 with a heart transplant, and another with rituximab-treated rheumatoid arthritis. “If you look at the clinical presentations, they’re quite diverse,” Gupta said.

In one early case in Washington State, [reported](#) in *Cell* in November 2020, a 71-year-old woman with chronic lymphocytic leukemia and acquired hypogammaglobulinemia had culturable virus 70 days after her first positive polymerase chain reaction (PCR) test, despite being asymptomatic over the entire course of her infection.

“Not all immunocompromised patients are the same and the ones we are seeing with true chronic or recrudescing COVID tend to be patients who have significant impaired B-cell immunity, usually with some T-cell impairment: CAR-T recipients, lymphoma patients on treatment, rituximab users,” the late Francisco Marty, MD, wrote in a March email to *JAMA*. (Marty, who was an infectious disease physician at Brigham and Women’s Hospital and editor in chief of the journal *Transplant Infectious Disease*, died in April.)

Complicating the matter, some severely immunocompromised patients don’t mount a robust response to standard vaccines, like those for influenza and hepatitis B, Mellors said. [Research](#) is starting to show that the same is likely true for the novel coronavirus. In a recent study at the Johns Hopkins University School of Medicine, only about half of 658 fully vaccinated solid organ transplant recipients generated SARS-CoV-2 antibodies.

Severely immunosuppressed patients are therefore uniquely vulnerable not only to becoming infected, but also to being chronically infected—and infectious. Researchers are interested in using monoclonal antibodies prophylactically in these

patients. In the meantime, it’s critical that family members and caregivers are vaccinated to create a “bubble” around people with weakened immune systems, said Joshua A. Hill, MD, an assistant professor in the Vaccine and Infectious Disease Division of the Fred Hutchinson Cancer Research Center (Fred Hutch) and the Allergy and Infectious Disease Division of the University of Washington.

The Problem With Plasma

Without the assurance of vaccine protection, effective therapies are of paramount importance for these individuals. But “basically none of the medical interventions for treatment of COVID-19 infection have really been well studied in immunocompromised patients,” Hill said in an interview.

For now, monoclonal antibodies offer the best hope for people with COVID-19 who can’t produce their own antibodies. But in regions where they aren’t yet approved or widely available outside of clinical trials, like the UK, clinicians often rely on convalescent plasma for these patients, Gupta said. While monoclonals are standardized, the level of neutralizing antibodies in plasma from patients who have recovered from COVID-19 isn’t and may not be optimal.

High antibody titers are also key to avoiding variant evolution. A treatment that helps keep patients alive for a time without delivering a knockout punch could give the virus a chance to adapt.

Haider and Mellors were coauthors of a [case study](#) in *Clinical Infectious Diseases* describing a [CAR-T therapy recipient](#) with treatment-resistant multiple myeloma who had infectious SARS-CoV-2 in endotracheal aspirate 72 days after his COVID-19 diagnosis. Genomic sequencing identified 5 variants that arose within the individual after his initial infection with the dominant strain that was circulating in Pittsburgh. “Our patient had 2 rounds of convalescent plasma, so I think it may have had some role,” Mellors said.

This also appears to be true for Gupta’s patient, who developed what’s known as a double mutant variant. “The big shifts in the virus only really came after the plasma was infused,” Gupta said.

The 2 mutations, both in the spike protein, were troubling. One bestowed modest resistance to the plasma antibodies but decreased infectivity. The other—a dele-

tion also found in the B.1.1.7 variant—appeared to compensate for the reduction, making the variant just as infectious as the dominant strain.

About 3 weeks after the first round of convalescent plasma, when the antibodies had likely waned, different variants took over—that is, until the next infusion, when the antibody-resistant variant resurfaced and outcompeted the rest.

Gupta called the pace of changes within a single patient “absolutely staggering.” The virus’s ability to infect many different cell and tissue types, a feature known as tropism, may have enabled some of the quick shifts. According to Gupta, this trait potentially allows the pathogen to acquire different mutations as it replicates in the various organs of a single host. “It’s got all these different reservoirs,” he said. “It’s very much like HIV in that sense.”

Gupta is an HIV researcher who is known for having treated the so-called [London patient](#), the second person to be functionally cured of the virus. For him, there are “a lot of parallels between HIV and what’s going on with this virus and chronic infection.” In both, the virus wages an ongoing war against the host immune system, the treatments, and even itself. “There’s a battle between different variants going on,” he said.

All this means that therapies that put evolutionary pressure on the virus should be considered that much more carefully for immunocompromised patients.

Last October, Adam Lauring, MD, PhD, a University of Michigan Medical School infectious disease professor, and colleagues published one of the first [accounts](#) of prolonged SARS-CoV-2 infection in an immunocompromised person. The patient with mantle cell lymphoma was hospitalized 3 times for COVID-19 and was infectious for at least 119 days. Two courses of remdesivir and convalescent plasma helped resolve his symptoms, but each time the improvements were fleeting. “You get a transient benefit, but then the virus just comes back,” Lauring said in an interview. “So I’m less enthusiastic about convalescent plasma in general.”

Mellors cautioned that, if used, high-titer convalescent plasma should be given early in the course of infection, when the antibodies it contains are more likely to fully block viral replication and evolution. “Don’t just give it because it’s available” or as “a Hail Mary pass,” he said.

Contagious or Not?

Isolating potentially contagious patients is a sound public health tactic but can negatively affect the individuals' emotional well-being. For that reason, clinicians who care for these patients want to know when enough is enough.

The Centers for Disease Control and Prevention (CDC) says that most adults with COVID-19 can [stop isolating](#) 10 days after their symptoms began but that some people with severe illness may need to be isolated for up to 20 days. Recognizing that some severely immunocompromised patients with COVID-19 can be infectious for even longer, the CDC now says physicians can consider using a [test-based strategy](#) to decide when to stop isolating these individuals.

The protocols differ from one health facility to another. "Right now I feel like each center is doing its own thing," Aslam said in an interview. Haidar agreed: "We've had discussions about this issue with colleagues from other large transplant and cancer centers, and the lack of a uniform approach to this problem is striking."

At Fred Hutch, Hill said severely immunosuppressed cancer patients hospitalized with COVID-19 are isolated for at least 20 days. They need a negative PCR test to get out of isolation, and they must be fever-free for at least a day without using fever-reducing medications, with improvements in other symptoms like cough or shortness of breath.

At UC San Diego Health, where Aslam directs the Solid Organ Transplant Infec-

tious Diseases Service, severely immunocompromised patients whose COVID-19 symptoms have resolved must have at least 2 negative PCR tests separated by at least 24 hours before the hospital discontinues isolation. But because the test results can remain positive for some time even without replicating virus, clinicians there also consider the tests' Ct, or cycle threshold, values, which correlate with viral load and can indicate whether the infection is resolving.

"The most important thing is to figure out whether their secretions still have lots of virus," Mellors said. "If they have lots of RNA in them, they probably have replicating virus that is potentially infectious."

Lauring's laboratory has looked at [subgenomic RNA](#)—small RNA strands the virus makes when it's actively replicating—as a marker for infectivity. "It sounds great," he said. But "what we found, and I think what others have found, is it might not be any better than just looking at the overall viral load over time."

As for immunosuppressed outpatients, Aslam said she is comfortable with them coming out of isolation after 20 days if their COVID-19 symptoms have resolved. For those with ongoing symptoms, she waits for a negative PCR test result before ending isolation.

Evolution Within a Host

These precautions are intended to prevent highly infectious patients from transmitting the virus—and new variants—to others. At the end of the UPMC patient's life, his level of virus replication was enormous, Mellors said. "The potential was for him to be a

source of transmission of one or more of those variants," he noted. "But because of good infection control practices and spending the majority of his time out of the hospital in a relatively isolated environment, that didn't occur."

The first 3 variants of concern identified globally all had accumulated several mutations by the time they were discovered, which to some suggests that they evolved in individuals with chronic infections and then were transmitted to others. "That is likely, in my mind, to be the source of these 3 types of variants," Mellors said.

"It's not stepwise evolution—it's evolution within a host," Gupta said. "It's being hidden from the surveillance that we have because it's going on in 1 person for 3, 4 months undetected, and then it causes an infection of someone else, and then it starts spreading."

In Lauring's view, the best case can be made for B.1.1.7. The variant had 17 strain-defining mutations when it was first detected in the UK last September, more changes than should have accumulated in that time. "It was kind of ticking to a different clock," he said, which argues for it having evolved in an unusual setting. What's more, some of its mutations have also been detected in immunocompromised patients with prolonged SARS-CoV-2 infections.

"All that, I think, is suggestive," Lauring said. "It's not an airtight case but given that we probably won't ever find the smoking gun, it's I think a reasonable hypothesis." ■

Note: Source references are available through embedded hyperlinks in the article text online.