Collection and Transfusion of Convalescent Plasma
An approachable guide to molecular testing in blood banking and immunohematology.

Molecular testing methods have become remarkable tools for the resolution of challenging problems in blood transfusion needs for patients with complex diagnoses and evolving treatment modalities. As these methods expand into more facilities, staff are increasingly using technology they may have not been trained to use or interpret.

This approachable and complete guide to molecular testing is the result of a multidisciplinary group of authors – including serologists, a molecular biologist and a transfusion medicine physician. Methods are discussed, allele tables are explained, nuances are taught and users can quickly refer to it to check the interpretation of a report from an IRL.

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Something Old, Something New: Convalescent Plasma from Smallpox to COVID-19

Variolation by the Chinese in the 10th century is a precursor to the modern use of convalescent plasma to treat severe COVID-19.

COVID-19: Responding to the Pandemic

Government agencies are responding to the pandemic with collaborations, guidances and regulatory changes.

Controversial Uses of Blood Components

Some claim that blood products can reverse the effects of aging and repair orthopedic injuries. What does the research say?
During these difficult times, I’m sending you warm wishes. AABB, the Board and I are here to support you. Please don’t hesitate to reach out. We need to remain connected in this time of social distancing and continue working together to fight COVID-19.

An Opportune Time to Focus on Plasma

We typically plan AABB News far in advance. When we started on this issue, we couldn’t know how much the COVID-19 pandemic would upend our lives. It’s a coincidence that this month’s theme, blood components, comes when one particular component — plasma — has become a hot topic.

COVID-19 convalescent plasma (CCP), the focus of the first feature, is on the minds of many collection and transfusion professionals and the physicians treating patients with COVID-19. Fortunately, there are quality studies happening worldwide to help answer some of our many questions.

These questions came up during a recent Twitter chat about collecting CCP. I was pleased to see so many come together to share information that could help us fight this deadly disease. A recent Facebook Live Q&A with AABB Chief Medical Officer Claudia Cohn, MD, PhD; and Diana Berrent, a COVID-19 survivor and founder of the grassroots organization Survivor Corps, also centered on CCP.

Expanded Efforts to Reach the Community

AABB is reaching out in new ways to members of the health care community, donors and the public, especially those who have recovered from COVID-19. Our new website for clinicians, collectors and patients, COVIDPlasma.org, spells out the potential benefits of CCP and includes links to connect potential donors to their nearest collection centers.

At last month’s Board meeting, COVID-19 overshadowed every discussion. A significant challenge facing our community is the financial impact of the pandemic. Without office visits and elective surgeries, hospitals and blood centers are facing financial hardship, and blood centers don’t know how and when to scale up production. Board members reported that our colleagues need data — and they need it fast. We hear you and will do everything in our power to get you the information you need as quickly as possible.

We’re also aware of concerns about the upcoming 2020 AABB Annual Meeting, scheduled for Oct. 3-6 in Baltimore. AABB is working on contingency plans to minimize financial and travel disruptions while maximizing the meeting’s benefits of learning, sharing knowledge and connecting.

Beth Shaz, MD
AABB President
The 2020 AABB Annual Meeting is the premier meeting connecting professionals in transfusion medicine and biotherapies, while providing the information you need about groundbreaking research and practice-changing advancements. Expand your knowledge while connecting with fellow attendees who share your passion for the field.

Visit aabb.org/AnnualMeeting for more information, including meeting rates.
AABB and NBF Launch New Initiatives to Foster Community Engagement

AABB and the National Blood Foundation are pleased to introduce a new program, #TeamBlood: In This Together, to provide new ways for members of the blood and biotherapies communities to connect during this time of forced separations. One new offering, Share a Story, provides an opportunity for members to tell their account about working during the COVID pandemic. These narratives can be about happenings big or small, anything from a thank you note to a novel intervention. Add your story about the funny, the sad, the challenging or the generous via the AABB website at aabb.org/teamblood. Stories may appear in a future issue of AABB News.

The web page will also provide a means to dedicate a donation in honor or memory of a friend or colleague. Donations support innovative research that could help launch the career of someone like Krystalyn Hudson, the subject of this month’s White Coats column.

The pandemic is also creating financial hardship for many in the community, especially those starting a career. The NBF has introduced a means to sponsor AABB membership for a colleague who has been forced to drop it. Contact the AABB Membership department for additional information at +301.215.6489 or membership@aabb.org.

Shared Stories in Quarantine: How Has COVID-19 Affected You?

AABB President Beth Shaz, MD, is the executive vice president and chief medical and scientific officer at the New York Blood Center enterprises (NYBCe) in New York. Being responsible for all medical and scientific activities throughout the NYBCe, Shaz has seen the pandemic unfold from a broad vantage point. Shaz told AABB News that COVID-19 has had a drastic impact on her work and NYBCe as a whole. “NYBC employees have been severely affected by COVID-19 personally and professionally,” she said. “We are constantly adjusting what we do — like stopping mobile blood drives, increasing the collection of convalescent plasma and changing the workplace environment — to protect our employees and donors and to limit the destruction from COVID on our community and nation.”

She said that she is thankful to have a phenomenal team at NYBCe and to have met amazing individuals through this experience, both in her community and around the country. “Like Mordy and Chaim, who have organized thousands of Orthodox Jews to donate convalescent plasma and make sure we never have an empty donor chair. They also help hospitals enroll in the Mayo Clinic Expanded Access Protocol and educate physicians on the use of convalescent plasma,” she said. “Like wonderful partners at Wadsworth Center NYS Department of Health (Michael Ryan and Victoria Derbyshire), Columbia University (Ian Lipkin and Steve Spitalnik), Johns Hopkins University (Evan Bloch and Aaron Tobian) and Mayo Clinic (Mike Joyner and Jeff Winters),” she added. “We are all working together to help provide convalescent plasma treatment and gain critical scientific knowledge.”

“Through all the death and destruction, there is immense collaboration, respect and focus on regaining the health of our community,” she concluded. “We know we have to work together.”

Shaz received an NBF early-career Scientific Research Grant in 2008, which she credits as being a critical step in her academic career. She was inducted into the NBF Hall of Fame in 2019.
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Something Old, Something New:
Convalescent Plasma from Smallpox to COVID-19

By Kerri Wachter
Contributing Writer
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 17th 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. This technique, called variolation, is one of the forerunners 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. 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

*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)
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. 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. 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.

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. 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.

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. Only eight studies met the inclusion criteria, and data quality was considered poor. Nonetheless, patients who received CP fared 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. Despite a handful of successful cases of convalescent plasma treatment, results were generally disappointing for this approach. No significant improvement was seen in a non-randomized trial of 99 patients in Guinea.

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

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. 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. Clinical condition improved and antibody levels rose in these patients as well.

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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...
AABB.org May 2020 AABB News

“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.”

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.”
 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 COVID-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**

2. Ibid
4. Gross
6. Ibid
7. Ibid

**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](https://www.aabb.org/advocacy/regulatory-affairs/aabb-coronavirus-resources) at Advocacy > Regulatory Affairs > AABB’s Coronavirus Resources.
Research Is Just the Beginning

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Support advances in patient and donor care when you donate to the AABB’s National Blood Foundation (NBF).

The NBF has provided more than $9 million to fund the early-stage research of more than 200 investigators. This research has formed a basis for advanced treatments across many disciplines, including pediatrics, oncology, cardiology and transplantation.

Give to the future of patient and donor care – Donate to the National Blood Foundation today.

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BARDA Announces Partnerships to Develop Investigational COVID-19 Therapies

The Biomedical Advanced Research and Development Authority (BARDA), part of the United States Department of Health and Human Services’ (HHS) office of the Assistant Secretary for Preparedness and Response, announced a new collaboration with multiple non-government organizations to develop investigational treatments for coronavirus disease 2019 (COVID-19). The products in development include COVID-19 convalescent plasma (CCP) and hyperimmune globulin, both developed from the plasma of people who have recovered from COVID-19.

BARDA is collaborating with the American Red Cross and America’s Blood Centers to ensure the collection and distribution of convalescent plasma across the country. The agency will also partner with Emergent BioSolutions to collect donated plasma and manufacture COVID-19 hyperimmune globulin and with both the Department of Defense’s Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) and Grifols to collect plasma and manufacture CCP and hyperimmune globulin.

Additionally, BARDA announced a new partnership with JPEO-CBRND and SAb Biotherapeutics to develop a new immunotherapy called SAB-185, which is produced from human antibodies without plasma donated from recovered patients. This approach produces greater quantities of the product than traditional methods that rely on donated blood. BARDA could support a phase 1 clinical trial for initial testing in humans.

CMS Announces Expanded COVID-19 Testing, Changes to Medicare Payment Programs

The Centers for Medicare and Medicaid Services (CMS) recently announced several regulatory waivers and rule changes to deliver expanded care to Medicare and Medicaid beneficiaries and provide flexibility to the health care system in response to the COVID-19 pandemic. The agency announced the actions to help ensure that states and localities have the flexibility they need to ramp up diagnostic testing and access to medical care — key precursors to ensuring a phased, safe and gradual reopening of the country. These changes include new rules to support and expand COVID-19 diagnostic testing for Medicare and Medicaid beneficiaries. Medicare will now cover COVID-19 testing when ordered by any health care professional authorized to do so under state law. A written practitioner’s order is no longer required for the COVID-19 test for Medicare payment purposes, as well.

Medicare and Medicaid will also cover certain serology tests, which may help determine whether a person has developed an immune response and might not be at immediate risk for COVID-19 reinfection. Medicare and Medicaid will cover laboratory processing of certain tests authorized by the Food and Drug Administration that beneficiaries self-collect at home. Additional actions aim to increase hospital capacity, expand the health care workforce and reduce administrative burden. These changes take effect immediately and will last throughout the duration of the public health emergency declaration.

CMS also announced its suspension of an advanced payment program to Medicare Part B suppliers, effective immediately and plans to reevaluate the amounts paid to health systems under an accelerated payment program, through which CMS has paid health providers and suppliers more than $100 billion since March 28. Funding remains available to hospitals and other health care providers responding to COVID-19 through the provider relief fund.
CBER Issues Updated Letter to Sponsors, Applicants and Regulated Entities on COVID-19

The Center for Biologics Evaluation and Research (CBER) updated a March 27 letter to sponsors, applicants and regulated entities outlining the agency’s efforts to advance the national response to the COVID-19 pandemic. CBER converted in-person meetings with industry representatives to teleconferences through May 29. The agency will continue to assess whether in-person meetings scheduled later than May 29 should be converted to teleconferences and will provide periodic updates. In addition, CBER’s document control center ceased processing paper submissions received after Wednesday, April 29, until further notice. CBER strongly encourages sending submissions through FDA’s preferred secure method of transmission, the Electronic Submissions Gateway.

FDA, EC Issue Updated Guidances on Conducting Clinical Trials During COVID-19 Pandemic

FDA recently added additional questions and answers to the appendix of its March 2020 guidance on conducting clinical trials during the COVID-19 pandemic. The guidance provides recommendations on obtaining informed consent during the pandemic, considerations for remote clinical outcome assessments, remote site monitoring and electronic common technical document waivers. The European Commission (EC) also updated its guidance on managing clinical trials during the pandemic to include advice on distributing medicine to patients participating in clinical trials, remote source data verification and communicating actions to protect trial patient safety with authorities.

House Members Release Concept Paper to Improve Health Care Delivery, Pandemic Response

Reps. Diana DeGette (D-Colo.) and Fred Upton (R-Mich.) released a concept paper for their bipartisan “Cures 2.0” effort, which aims to safely and efficiently modernize the delivery of health care in the wake of the coronavirus pandemic. Cures 2.0 is the follow-up legislation to the bipartisan 21st Century Cures Act, enacted in 2016, which aimed to accelerate the discovery and development of new medicines and devices.

In the paper, DeGette and Upton address six high-level focus areas comprising several topics of interest to AABB members, including the following:

- Improving the nation’s surveillance and testing capabilities to support the U.S. response to the COVID-19 pandemic, as well as future pandemics.
- Supporting innovative clinical trial design.
- Improving FDA-CMS communication regarding transformative new therapies.
- Requiring HHS to establish a regulatory framework for the recognition and utilization of real-world evidence.
- Modernizing coverage and reimbursement approaches for new medical products.
- Addressing barriers to coverage and patient access to new cell and gene therapy products.

AABB will continue to monitor the development of this bill and update members as new information becomes available.

FDA Accepts Version 2.1 DHQ; AABB Issues Association Bulletin #20-04

FDA formally recognized AABB’s version 2.1 full-length and abbreviated Donor History Questionnaires (DHQs) as acceptable mechanisms for collecting blood donor history information from donors of blood and blood components. The scope of revisions in these versions and related materials were limited to those necessary for FDA’s expedited review of recommendations to address the urgent need for blood during the pandemic.

This expedited timeline captured recommendations related to HIV risk, variant Creutzfeldt-Jakob disease and malaria; it did not permit a review of the full version 3.0 update planned by the AABB Donor History Task Force (the DHTF), including new donor eligibility questions related to prophylactic use of HIV medications. Consequently, it is necessary to capture these donor eligibility questions at the end of the v2.1 DHQ, as described in Association Bulletin (AB) #20-04, The Impact on Blood Safety of Effective Antiretroviral Medications for HIV Prevention and Treatment, which AABB released concurrently to reduce the operational complexity of implementing multiple updates.

These recommendations were developed by the Transfusion Transmitted Diseases Committee and the DHTF. AABB Regulatory Affairs also developed a DHQ v2.1 Implementation Toolkit to help members identify changes in DHQ v2.1 and related materials. Facilities may contact regulatory@aabb.org with any questions regarding the v2.1 DHQs and Related Materials and their FDA consumer safety officer with questions regarding implementation.