

Supply and demand for plasma-derived medicinal products - A critical reassessment amid the COVID-19 pandemic

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Plasma-derived medicinal products (PDMPs) play an integral role in medical treatment and prophylaxis. Plasma products are critical for managing bleeding emergencies, autoimmune disorders, and a number of chronic conditions, such as hemophilia, congenital and acquired immunodeficiencies, and other inherited protein disorders. Driven by increased access to medical care, new products and applications, and diagnostic advances, the demand for PDMPs has been steadily growing. Plasma for fractionation, the raw material for PDMPs, is considered a strategic resource, and PDMPs are listed by the World Health Organization as essential medicines.¹

Eighty-five percent to 90% of plasma used for manufacturing medicinal products is collected as *source plasma* by apheresis from donors in dedicated plasma collection centers. A small fraction (approx. 10%-15%) is contributed by *recovered plasma*, unused plasma derived from whole blood donated for transfusion purposes. With the decline in red blood cell transfusions worldwide,² the amount of available recovered plasma appears to be stable to declining. Source plasma collections, on the other hand, have increased by a factor of 3.4 from 2000 to 2017.³

The United States is by far the largest contributor to the global source plasma supply (71% in 2017, according to the above-mentioned plasma protein therapeutics association (PPTA) analysis). The combination of favorable regulatory conditions, the ability to compensate donors, an efficient

plasma collection infrastructure, and millions of donors have made this possible. In 2019 alone, close to 40 million L of source plasma were collected in the United States in over 50 million collections.⁴

Plasma supply and demand are held in a fine balance. If demand outpaces supply, or in cases of disruptions to the supply chain, shortages of PDMPs can occur. In the past, shortages of plasma-derived coagulation factors and albumin concentrates have altered medical practice. More recently, intravenous immunoglobulin (IVIG) has been in short supply. In 2019, a significant scarcity of IVIG resulted in local shortages and rationing.^{5,6}

The coronavirus disease 2019 (COVID-19) pandemic has introduced additional stress on the plasma supply. At the same time, because of the absence of a vaccine or other specific drugs, plasma-derived medicinal products have been proposed for the treatment of this new disease.⁷ Transfusions of convalescent plasma are under investigation, with promising early safety and efficacy signals.^{8,9} Likewise, hyperimmune globulins derived from convalescent plasma have been produced for research use in clinical trials. The CoViG-19 Plasma Alliance is an active group of manufacturers (CSL, Takeda, Octapharma, and others) that have combined efforts to collect convalescent plasma and to produce an unbranded hyperimmune globulin. Another manufacturer, Grifols, is developing hyperimmune globulin in collaboration with the US Food and Drug Administration (FDA), the Biomedical Advanced Research Development Authority, and the National Institutes of Health. Finally, research teams are also testing licensed IVIG derived

Abbreviations: COVID-19, coronavirus disease 2019; IVIG, intravenous immunoglobulin; PDMPs, plasma-derived medicinal products; PPTA, plasma protein therapeutics association.

from standard donor plasmapheresis, particularly for the autoimmune and inflammatory syndromes associated with COVID-19 such as Guillain-Barre syndrome and the multisystem inflammatory syndrome in children.¹⁰

Given the criticality of the plasma supply in general and the potential application for experimental treatments for COVID-19 specifically, plasma collections have been deemed an essential component of the critical infrastructure during this pandemic. Like whole blood donations, plasma collections were allowed to continue through all phases of the pandemic response by both the US Department of Homeland Security and the European Commission.

1 | DEMAND

Fractionation of human plasma provides a range of more than two dozen therapeutic proteins used worldwide.^{11,12} For major bleeding, prothrombin complex is used to treat patients anticoagulated with vitamin K antagonists as well as factor Xa-related inhibitors. While currently approved only for congenital hypofibrinogenemia in the United States, fibrinogen has been proposed as an alternative to cryoprecipitate for severe acquired hypofibrinogenemia, for example, in trauma, postpartum hemorrhage, or cardiac surgery. The recent FIBRES (Fibrinogen Replenishment in Surgery) trial in the cardiovascular treatment space may lead to a broadened regulatory approval in the United States.¹³ Many European countries have already allowed the use of fibrinogen in acquired hypofibrinogenemia and bleeding.

Use of plasma-derived medicinal products in chronic conditions is extensive and growing. Specific plasma fractions are used to replace congenital protein deficiencies such as antithrombin deficiency, protein C deficiency, and C1-esterase deficiency. Even for the hemophilias, where recombinant factor concentrates and novel antibody-based medications have been developed, human factor concentrates remain important, for example, plasma-derived factor VIII concentrate,^{14,15} particularly in developing countries and where cost is a deciding factor.

The need for polyvalent IVIG is the most substantial driver of the plasma fractionation industry. IVIG and subcutaneous immunoglobulin are essential therapeutic products for chronic treatment of patients with primary and secondary immune deficiencies, such as those resulting from cancer chemotherapy and stem cell transplant. IVIG has numerous applications as an immunomodulatory therapy in such diverse disorders as idiopathic thrombocytopenic purpura, myasthenia gravis,^{11,12} and chronic inflammatory demyelinating

polyneuropathy. In addition, there are a number of investigational uses under study including Alzheimer disease.¹⁶

The COVID-19 pandemic has introduced an additional need for plasma that threatens an already strained system. Given the absence of proven and effective therapies for the syndromes caused by the severe acute respiratory syndrome coronavirus 2 and given the long lead time to develop effective vaccines or drug treatments, researchers have begun exploring the therapeutic use of convalescent plasma, a therapy first described during the Spanish flu of 1918. Since then, convalescent plasma has been tried during various pandemics.^{7,17,18} While it has been difficult to confirm effectiveness in some diseases such as Ebola,¹⁹ some patients treated during influenza and particularly other coronavirus-related pandemics seemed to improve. A systematic review and exploratory meta-analysis of the use of convalescent plasma and hyperimmune globulins suggested some efficacy and an acceptable safety profile.²⁰

Early reports, specifically on patients from China with COVID-19, were likewise encouraging^{21,22} and led to intense research efforts in the United States and Europe. First results are now emerging from trials in the United States and seem to indicate an acceptable safety profile and encouraging efficacy data.^{8,9,23} A first randomized controlled trial from China²⁴ showed no significant improvement with convalescent plasma therapy. However, this study was terminated prematurely due to enrollment issues and was underpowered. The authors did report positive trends, particularly for severe cases.

In addition to the transfusion-based use of convalescent plasma, there are also ongoing studies to understand the therapeutic potential of hyperimmune globulins for COVID-19 patients. Finally, regular healthy donor-derived IVIG has been proposed as a potential therapeutic option in patients with COVID-19 as well.^{25,26} All of these treatments acutely raise the demand for (convalescent) plasma.

2 | SUPPLY

Unlike for small molecule pharmaceuticals, the most challenging aspect of manufacturing plasma-derived medicinal products is provision of the raw material, plasma. Most plasma for medicinal products is derived from source plasma collection. Recovered plasma adds to the supply, but its collection volume has at best been stable and is declining in several countries as whole blood collections decline. Source plasma collection is the only practical way to meet increasing demand.

The United States is the major global supplier of (source) plasma, in part due to local regulations that

allow for source plasma donations to be compensated. Only four European countries (Germany, Austria, Czech Republic, and Hungary) allow remuneration for plasma donors. Likewise, China allows for donor compensation and collects a significant portion of the global plasma supply, although retained within China. Other countries are dependent on the import of plasma or the derived products to meet their demand, while self-sufficiency remains a declared goal of many countries, particularly in Europe.

In 2019, in the United States nearly 40 million L of source plasma were collected by plasmapheresis in over 50 million collections. The collected volume depends on a number of factors (Figure 1):

- Number of donors (donor pool)
- Number of collections per donor
 - Frequency of donations
 - Duration of active donor status
- Plasma volume extracted per collection

As the plasma donor pool is relatively limited, donor recruitment is a key objective for plasma collectors and includes opening of strategically located new centers, identification of potential new donors and financial incentives.

Once donors have been recruited, it is critical to retain them as active donors. While local regulations determine the allowed frequency of donations (eg, two times per week, with two off-days in between in the United States), donor satisfaction plays a critical role in driving frequent donations and, more importantly, in keeping donors active for longer periods. On average, donors in the United States donate for only 6 months.²⁷

While much emphasis has been put on the number of donors and the number of collections per donor, the collection volume per donor has been mostly driven by the local regulations. In the case of the United States, this is a nomogram issued by the FDA in 1992 that has been in place unchanged for the past 30 years. It employs three weight categories that define upper limits for extracted plasma volume or collection volume (mixed with anticoagulant).

That nomogram was instituted to simplify the multitude of available nomograms at different centers and for different devices from different manufacturers, and to thereby reduce the risk of human error. Over time, this nomogram has served donors well and has proved safe. While the simplicity reduced the risk of human errors, it came with the limitation of focusing only on weight, ignoring other important factors, such as hematocrit, weight, height, or body mass index that are known to influence the total plasma volume of a donor.²⁸ Moreover, it created a paradoxical situation where low-weight donors with the lowest total plasma volume are allowed to donate up to twice the percentage of their total plasma volume compared to heavier donors at the other end of the spectrum.²⁹

Given that collection technology has advanced and current apheresis devices allow automated entry of such data as physical measurements, laboratory information, and target collection setting, it seems appropriate to rethink the current approach and to potentially introduce a more personalized method focused on the individual donor's total plasma volume (TPV). Such strategy could potentially reduce the volume challenge for some donors, while allowing others to safely donate larger volumes of plasma. Clinical trials will be needed to test this hypothesis.

From time to time, clinical demand has outgrown the available supply. Shortages can also occur in the event of a supply disruption, for example, a natural disaster at a key production site.⁶ Last year, a significant shortage developed in the United States that led to rationing of IVIG products and necessary triaging and prioritization of patients' demands. Under these circumstances, many investigational uses were limited, but also in approved key indications like primary immunodeficiency, painful restrictions, and modification of approved therapy had to be implemented.⁵

With the COVID-19 pandemic the global plasma supply has come under additional pressure. The donor pool has been reduced by COVID-19 infections or fear of exposure to COVID-19 in the collection center setting, and the number of collections per donor has suffered as well. Collection centers in college towns and along the US-Mexico

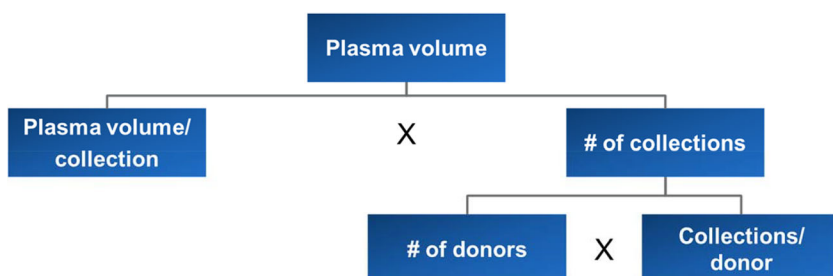


FIGURE 1 Drivers of plasma volume availability [Color figure can be viewed at wileyonlinelibrary.com]

border are hit particularly hard, but across the country limited public transport, limited child care options, and other logistical factors contribute to a shortage of donations.

Collection centers put a strong emphasis on safety and have rapidly adopted social distancing and other safety measures (eg, use of face masks, enhanced cleaning standards) as the crisis unfolded. As a result, collection capacity at the center level is reduced.

Convalescent plasma for transfusion is currently almost exclusively collected in blood centers and hospital-based transfusion medicine departments, using multicomponent collection devices for plasmapheresis. In contrast, the production of hyperimmune globulins based on convalescent plasma is mostly driven by a consortium of commercial plasma collectors who use specialized plasma collection systems that were designed for efficient plasmapheresis.

Independent of the setting, the frequency and number of donations are closely regulated by the same FDA guidance mentioned above. The current nomogram allows collection of up to 800 mL of plasma.²⁹ That way, a donation from a single convalescent donor can yield up to 3 units of convalescent plasma product (approx. 200-250 mL).

3 | DISCUSSION

Driven by constantly increasing organic demand in core indications as well as growing investigational uses, the system for plasma-derived therapeutics has been under pressure for a while. Last year's IVIG shortage painfully demonstrated the fragility of this system.⁵

With the onset of the COVID-19 pandemic, further stress has been applied to the system by both increasing demand for investigational therapies for COVID-19 and by disrupting supply.

If unaddressed, this will soon lead to shortages. The plasma fractionation process takes months, and supply disruptions are expected to become apparent by early 2021. The time to act is now. Action should be focused on boosting plasma supply and on planning for potential shortages.

Ongoing efforts of donor recruitment and retention need to be intensified. Countries that currently do not allow the remuneration of plasma donors should critically rethink that approach (at least temporarily) to add to the global supply. Protocols to assure donors of the safety of collection facilities and of the collection process in the midst of the pandemic are essential. Donor satisfaction should be improved to increase donation frequencies and duration of active donor status. Finally, it will be key to optimize the collection from each individual donor.

Some solutions are already in place, for example, technology to safely collect the maximum allowable collection volume (without anticoagulant) and technology to reduce the wastage in the collection disposable sets. Also, clinical studies with intensified donation schemes demonstrated the potential to safely collect more plasma in individual donors.³⁰ Findings from a real-world data analysis of plasma donations demonstrated that the percentage of donated plasma can differ by more than factor two, and that donors with low TPV give on average higher percentages, while donors with high TPV only give a low percentage and may be able to donate more.²⁹ Clinical trials should be conducted to test the safety and effectiveness of more personalized approaches to determine the individual target collection volume.

While maximizing the plasma supply, every effort should be made to anticipate and identify potential shortages early and to put mitigation plans in place. This could include clear guidance for triaging and prioritizing of available immunoglobulin by indication and severity of disease, which should be driven by clinical, health-economic, and ethical considerations. Expert representatives from all these groups should be involved.

CONFLICT OF INTEREST

J.H. is an employee of Haemonetics Corporation. H.G.K. has recently served on a Data Monitoring Committee for Haemonetics. His opinions do not reflect the policy of the National Institutes of Health or the Department of Health and Human Services.

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