Something Old, Something New:

Convalescent Plasma from Smallpox to COVID-19

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The concept of immunity to infectious diseases has been around literally for centuries. The ancient Greeks recognized that individuals who had recovered from an infection would no longer develop the disease when exposed again. In his account of the Peloponnesian war, the Greek historian Thucydides describes a plague — now considered by many to have been smallpox — that ravaged Athens around 430 B.C., noting that he himself had survived the disease.

"Those who had recovered from the disease … had now no fear for themselves; for the same man was never attacked twice — never at least fatally."

In the 10th century, there are reports from China of collecting material from open sores of infected patients, drying it and introducing it into the noses of uninfected individuals with the hope of inducing some immunity to the infection.[1] This technique, called variolation, is one of the forbears of today's modern vaccines and a close relation to convalescent plasma (CP).

Fast forward several centuries to 2020, which brought with it the coronavirus disease (COVID-19) pandemic. At press time, there were 1.23 million confirmed infections and 71,532 deaths from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Even as you read this article, experts around the world are racing to identify treatments from existing drugs and biologics, develop new treatments and manufacture vaccines.

Convalescent plasma — plasma collected from individuals who have recovered from a disease — has emerged from history to become one of the most sought-after treatments to minimize the severity of COVID-19 symptoms. Patients and families are desperate to find it. Physicians, other health care professionals and hospitals are scrambling to secure supplies for their sickest patients. Blood centers and laboratories are working as fast as possible to identify and screen potential donors, collect plasma and run a battery of screening tests. AABB has worked closely with federal regulators and other experts to develop guidance and resources for blood and plasma collection facilities.

What's behind all of this excitement? CP is a simple concept, similar to the way that a mother passes protective antibodies to her newborn. CP is a form of passive immunity that, when collected from someone who has recovered from an infection, transfers antibodies developed by the survivor's body to combat bacteria or viruses — in this case SARS-CoV-2 — passively to someone who has a current infection.[2]

The antibodies in the CP are released into the recipient's body and begin fighting the infection, allowing a faster recovery. CP is not a cure, nor does it offer prolonged immunity. The patient's immune system does not learn to recognize and destroy this viral foreign invader, it simply borrows some measure of protection from a recovered patient.

From Smallpox to Ebola

Variolation — typically using powdered pus from an open wound — was a known, but not well understood, practice in the late 1700s. Around that time, the English began introducing the infectious material into a

Left: Edward Jenner, an English physician, observed that milkmaids infected with cowpox did not develop smallpox.
Center: Japanese physician and bacteriologist Shibasaburō Kitasato's work with tetanus helped found the field of immunology.
Right: Emil von Behring, working with Kitasato, developed "antitoxins" (now called antibodies) using blood serum that provided protection against diphtheria and tetanus.

*Although Jenner has gone down in history as the first person to make the connection between cowpox and smallpox, and to provide vaccinations based on this premise, he may not have been the first. In 1774, an English farmer named Benjamin Jesty recognized that two of his milkmaids, who had recovered from cowpox, appeared to be immune to smallpox despite close exposure. Jesty — who had also recovered from cowpox — vaccinated his wife and two sons in 1789 using cowpox pus from a neighbor's cows. The family avoided infection during a local outbreak of smallpox. (Summary from "The Myth of the Medical Breakthrough: Smallpox, Vaccination, and Jenner Reconsidered," Cary Gross, MD; and Kent A. Sepkowitz, MD)

small puncture wound in the patient. Variolation, which had a number of proponents advocating its use to avoid smallpox, had a downside, as well: the prospect of infecting the recipient with full-blown infection.[3]

The English surgeon Edward Jenner is credited with performing the first vaccination in 1794, after hearing about milkmaids who were immune to smallpox after being infected with the closely related cowpox virus, ushering in the era of vaccinations.[4]

Work by Japanese physiologist Shibasaburō Kitasato and German physiologist Emil von Behring in the late 1800s led to the use of blood serum to treat diphtheria.[5] Serum differs from plasma in that its clotting factors have been removed. Antibody-containing serum was first collected from animals, before the use of human whole blood donations.[6]

While research continued in the early 1900s on the use of blood products to prevent or treat other diseases, the Spanish influenza pandemic triggered a number of studies of CP as a potential treatment for various viral infections. Since then, CP has been tried — with mixed results — as a treatment for infectious agents ranging from influenza and chickenpox to the 2013-2016 Ebola virus outbreak in Western Africa.

The Evidence for Convalescent Plasma

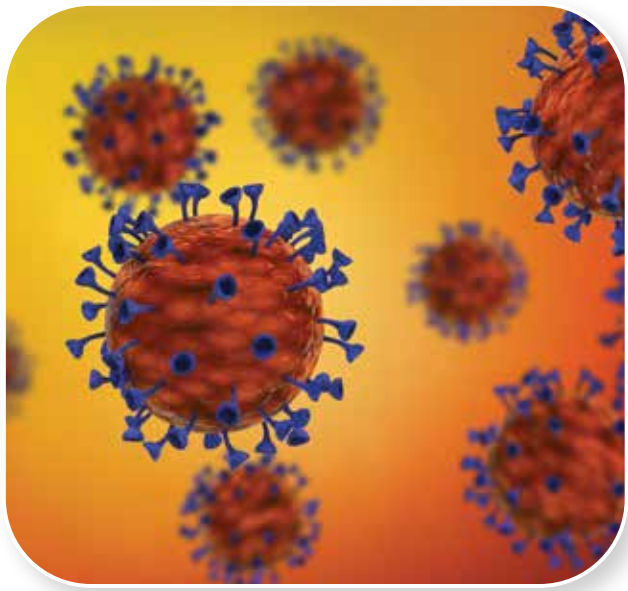
At least 27 reports assessed the use of CP during the 1918 influenza pandemic (also known as the Spanish flu), according to a 2006 meta-analysis of the findings.[8] Only eight studies met the inclusion criteria, and data quality was considered poor. Nonetheless, patients who received CP faired considerably better than controls, with overall crude case-fatality rates of 16% and 37% respectively.

In 2013-2016, an Ebola virus outbreak ravaged Western Africa, reaching as far away as the United States. More than 11,300 deaths occurred as a result of the highly contagious and often fatal Ebola virus disease, a hemorrhagic illness spread through contact with infected animals or bodily fluids from infected humans.[9] Despite a handful of successful cases of convalescent plasma treatment,[10, 11] results were generally disappointing for this approach.[12] No significant improvement was seen in a non-randomized trial of 99 patients in Guinea.[13]

However, CP did prove to reduce mortality risk in a meta-analysis of 32 studies of SARS coronavirus infection and severe influenza.[14]

Enter COVID-19

In the midst of the worldwide COVID-19 pandemic, preliminary evidence suggests that CP may lessen the severity of COVID-19. A study from Shenzhen,



China reported a preliminary uncontrolled study of five severely ill patients with COVID-19 who were treated using COVID-19 convalescent plasma (CCP). The patients continued to receive antiviral treatment along with CCP.[15] Their condition improved and antibody titers (both specific to SARS-CoV-2 and neutralizing antibodies) increased. A similar study (though not peer reviewed or published at press time) from Wuhan province in China — where the virus is thought to have originated — six patients with severe disease were treated with CCP.[16] Clinical condition improved and antibody levels rose in these patients as well.

In early March, immunology and infectious disease specialists Arturo Casadevall, MD, PhD, and Liise-anne Pirofski, MD, laid out the case for the use of CCP to treat COVID-19 in the *Journal of Clinical Investigation* and urged emergency use of CCP as soon as possible.[17]

In early April 2020, the Food and Drug Administration announced a program to expand national access to investigational CCP for patients hospitalized with severe or life-threatening COVID-19, or those at high risk of progression to severe or life-threatening disease.[18] The program facilitates access to CCP and hyperimmune globulin (hyper-IG) — a blood product made from CCP — using multiple pathways. FDA's initial effort was focused on facilitating access to CCP through an emergency investigational new drug (IND) process.

FDA and industry, academic and government partners developed and implemented a protocol to provide CCP to patients who may not have access to institutions with clinical trials in place. The Biomedical Advanced Research and Development Authority

(BARDA) also announced it will collaborate with multiple non-government organizations to develop investigational treatments, including convalescent plasma and hyperimmune globulin, from the plasma of those who have recovered from COVID-19.

From a blood collector's perspective, much of the plasma collection process is the same as usual. "We're trying to do this through the normal supply chains, where a physician orders a unit of fresh frozen plasma for one of their patients in a hospital. The collection goes through the normal process in a blood facility, and it's delivered to a hospital from their normal supplier," said Michael J. Joyner, MD, a Mayo anesthesiologist who is the principal investigator for the Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19 protocol.

"The problems with convalescent plasma are logistical: getting people identified, getting it collected, getting it distributed in a safe way that is consistent with blood banking systems and procedures," said Joyner. "You've got to take that extra step of screening a potential donor to determine if the person was COVID positive; that they've been convalescing for the required amount of time; and that they are either negative on a second COVID-19 test or they're 21-28 days post recovery," he said.

To qualify as a donor, a recovered COVID patient must prove they have had the disease. This means either a positive viral test when they were ill or a positive antibody test drawn 14-28 days after they recovered and were symptom-free. Blood centers will ask for proof of these tests when someone signs up to donate, but most blood centers will do the antibody test on the day of donation, if necessary.

Claudia Cohn, MD, PhD, director of the blood bank laboratory at the University of Minnesota Medical School agreed. "It seems that the largest barrier to collections has been the FDA requirement to have laboratory proof of a COVID diagnosis for donation. The test shortage has left thousands of recovered patients with no proof that they were infected with the SARS CoV 2 virus."

Collection and distribution of CCP have also required "significant work for IT professionals as new component codes were added to our laboratory information system," said Cohn. At the University of Minnesota lab, IT developed and validated a new order set in the electronic medical record. "There has also been extra work for study coordinators and nurses as they learn about CCP. Finally, the social workers, nurses and doctors have been educating patients as they recover from COVID, in the hope that they will donate CCP 14 to 28 days after they are symptom-free."

Unfortunately, while the demand for CCP is high, the potential donor pool lags. "This is happening in real time," said Joyner. "If you look at the requirements to qualify as a donor, the first donors who are now eligible would have had to have been infected in early March. This donor pool is always going to be delayed — 21 days behind the crest of a wave."

Reaching out to Donors

FDA is encouraging individuals who have recovered from COVID-19 to contact their local blood collection center to discuss CCP donation. Preliminary findings indicate that CCP has the potential to lessen the severity or shorten the length of illness caused by COVID-19. Agency representatives emphasized that those who have recovered from COVID-19 could have an immediate impact in helping others who are severely ill, noting that one

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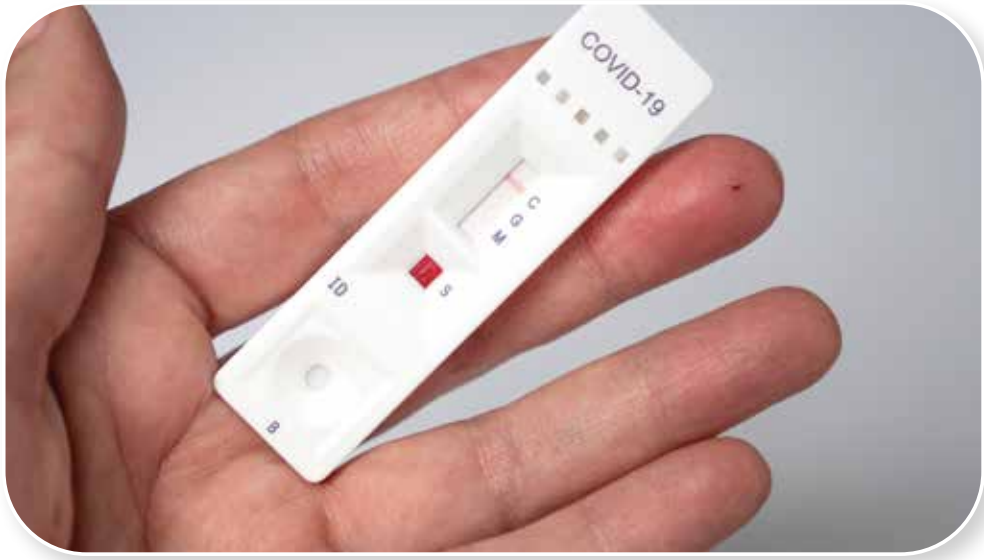

donation has the potential to help up to four patients. In addition, CCP can be used to manufacture hyper-IG, which can likewise be used to treat patients with COVID-19. Individuals who have fully recovered from COVID-19 and been asymptomatic for at least 2 weeks can contact their local blood center to schedule an appointment. AABB's COVIDplasma.org web page features additional resources and a blood bank locator for potential CCP donors, as well as information for blood centers and hospital transfusion services.

Finding Survivors Without Symptoms

It is impossible to know how many individuals who never had symptoms have recovered from a COVIC-19 infection, although they undoubtedly exist. Investigators at the National Institutes of Health (NIH) have launched a new study to help determine how many adults in the U.S. without a confirmed history of infection have antibodies to the virus.

Investigators will collect and analyze blood samples from as many as 10,000 volunteers to help illuminate the extent to which the novel coronavirus has spread in the U.S. and provide insights into which communities and populations are most affected.

Healthy adults from anywhere in the U.S. can participate, although individuals with a confirmed history of COVID-19 or current symptoms consistent with COVID-19 are ineligible. Those interested may volunteer to join the study by contacting clinicalstudiesunit@nih.gov.

The ability to screen individuals, especially potential blood donors, to identify those with antibodies to COVID-19 could significantly increase the number of patients receiving CCP. Depending on the as-yet-undetermined persistence of CCP-related immunity, such a test and other necessary screening tools could buy enough time to develop and rigorously test an effective and safe vaccine. ■

ENDNOTES

1. Gross CP, Sepkowitz KA. The myth of the medical breakthrough: smallpox, vaccination, and Jenner reconsidered. Int J Infect Dis. 1998;3:54-60.
2. Ibid
3. U.S. National Library of Medicine. Small Pox: A Great and Terrible Scourge. Last updated: July 30, 2013 https://www.nlm.nih.gov/exhibition/smallpox/sp_variolation.html
4. Gross
5. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016;14: 152–157.
6. Ibid
7. Ibid
8. Luke TC, Kilbane EM, Jackson JL, et al. Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?. Ann Intern Med. 2006;145:599–609.
9. U.S. Centers for Disease Control and Prevention, 2014-2016 Ebola Outbreak in West Africa. Last reviewed: March 8, 2019. https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html
10. Mora-Rillo M, et al. Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. Lancet Respir Med. 2015. doi:10.1016/S2213-2600(15)00180-0
11. Feldmann, H., Jones, S., Klenk, H. et al. Ebola virus: from discovery to vaccine. Nat Rev Immunol 2003;3, 677–685.
12. Colebunders RL, Cannon RO. Large-scale convalescent blood and plasma transfusion therapy for Ebola virus disease. Infect Dis. 2015;211:1208-10.
13. van Griensven J, Edwards T, de Lamballerie X, et al. Ebola-Tx Consortium, Evaluation of convalescent plasma for Ebola virus disease in Guinea. *N. Engl. J. Med.* 2016;374:33–42.
14. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. Convalescent Plasma Study Group, The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. J. Infect. Dis. 2015;211:80–90.
15. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA.* Published online March 27, 2020. doi:10.1001/jama.2020.4783
16. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. 15 April 2020. https://doi.org/10.1002/jmv.25882
17. Casadeval A and Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130(4):1545–1548.
18. FDA News Release, Coronavirus (COVID-19) Update: FDA Coordinates National Effort to Develop Blood-Related Therapies for COVID-19 https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19

COVIDPlasma.org is AABB's primary resource to educate interested donors, the health care community and the public on the rapidly evolving therapy of COVID-19 convalescent plasma.

Additional information for AABB members is available on **AABB's Coronavirus Resources web page** at Advocacy > Regulatory Affairs > AABB's Coronavirus Resources.