

Medical News & Perspectives

Testing an Old Therapy Against a New Disease: Convalescent Plasma for COVID-19

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As deaths from coronavirus disease 2019 (COVID-19) continue to mount, desperation has driven physicians to try therapies backed by little or no evidence.

Perhaps the greatest excitement surrounds convalescent plasma, a treatment more than a century old that has gone in and out of fashion—in when infectious disease outbreaks occurred and then out when treatments and vaccines that could be mass-produced were developed to contain them.

Taken from healthy people (or in the earliest reported cases, animals) who have recovered from the infectious disease of interest, antibody-rich convalescent plasma is thought to give recipients' immune systems a running start.

"To explain how desperate the need is, we probably have at least 300 [COVID-19] patients in the hospital today, over a third of them intubated," anesthesiologist Elliott Bennett-Guerrero, MD, said in mid-April. He's the principal investigator of a just-launched convalescent plasma trial at Stony Brook Hospital in New York with a planned enrollment of up to 500 hospitalized patients with COVID-19, a third of whom probably will be intubated. "We are at lightning speed ramping up production and processes for collecting convalescent plasma," Bennett-Guerrero explained.

The first published report of convalescent plasma against COVID-19, a preliminary communication in *JAMA* about 5 seriously ill patients in China, was posted online March 27. Two more reports from Wuhan, one published April 6 and the other published April 15, described infusing convalescent plasma into a total of 16 patients seriously ill with COVID-19. All 3 articles said the therapy appeared to save lives; the authors called for randomized controlled trials to confirm their findings.

Uncontrolled

Without randomized controlled trials, researchers can't be sure whether patients



recovered because of an experimental therapy or in spite of it. Yet virtually everything that's known about the use of convalescent plasma against infectious diseases comes from studies in which every patient received the treatment.

"We do not know if this is safe and effective," Bennett-Guerrero acknowledged in an interview. "We hope it is, because we desperately want to help our patients."

His study does include a control group, but 80% of participants will receive the active treatment—a higher proportion than in most randomized controlled trials.

"We think that we're doing the responsible thing by trying to maximize the number of people who may potentially benefit," Bennett-Guerrero said. The remaining participants will receive plasma donated by people who had not been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and, therefore, lack antibodies against it.

Pulmonologist A. Whitney Brown, MD, of the Inova Advanced Lung Disease and Transplant Program at Inova Fairfax Hospital in Virginia, and her coprincipal investiga-

tor, Grace Banez-Sese, MD, director of Inova Blood Donor Services, thought long and hard about whether to include a control group in their just-launched convalescent plasma trial in seriously ill patients.

"I think that's something everybody is struggling with," Brown said in an interview. "That's been our problem historically with convalescent plasma. You use convalescent plasma when you have no treatment, when you have no vaccine. You just want to help as many people as you can and not hold back."

She and Banez-Sese hope to enroll 200 or more patients into their study. They considered including a control group that would receive plasma without SARS-CoV-2 antibodies, as Stony Brook is doing, Brown said. "The ethical concern is we think COVID-19 may cause increased clotting." Plasma is rich in clotting factors and typically used to reverse bleeding problems, Brown noted, so it theoretically could increase clotting risk in patients with COVID-19 without any promise of benefit. (Bennett-Guerrero noted that in some conditions, plasma promotes anticoagulation.)

Still, she added, "I would love a control group. I would love to rigorously prove" that convalescent plasma works. But instead of a control group, Brown said, she and Banez-Sese will compare trial participants to published case reports of patients with COVID-19 who weren't treated with convalescent plasma.

Due to the dearth of randomized controlled trials, "there are no data that I'm aware of that clearly demonstrate the value of [convalescent plasma] for an infectious disease," said H. Clifford Lane, MD, clinical director of the National Institute of Allergy and Infectious Diseases (NIAID).

In 2019, Lane coauthored one of the few published [randomized trials](#) of convalescent plasma. He and his collaborators randomized 140 children and adults with influenza to either convalescent plasma with high levels of anti-influenza antibodies or to standard plasma. The double-blind study concluded that the anti-influenza convalescent plasma conferred no significant benefit over standard plasma.

The NIAID will not pursue a similar trial involving patients with COVID-19, Lane said.

"I'm a little bit more on the physician-do-no-harm end of the spectrum," he said. "Many of the things that are so promising in theory fall apart when really studied rigorously."

But, Lane said, he understands why the treatment has captured the attention of so many physicians, scientists, and patients and their families.

"Everything that's going on right now in terms of trying to find an effective treatment for COVID-19 is driven by fear and this strong desire to do something for patients," he said.

Seeking Answers

The US Food and Drug Administration (FDA) first announced [March 24](#), with more details [April 3](#) and [April 13](#), that it would facilitate access to convalescent plasma for treating COVID-19 via 3 regulatory pathways. For now, they're the only avenues for obtaining convalescent plasma, an investigational medical product, to treat patients.

"Although promising, convalescent plasma has not yet been shown to be effective in COVID-19," the FDA cautioned. "It is therefore important to determine through clinical trials, before routinely administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so."

One way to administer convalescent plasma is by conducting a clinical trial, as Bennett-Guerrero and Brown have opted to do, under the traditional [investigational new drug \(IND\)](#) regulatory pathway. Another is [expanded access](#), also called "compassionate use," which enables patients with a serious or life-threatening disease to obtain an investigational medical product outside of a clinical trial when there is no alternative treatment available. If such patients can't obtain convalescent plasma through clinical trials or an expanded-use protocol, their physician can request a single-patient [emergency Investigational New Drug Application \(eIND\)](#). Houston Methodist Hospital [reported](#) that on March 28, it became the first US hospital to provide convalescent plasma to a patient with COVID-19, in this case under an eIND.

The FDA's [National Expanded Access Treatment Protocol](#) entry criteria are fairly broad: Adults aged 18 years or older with COVID-19 whose disease is severe to life-threatening or deemed by their physician likely to become so are eligible. By April 27, 2115 sites had registered to participate and enrolled 5968 patients, 2576 of whom had received convalescent plasma.

As the FDA [notes](#) on the expanded access program's website, though, "the focus of an EAP is to provide treatment whereas a clinical trial is focused on research." However, the expanded access program is collecting information about treated patients from their physicians, who are asked to complete short forms 4 hours, 7 days, and 30 days after infusion if their patients remain hospitalized that long.

Practically every day, another medical center announces plans to begin administering convalescent plasma to patients with COVID-19. "The use in the United States is mushrooming very rapidly," said Arturo Casadevall, MD, PhD, chair of molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health.

A Blast From the Past

In the first known trial of convalescent serum, as [described in JAMA](#) in 1893, German scientists used serum from animals immunized against diphtheria to treat patients with the disease. By 1901, [Emil von Behring](#) had won the first Nobel Prize in Medicine or Physiology for his research demonstrating that neutralizing antibodies, or antitoxins, could be transferred from one person or ani-

mal to another. (Von Behring carried out his research into treating diphtheria with antibody-rich plasma with [Paul Ehrlich](#), who shared the 1908 Nobel Prize in Medicine or Physiology for his immunology work.)

Over the next 120 years or so, convalescent plasma was also used against the [1918 pandemic flu](#), measles, [Middle East respiratory syndrome coronavirus \(MERS-CoV\)](#), 2003's [severe acute respiratory syndrome \(SARS\)](#), and [Ebola virus disease](#).

"For most people, this was forgotten history," said Casadevall, a self-described history buff. By late January, he said, he recognized that SARS-CoV-2 "was going to be bad" and felt compelled to refresh people's memories about convalescent plasma.

He recalled reading of a prep school physician in Pottstown, Pennsylvania, who had suppressed a measles outbreak by infusing students with plasma taken from a classmate who'd recovered from the disease. Casadevall figured that the 85-year-old [report](#) would be particularly engaging because it involved children.

To raise awareness as quickly as possible, he dashed off a 600-word op-ed piece about the prep school physician's experiment and how convalescent plasma was worth trying against COVID-19. The article was rejected by a few newspapers before the [Wall Street Journal published it](#) February 27.

Casadevall followed up the op-ed column March 13 with a scientific journal [article](#) about the use of convalescent sera for containing COVID-19. That article spurred the establishment of the [National COVID-19 Convalescent Plasma Project](#)—"a decentralized grass roots effort from academic institutions...to deploy the use of plasma in this emergency." Casadevall chairs the group.

"Dr Casadevall has inspired the national movement of convalescent plasma," University of Chicago lung and thoracic surgeon Maria Lucia Madariaga, MD, said April 13 at a press conference announcing the launch of her institution's [10-patient open-label trial](#) of the investigational treatment.

Casadevall distributed his op-ed piece to 20 close scientist friends. "We are a very eclectic group who are very concerned about the direction of science," he said. "We converse all the time by email." Upon reading it, Casadevall said, his friends were eager to test the treatment. Among them was Michael Joyner, MD, an anesthesiologist and physiologist at the

Mayo Clinic in Rochester, Minnesota, whose main research interests had been exercise physiology and human performance.

"I immediately asked, 'Arturo, what can I do?'" Joyner recalled in an interview.

Little more than a month later, Joyner had become the point person for the National Expanded Access Treatment Protocol.

It seems only appropriate that he quoted legendary football coach Vince Lombardi in a recent tweet about efforts to deliver convalescent plasma to patients with COVID-19: "People who work together will win, whether it be against complex football defenses or the problems of modern society."

Supply and Demand

Individuals who want to donate convalescent plasma must be able to document that they had COVID-19 with a laboratory test, according to the FDA, which has compiled resources for people who'd like to donate.

At the beginning of the US COVID-19 outbreak, many symptomatic individuals were unable to get a confirmatory nose or throat swab polymerase chain reaction (PCR) test, so at first, they were ineligible to donate convalescent plasma.

However, the FDA now accepts a positive blood antibody test as proof of prior infection. "The people doing the plasma collection are very interested in increasing the pool of donors based on the lookback test," said Joyner, referring to antibody testing of individuals presumed to have recovered from COVID-19 that was not confirmed when they were sick. Still, some collection organizations, such as Inova Blood Donor Services, require that convalescent plasma donors have had a confirmatory PCR test because of questions about the antibody tests' accuracy. "They're not fully vetted," Brown said of the tests.

The FDA has not yet cleared any SARS-CoV-2 antibody tests for marketing, but it has granted several emergency use authorizations so blood centers can screen prospective convalescent plasma donors who had not had a confirmatory PCR test when they were sick.

Prospective donors must be symptom-free for at least 28 days, or, alternatively, for at least 14 days if they get a negative PCR test for SARS-CoV-2, indicating that they are no longer infectious, according to the FDA. They must also be eligible to donate blood.

The American Red Cross is fulfilling orders for convalescent plasma through both

the expanded access treatment protocol and eINDs. "While the Red Cross first meets the needs of area hospitals, it can also provide convalescent plasma...throughout the country," spokeswoman Stephanie Rendon said in an email. As of April 20, the Red Cross had collected convalescent plasma from about 110 donors, which translated into nearly 250 units, 120 of which had already been delivered to hospitals treating critically ill COVID-19 patients, Rendon said.

As the number of COVID-19 cases continues to rise, many people have taken to social media to plead for convalescent plasma for their seriously ill loved ones. However, blood collection centers generally do not permit donors to designate their blood for a specific patient. Instead, Brown said, she encourages people interested in making a designated donation to pay it forward and donate to replace the convalescent plasma used by their intended recipient.

The AABB (formerly the American Association of Blood Banks) and the New York Blood Center and several other community-based blood centers have partnered with Survivor Corps—a grassroots organization of COVID-19 survivors whose mission is to support research into developing a cure and a vaccine—to increase convalescent plasma donations.

Timing and Dosing

In 2016, an international team of researchers published findings from a trial of convalescent plasma involving 84 patients with Ebola virus disease in Africa. The patients were compared with 418 patients who had been treated for Ebola during the previous 5 months at the same hospital. Convalescent plasma was not associated with a significant improvement in survival, the study found.

The Ebola trial doesn't dissuade Christopher Hillyer, MD, president and CEO of the nonprofit New York Blood Center, which is collecting and banking convalescent plasma for use by hospitals throughout the country, and, as of April 22, had shipped 2700 units. "They were giving it to extremely ill people," Hillyer explained.

For patients with COVID-19, convalescent plasma seems more effective if it's given earlier in the course of the disease, according to Beth Shaz, MD, New York Blood Center's chief medical officer. "It appears to slow progression of disease and keep people out

of the ICU. Some are getting extubated shortly after transfusion," she said on April 15 in an email to Hillyer and other colleagues.

In patients critically ill with acute respiratory distress syndrome, though, convalescent plasma doesn't seem to be as effective, wrote Shaz, who also is president of AABB.

Stanford University researchers will soon begin testing convalescent plasma in emergency department patients with COVID-19 respiratory symptoms who aren't yet sick enough to be admitted to the hospital. They hope to enroll 206 patients in their double-blinded, randomized controlled trial that will compare convalescent plasma with plasma that does not contain SARS-CoV-2 antibodies.

Johns Hopkins scientists have launched a triple-blinded randomized controlled trial of convalescent plasma in 150 adults who aren't even sick. Eligible participants are high-risk based on age and overall health. They must have had close contact with a COVID-19 patient within 96 hours of enrolling in the study. Participants will receive either convalescent plasma or plasma without SARS-CoV-2 antibodies within 120 hours of having close contact with a COVID-19 patient.

Plasma with higher titers of anti-COVID-19 neutralizing antibodies is thought to be most effective, but many patients are receiving plasma with unknown titer levels. The FDA advises that if collection centers don't measure antibody titers before convalescent plasma is infused, they should save a bit of the donor's blood for future testing to see if higher titers do indeed correlate with better outcomes.

Many patients are receiving a 1-time dose of 1 unit of plasma, but some institutions think 2 units, administered 24 hours apart, helps address the variability in donors' antibody titers, Shaz said.

Next Steps

Convalescent plasma is like a bridge. It's thought to help defend patients against SARS-CoV-2 until their own immune systems get up to speed. And in the minds of some scientists, it's a stopgap measure until more refined treatments and a vaccine can be mass-produced.

One of those treatments is intravenous (IV) immunoglobulin, made of pooled IgG from convalescent plasma. The NIAID has been working to develop and launch

a placebo-controlled trial of IV IgG to treat COVID-19, Lane said. Unlike convalescent plasma, IV IgG can be standardized and used to treat anyone, no matter their blood type.

Chinese scientists in March [reported on 3](#) Wuhan patients with severe COVID-19 who recovered after receiving high-dose IV IgG. They concluded that randomized trials of high-dose IV IgG in deteriorating patients infected with COVID-19 should be considered.

Further down the road is the development of monoclonal antibodies targeting SARS-CoV-2. The Gates Foundation, Wellcome, and Mastercard have launched a COVID-19 [Therapeutics Accelerator](#), which will screen new monoclonal antibodies

for possible anti-COVID-19 activity. Those that pass would be developed by an industry partner.

Patrick Wilson, PhD, an antibody biology researcher at the University of Chicago, plans to isolate B cells, which produce antibodies, from convalescent plasma donors' white blood cells. Every B cell produces a unique antibody as part of the immune response. Wilson said his lab will clone antibody genes from COVID-19-induced B cells to try to determine which one accounts for a convalescent plasma donor's effective immune response against SARS-CoV-2.

Because monoclonal antibodies have already been developed to treat cancers, "the infrastructure's there," Wilson said. "We can

grow a lot of antibodies really efficiently." However, he added, "Testing [monoclonal antibodies] in patients, that would take a while, regrettably."

For now—and possibly the next 18 to 24 months, Bennett-Guerrero said—convalescent plasma, despite supply issues and questions about efficacy and who is most likely to benefit from treatment, remains the only off-the-shelf therapy for COVID-19.

"All of these convalescent plasma programs are against the backdrop of a massively dangerous infection," Hillyer noted. "This is an imperfect science, but it's better than dying." ■

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