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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Organ transplants and reinfection. Viral genetics answer a crucial question.

In 2018, over 36,000 organ transplants were performed in the United States. In order to keep these organs from being rejected via life-threatening immune responses, recipients must take immune-suppressing medications for life. With these medications, however, comes the risk of infection by viruses, bacteria, and fungi, that normally do not pose a threat to most people. In addition, patients on immune-suppressing medications carry a substantial risk of repeated infections, because the immune system does not respond as robustly and therefore long-lasting antibodies are not generated.

Does this mean that repeated infections with SARS-CoV-2 are more likely to occur among organ recipients? It's possible. A new case report in the *Annals of Internal Medicine* describes a case of repeat infection in a liver transplant recipient, who was taking a typical combination of anti-rejection immune-suppressing medications.

Yes, we already know repeat coronavirus infections can occur, albeit in a small fraction of cases. So in a sense, this is not news. What makes this report noteworthy is that the authors teased out the answer to a crucial question; was the second bout of covid-19, which occurred over 3 and half months after the first one, a new infection or an exacerbation of a dormant one? First off, the patient tested negative twice between the two illnesses. But even that would not be enough to determine the answer—a dormant infection might evade routine testing but could still be hiding somewhere in the body. Fortunately, the researchers had viral swabs from both the first and second bouts of the patient's illness. That meant that genetic sequencing might hold the answer. Genetic sequences generated from swabs taken during the second illness were far too genetically dissimilar from those taken during the first illness for this to have been an "awakening" of a dormant infection. While some degree of mutation can occur over time, the rate of change in the genetic sequence of SARS-CoV-2 is quite well-established. There is simply no way that these the isolated variants had a common ancestor recently enough that the second viral sequence could have evolved from the first one within a person's body in such a short time frame. (This is especially the case as the patient did not receive any medications that might accelerate an evolutionary selective pressure, including convalescent plasma, during the first illness). This suggests that patients with substantial immune suppression—including organ transplant recipients and patients with certain blood cancers—might be at an increased risk of SARS-CoV-2 reinfection and repeat covid-19 illness.

The key question is whether or not the immune system remembered the initial infection at all. The answer is uncertain but disheartening. Antibody levels after the first infection were not detectable at the time of the second illness, which is disappointing (levels were higher after the second bout, although the patient eventually received convalescent plasma which contain antibodies). That said, there are many ways to measure the body's immune response, beyond simple antibody levels. One way is to simply monitor how sick a reinfected patient becomes. Fortunately, most reinfections have not been severe. In this case, the second bout was not detected because of covid-19 symptoms, but rather because the patient experienced a stroke in the back of his brain. In fact, the patient had no slam dunk covid-19 symptoms at the time of his second diagnosis; he happened to be tested for SARS-CoV-2 as part of his hospitalization protocol for stroke treatment. However, hat positive test led the investigators to dig into the case

(of note, he eventually developed low oxygen levels, a cardinal sign of severe covid-19, and required extensive treatment before recovering).

This case report also obliquely points at another developing story in the covid-19. Strokes like the one experienced in this case are caused by blood clots in the vessels of the brain. Many clinicians have observed that stroke rates are up among covid-19 patients and possibly even among patients who have recovered from the disease. While this case report did not delve deeply in that question, it certainly was a conspicuous detail. We expect more data on covid-19-related, and post-covid-19 strokes to emerge soon, especially as the background rate of clots of all kinds becomes an area of increasing interest, given that both the AstraZeneca and Johnson & Johnson vaccines have been linked to rare blood clot-related complications.

—Jeremy Samuel Faust, MD MS

POLICY BRIEFING

Coverage from above for coronavirus vaccines.

Surprise billing has long been a pain point for patients. Surprise billing occurs when a patient's insurance does not pay for the full cost of a medical therapy that was seemingly "covered" by the plan, and the remainder of the balance charged by the healthcare provider is billed to patient directly. The CARES Act forbade collection of expenses incurred relating to the coronavirus, with the caveat that the patient must have had a positive screening test, a loophole used by insurance companies. If a patient have all the signs of covid-19, but never got a positive test (which was not uncommon early in the pandemic before widespread testing became available), insurance companies could throw surprise bills at patients without recourse. The Trump administration previously announced an initiative to address this problem but never provided a resolution process for violation complaints.

This week the US Department of Health and Human Services (HHS) sought to address another aspect of surprise billing: vaccination. According to the memo, as a result of all vaccines currently being distributed in the United States falling under the auspices of the US Centers for Disease Control and Prevention (CDC)'s COVID-19 Vaccination Program, no office visit or additional fees may be charged to patients if the sole intent of the interaction was vaccination. Despite this, the HHS Office of the Inspector General (OIG) acknowledged multiple complaints of just such instances occurring. Unfortunately, this requirement only applies to Medicare, Medicaid, the Health Resources and Services Administration's (HRSA's) COVID-19 Uninsured Program, and insurance plans funded by the Affordable Care Act. Similarly, while providers cannot bill a patient directly, they can bill third-party payers for administrative fees that may then ultimately be charged to the patient.

Both the Trump and Biden administrations stated that US residents should pay out-of-pocket to be vaccinated or receive care for covid-19 illnesses. The Biden administration is now working to close the gaps between theory and reality, as they become apparent. *Various.*

—Brief19 Policy Team

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