Special Covid-19 Communication to CMS Members
September 24, 2020

Convalescent Plasma Therapy Update

The Chicago Medical Society considers convalescent plasma therapy—infusions containing antibodies from recovered individuals—to be a promising therapeutic against coronavirus disease 2019 (Covid-19). The therapy is well positioned at intersecting lines of safety, availability for further use and investigation, reasonable cost—and most important—potential to help an increasing number of patients, as suggested by its investigational use against Covid-19 to date and past effectiveness with other deadly diseases.

Controversies
Parsing through purely clinical evidence and its implications while under the weight of a deadly pandemic is difficult enough. In this instance, a swarm of controversies has surrounded the FDA Emergency Use Authorization (EUA). Critics charge that it was politicized, rushed, and that the president and other government officials exaggerated the therapy's effectiveness at the announcement.

Following the EUA, the National Institutes of Health's COVID-19 treatment guidelines panel issued a statement that, in part, honed in on survival among patients who received plasma with high titers of antibodies versus low titers of antibodies. The panel noted an FDA analysis that found no difference in seven-day survival overall. However, the panel did acknowledge that data "suggest that convalescent plasma with high antibody titers may be beneficial in nonintubated patients." The panel concluded there was insufficient data for recommending neither for nor against the treatment, and said it should not be considered a standard of care.

Other skeptics say attention given to the treatment will preclude necessary double-blind studies, by discouraging patients who are afraid of receiving a placebo. One answer to that may come soon. Vanderbilt University Medical Center is sponsoring the random controlled Passive Immunity Trial of the Nation for COVID-19 (PassItOnII), which reportedly may reach its 1,000-patient goal late in October.

Urgency for the therapy's continued use and study is underscored by the greater than 190,000 Covid-19 deaths nationally, including more than 5,000 in Cook County. Other treatments are being used, but as is also the case with convalescent plasma therapy, none are approved. A vaccine, let alone clarity on the complexities of its production and distribution, will likely not arrive soon.

This Special Communication is intended to keep CMS members informed on recent developments. The Society's own activities have gone beyond its advocacy role and into direct support for clinical care. The CMS is a founding member of a partnership that has collected plasma allowing for treatment of many Chicago-area patients. The Society has and will continue to call for increased public- and private-sector support for the therapy's appropriate use and investigation. That applies to both inpatient and outpatient settings. This update was prepared based on insights from the CMS Covid-19 Taskforce, as well as physician interviews, studies, official documents, and the latest reporting on the issue.

FDA Emergency Use Authorization (EUA)
On August 23, the Trump Administration announced the EUA at a presidential press conference and in a seven-page letter from Food and Drug Administration Chief Scientist Denise Hinton.

"Based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent

plasma conducted during the current outbreak, and data obtained from the ongoing National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic, it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19," concluded Hinton.

The EUA allows the treatment to be used for hospitalized Covid-19 patients without the requirement of participation in a clinical trial, although trials are encouraged. Outpatient studies subject to investigational rules also are allowed, and CMS is helping to recruit volunteers for one such trial.

Convalescent plasma therapy remains regulated as an investigational product. The FDA letter and subsequent, September 2 recommendations for investigators and industry guidance provide full details on terms of the EUA.

Mayo Clinic Safety and Effectiveness Data
The Mayo-sponsored EAP was a large, multi-site study designed to evaluate the safety in hospitalized Covid-19 patients at risk for progression to a condition that was severe or life threatening. The safety results for the now-terminated study—"Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients"—were released in June.

Mayo announced serious adverse events were less than one percent. It also highlighted the diversity of the patients studied. In round numbers, the population studied was 40% women, 20% Black, and 35% Hispanic.

However, soon to take center stage were EAP observational findings on the effectiveness of the therapy, delivered to more than 35,000 transfused hospital patients. That data—"Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three Month Experience"—heavily influenced the EUA decision. It was presented online August 12, prior to peer review.

Seven-day and 30-day mortality were reported for infused patients, many of whom were critically ill. At the time of infusion, just over half were in an intensive care unit and slightly more than a quarter were on a ventilator. Early use—infusion within the first three days of diagnosis—and higher levels of antibodies were associated with lower rates of seven-day and 30-day mortality.

By the numbers, the seven-day mortality rate was 8.7% among patients studied who received the treatment within three days of being diagnosed. The mortality rate was 11.9% among patients who were transfused four or more days following diagnosis. The researchers reported similar findings for 30-day mortality, 21.6% versus 26.7%. The data was collected on three antibody titer levels—high, medium and low. Patients who received high titer plasma, with a signal-to-cutoff (S/Co) value of greater than 18.45, had a seven-day mortality of 8.9%. At medium titer, 4.62 to 18.45 S/Co, the rate was 11.6%. Patients receiving the low titer, below 4.62 S/Co, had a 13.7% rate.

Covid-19 has brought renewed attention to the therapy, which dates back to the 1890s. Notable instances in which it was used include the 1918 influenza pandemic, the 2009 H1N1 influenza pandemic, and the 2013 Ebola outbreak.

CMS Plasma Collection
In April, the CMS commenced an initiative with Metro Infectious Disease Consultants (MIDC), soon joined by Vitalant Blood Service, to recruit plasma donors under the EAP. The first units were collected in May. Volunteer sign-up, for the ongoing effort, is online at covid19chi.org. A GoFundMe campaign has been established to financially support the project.

Metro Infectious Disease Consultants is the nation's largest infectious disease group practice. It operates in seven states. Its physicians practice at a dozen Chicago and suburban locations, and many local hospitals. The nonprofit Vitalant, one of the nation's largest blood services organizations, serves almost 1,000 hospitals in 40 states.

Vitalant reports 4,700 therapeutic units as a result of collection efforts here to date, a substantial portion of that number was through the work of CMS and its partners. Each donor collection renders between three and four units of about 200ml each. In addition to units already supplied to hospitals throughout the Chicago area, there is a sizable inventory available for patients locally and where needed.

Nationally, Vitalant recently reached the 30,000-unit mark, from roughly 10,000 donor collections. Roughly 10,000 units remain in inventory.

Sources interviewed for this update reported per-unit prices at less than $100.

Additional CMS Advocacy
The CMS has joined with Rep. Danny Davis, and Chicago police and firefighters in a media event to build awareness and encourage plasma donations.

In an April 3 letter to Governor J.B. Pritzker, and subsequent contacts with his office, the CMS has made clear both the urgency of the situation and its willingness to partner with the state.

"We would like to work with you to convene a meeting with stakeholders in Illinois, including physicians, hospitals, insurers and blood banks to implement our plan via a multi-pronged approach so we have enough convalescent plasma to treat all who may benefit," wrote CMS leaders. "We would also like to explore a partnership with the Governor's Office to coordinate a statewide study in conjunction with the FDA, in which important outcomes data could be shared both with state and federal public health authorities."

To date, the governor's office has not moved forward with those proposals. However, the EUA provides a new starting point for cooperation.

Titer Labeling
Prior to the EUA, the FDA did not require antibody titer labeling for the convalescent plasma therapy units. A new requirement detailed in the September 2 industry guidance, set a 90-day transition period after which units are to be labeled as either high or low titer.

The FDA has specified only one type of test now meets its standard—the Ortho VITROS SARS-CoV-2 IgG test—although blood services can seek approval for an alternative test. Units "found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma," according to the FDA.

Plasma units currently in inventory may continue to be used during a 90-day period of FDA "enforcement discretion" as long as informed consent and other requirements are met.

Conclusion
Under the EUA, physicians have the latitude to form their own conclusions as to whether the criticisms are decisive or a distraction when assessing the therapy for patient care. Greater clinical experience and randomized controlled trials will settle the matter of the therapy's effectiveness and limitations, but clinical data so far has been presented in good faith that supports further engagement. Months before the FDA issued its EUA, the CMS acted boldly to ensure the final verdict on plasma infusion therapy would not be hindered by lack of supply. The Society remains committed to keeping it available to patients and the physicians who treat them.