Review Article

Blood derivative therapy

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Abstract: There are three main components manufactured from whole blood: red blood cells (RBCs), plasma, and platelets. Plasma contains a multitude of different proteins, peptides, and biologic substances. Approximately 53 million liters of plasma was collected in the United States in 2019. Following collection, plasma is frozen and manufactured into plasma-derived medicinal products (PDMPs). During the manufacture process, several thousand plasma units are pooled for Cohn fractionation, which is based upon cold ethanol precipitation of proteins. The PDMPs are further prepared using ion exchange or affinity chromatography and additional steps to inactivate and remove infectious diseases such as viruses. Almost 20 different therapeutic plasma proteins are purified from plasma via these multi-step manufacturing processes. Interestingly, the demand for pharmaceutical plasma products, particularly intravenous immunoglobulin (IVIG) products, has been increasing. The manufacture and therapeutic role of blood derivatives particularly immunoglobulin therapy, Rh immunoglobulin (RhIG), COVID-19 convalescent plasma (CCP) and hyperimmune globulins, albumin, clotting factors, fibrin sealants, and platelet rich plasma will be described.

Keywords: Plasma; plasma fractionation; source plasma; albumin

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Introduction

There are three main components manufactured from whole blood: red blood cells (RBCs), plasma, and platelets. Each of these components can also be collected individually through apheresis. RBCs are collected and stored at 4 ℃ with a variety of different solutions that confer different shelf-lives ranging from 21–42 days. RBCs that have rare antigens can be stored frozen for extended periods of time. Platelets have the shortest shelf-life of 5–7 days depending upon bacterial testing and pathogen inactivation. Lastly, plasma can be stored liquid for up to 5 days or frozen for up to 12 months or 7 years depending upon the freezing temperature. Plasma contains a multitude of different proteins, peptides, and biologic substances (1). Novel uses for these components are still being found.

Approximately 53 million liters of plasma was collected in the United States in 2019 (2). Between 2010 and 2019, plasma collections in the US nearly tripled and the number of source plasma collection centers doubled (401 to 832) (3). Currently, almost 20 different therapeutic plasma proteins are purified from plasma via multi-step processes including precipitation and/or chromatography. Interestingly, the demand for pharmaceutical plasma products, particularly intravenous immunoglobulin (IVIG) products, is increasing at the rate of 3–8% per year (1,4).

Plasma is classified according to the method of collection: recovered plasma or source plasma. Recovered plasma is typically collected by blood donor centers as a byproduct of a whole blood donation. Recovered plasma typically is comprised of 100–260 mL from a whole blood donation (4). Notably, in 2015, recovered plasma comprised only 13% of total fractionated plasma (5). Source plasma is collected via plasmapheresis at special plasma collection centers. Over two thirds of plasma used for fractionation comes from source plasma (6). During the plasmapheresis procedure,

the donor's blood is centrifuged to separate the components based upon density. The plasma is collected sterilely into a bag and the remaining components are returned along with normal saline. Source plasma volume per donation is typically ranges from 690–880 mL depending upon the donor's weight. Donors can donate source plasma more frequently than recovered plasma as longer time is needed to replace RBCs after a whole blood donation. A donor can donate plasma or platelets twice in a 7-day period with at least 48 hours between donations. In contrast, donors of whole blood or single unit RBCs can only donate every 56 days. In the US, source plasma donors can donate up to 104 times per year; however, only a small portion (0.3%) donate more than 100 times a year. Approximately 14% donate more than 50 times a year and 49% donate 10 or fewer times per year (4).

Plasma can also be classified as standard or hyperimmune. Hyperimmune plasma is collected from donors that have been vaccinated or inoculated with a particular antigen to produce a specific type of immunoglobulin such as Rh immunoglobulin (RhIG). Lastly, plasma types can be categorized based upon the remuneration status of the donor such as paid, compensated, or unpaid. Most donors at large plasma collection centers are paid/compensated for their time. The safety of paid versus unpaid plasma donation is a topic of great debate (7-10).

Blood and plasma donation is overseen in the US by the Food and Drug Administration (FDA). However, because the majority of source plasma for plasma-derived medicinal products (PDMPs) is collected in the US, most plasma donor centers in the US are also overseen by other health agencies such as the German Health Authority (GHA) in addition to the FDA. Additionally, most of the plasma donor centers in the US voluntarily participate in the International Quality Plasma Program (IQPP) certified by the Plasma Protein Therapeutic Association (PPTA). Notably, PDMPs are defines by the World Health Organization (WHO) as essential medicines and plasma for fractionation is a strategic resource (11).

Source plasma donors are typically screened at the time of donation using questionnaires, and they are also medically evaluated prior to donating. At initial donation, they receive a physical examination and have their total protein and hemoglobin quantitated at the plasma collection center using point of care testing. Each plasma donation is tested for infectious disease markers such as hepatitis B virus (HBV) antibodies and deoxyribonucleic acid (DNA), hepatitis C virus (HCV) antibodies and ribonucleic acid (RNA), human immunodeficiency virus (HIV) antibodies and RNA, as well as for RBC antibodies and Parvovirus B_{19} DNA. Notably, per IQPP standards, donors must pass two sets of qualifying measurements (have two successful donations) prior to the plasma being able to be used for further manufacture of PDMPs (3). In addition, the donors have serum or plasma protein electrophoresis (SPEP) performed at their first donation and every 4 months thereafter. The donors also undergo a physical evaluation every 6 months to one year depending upon the collection facility policy.

The cost of plasma accounts for 20–45% of the production costs in plasma fractionation industry (12). In general, blood products from unpaid donors are considered safer as there is less reason for donors to misrepresent their medical history. However, reliance on unpaid donors would not meet the current demand for plasma and its fractionated products. In countries where plasma donors are not remunerated, the percent of population donating is very low. For example, in Australia, only 0.13% are plasma donors (13). Thus, the safety of plasma and its derivatives relies on donor selection and screening as well as on efficient viral inactivation steps during processing and production. Importantly, there has not been any reported transmission of infectious blood borne diseases via plasma derivatives since 1994 (14).

There are some differences in the quantity of different proteins observed between source plasma and recovered plasma.9 Source plasma has been found to have lower IgG levels but higher amounts of clotting factors as compared to recovered plasma (15). Several other studies have shown decreases of IgG, IgA, IgM, albumin and total protein in apheresis plasma collected from long-term frequent plasma donors (16-18). Laub *et al.* studied recovered plasma from non-paid donors and apheresis plasma from remunerated and unpaid donors and compared the levels of total protein, 15 plasma protein markers, and anti-Parvovirus B_{19} and anti-*Streptococcus pneumoniae* IgG in donations from different countries including Belgium, Finland, France, the Netherlands, Germany, and the US. They found that plasma pools from paid donors at plasma collection centers in the United States had lower total protein (9%), albumin (15%), total IgG (24%), IgM (28%), hemopexin (11%) and retinol-binding protein (10%) (6). Interestingly, the paid donors had higher C1-inhibitor, pre-albumin and C-reactive protein (CRP) as compared to pools from unpaid European Union or US whole-blood or plasmapheresis donors (6). The minimum yield from a fractionated unit of fresh frozen plasma in Spain is 24 g of albumin, 4.025 g of IVIG, 80 IU

of FVIII, 105 IU of FIX, and 0.156 g of α_1-antitrypsin (19).

Source plasma donors have their RBCs returned to them and are at low risk of iron depletion. During source plasma donation, the collection device and tubing is rinsed with saline during the postdonation saline reinfusion. This helps reduce the RBC loss for each plasma donation to ~5 mL or less. For frequent plasma donors, this small loss could still add up to 250–500 mL RBC loss over the course of a year. A recent study by Schreiber *et al.* showed that iron depletion was not increased in frequent source plasma donors and that frequent plasma donation does not decrease iron stores (20). It has been hypothesized that the frequent plasma donations and exposure to citrate which is used as an anticoagulant could lead to osteoporosis; however, long-term observational studies have shown that this does not occur (21). Additionally, reaction rates for donors are quite low with <0.03% severe reactions (22).

Following collection, plasma is frozen and manufactured into PDMPs. During the manufacture process, several thousand plasma units are pooled for fractionation. During the manufacture process, the plasma undergoes Cohn fractionation which is based upon cold ethanol precipitation of proteins (23,24). The PDMPs are further prepared using ion exchange or affinity chromatography and additional steps to inactivate and remove infectious diseases such as viruses (25-27). PDMP manufacture requires at least two orthogonal virus reduction procedures that can inactivate or remove enveloped and nonenveloped viruses (28). Pasteurization is useful for inactivation of enveloped viruses and some nonenveloped viruses. Animal parvoviruses are not effectively inactivated with pasteurization (29). Hydrophobic chromatography and PEG precipitation are also effective at removing viruses (30). Filtration also effectively removes large and small viruses (31). Lastly, ammonium sulfate precipitation and hydrophobic chromatography have been shown to effectively remove prions (32). A recent study by Roth *et al.* looked at the prevalence of hepatitis E virus (HEV) in plasma donors in the US. HEV is of emerging concern in industrialized countries and transmission has been reported via transfusion of blood components but not PDMPs (33). Roth *et al.* found that the prevalence of HEV RNA was 0.002% and concluded that routine screening of source plasma donors for HEV would not substantially improve the safety of most PDMPs especially given the viral reduction steps present in manufacturing (33).

This paper will describe blood derivatives particularly immunoglobulin therapy, RhIG, COVID-19 convalescent plasma (CCP) and hyperimmune globulins, albumin, clotting factors, and fibrin sealants.

Immunoglobulin therapy

Human immunoglobulin products are made from large pools plasma from more than 10,000 donors to generate a broad range of immunoglobulins for use in immunodeficient patients. The plasma is fractionated as described above using Cohn fractionation. The fraction containing the majority of the immunoglobulin is referred to as Cohn Fraction II. Cohn fraction III also contains some immunoglobulins. These fractions then undergo several additional purification procedures such as pasteurization, ultrafiltration, acidification, chromatography, and solvent/detergent treatment depending upon the manufacturer. These additional procedures serve to remove pathogens, high-molecular-weight complexes, and soluble products from the plasma (34). Following purification, the immunoglobulin product has various stabilizers added and is tested for pathogens and pyrogenicity. To ensure pathogen removal, an aliquot is spiked with enveloped and non-enveloped DNA and RNA viruses as well as prion proteins. This aliquot is purified using the same purification process and tested for pathogens (35,36). If the product is from donors that were immunized against a certain pathogen such as HBV or rabies, the content is assessed for the specific antibody in question. Immunoglobulin therapy may still contain pathogens, particularly newer ones, that we may not have developed tests for, or pathogens that are resistant to the purification techniques employed.

Immunoglobulin therapy has been used to manage or treat several disorders such as primary immunodeficiency; Kawasaki disease; prevention of specific antibody production, such as anti-D in a RhD negative female; and treatment of certain types of infections. The largest use of immunoglobulin therapy is for acquired hypogammaglobulinemia due to hematological malignancy or post-stem cell transplant (4). Notably, indications for immunoglobulin therapy vary from country to country as does off-label use (4,37-39). Global use of immunoglobulin therapy has increased by 6-8% annually (40). Several studies have shown that immunoglobulins are being used outside established criteria in many countries. A study of clinical use of immunoglobulins in hospitals in Spain showed that 50% of immunoglobulins were administered for unapproved indications with half being for diseases in which immunoglobulins have no established efficacy (41). Notably,

Canada, Australia, and the US have high immunoglobulin use at 120–140 g/1,000 inhabitants per year. Use of immunoglobulins is lower in other developed countries such as Germany whose use is 41.5 g/1,000 inhabitants per year and the UK with 56 g/1,000 inhabitants per year (19). Recently, there have been shortages of immunoglobulins. A shortage occurred in 2019 and additional shortages have been caused by coronavirus disease 2019 (COVID-19) stressing the plasma supply. The COVID pandemic caused a reduction in plasma donations and also resulted in some plasma donors being redirected as convalescent COVID-19 plasma (CCP) donors. Another cause of limited supply is that source plasma donors typically only donate in the US for 6 months (42).

There are two main forms of immunoglobulins used as therapy: (I) standard immunoglobulin [available subcutaneous (SQ), intramuscular (IM), and intravenous (IV)]; (II) special immunoglobulins with known antibody content specific for a particular disease/infection, animal sera and antitoxins. The seroprevalence of antibodies to various infectious diseases such as measles and HAV has been shown to vary in donor populations. Ciencewicki *et al.* found that titers of anti-HAV immunoglobulin in source plasma varied from center to center with some centers having titers 3–5 times higher (43). Notably titers of CMV and measles antibodies were essentially the same across the donor centers (43). These differences are attributed to variances in food and water resources, vaccination, sanitation conditions, climate, and socioeconomics (43,44). For this reason, production of immunoglobulin therapy from donor plasma obtained from diverse donor populations from many regions is important. When administered to patients, these immunoglobulins typically will circulate for 1–6 weeks.

Preparations of high-titered disease specific human antibodies are available for administration to patients exposed to HBV, cytomegalovirus (CMV), vaccinia, botulism, rabies, varicella, tetanus, and for RhD negative individuals exposed to RhD positive RBCs. Although available for IM, SQ, and IV administration, immunoglobulin therapy is most frequently given via the IV route. The IV route has several advantages including: quick attainment of therapeutic levels, easy to give large immunoglobulin doses, no tissue loss due to proteolysis, and less painful administration as compared to IM or SQ.

IVIG administration typically takes several hours and should be infused while emergency medications such as epinephrine are easily accessible. Approximately 15% of patients receiving IVIG have adverse reactions such as nausea, backache, abdominal pain, chills, low-grade fever, and headaches which can be avoided by slowing the infusion rate. Premedication with acetaminophen, diphenhydramine, hydrocortisone, or nonsteroidal anti-inflammatory drugs may also be helpful in reducing adverse reactions to IVIG. Additionally, in some cases, the IVIG dose may be divided over 2 days. Switching to a different IVIG product may also be helpful in some patients. Severe immediate reactions to IVIG can occur and typically include chills, fever, severe headache, nausea, vomiting, rash, and/or myalgias. True anaphylaxis is rare. In patients who have a severe reaction to IVIG infusion, IgA deficiency should be ruled out as anti-IgA can cause significant anaphylactic reactions (45,46). IVIG infusion has been associated with other complications such as renal insufficiency, thrombosis, myocardial infarction, and pulmonary embolism (47).

Various mechanisms are used to reduce and eliminate infectious diseases such as viruses from blood derivative products. Common methodologies include heat treatment, solvent/detergent treatment, filtration, and fatty acids such as caprylic acid and octanoic acid (27,48-52). Heat treatment has been associated with aggregation of immunoglobulins (53). IVIG has been associated with a very low rate of infectious disease transmission; however, Parvovirus B19 transmission via IVIG therapy have also been reported (54,55). Unfortunately, Parvovirus B19 is resistant to solvent/detergent and heat treatment. Therefore, several large volume plasma collection centers are currently testing each donor's donation for Parvovirus B_{19}. There have been no reports of transmission of variant Creutzfeldt-Jakob disease (vCJD) and other prion diseases with immunoglobulin therapy. To date, there are no tests available to detect or screen for prion diseases.

RhIG therapy

Landsteiner and Wiener first discovered the Rhesus (Rh) blood group in 1940; however, it was not until 1941 that RhD was associated with hemolytic disease of the fetus and newborn (56,57). The risk of alloimmunization to RhD for a RhD negative mother carrying an ABO compatible RhD positive fetus was found to be ~16% (58). However, if the fetus was ABO incompatible with the mother, the risk of RhD alloimmunization was found to decrease to 2% (58). The incidence of hemolytic disease of the fetus/newborn varies by race as the percentage of people that are negative for RhD is higher in certain races and ethnic groups. In the US, ~15% of people of European ancestry are RhD

negative as compared to ~8% of African Americans and 1% of Asians and Native Americans. Hence, the rate of RhD incompatibility is highest in women of European descent where the chances of an RhD negative female having an RhD positive infant is ~60%.

RhIG is manufactured by collecting and purifying plasma of RhD negative donors who have been specifically exposed to the RhD antigen to generate RhD antibodies. RhIG was first available in the US in 1968. Currently, all licensed and available RhIG preparations are polyclonal and may be given IM or IV. The IM versions contain IgG aggregates as well as IgA, IgM, and other proteins that can cause anaphylaxis if given IV. Preparations for IV administration undergo additional purification via ion exchange chromatography and are purer.

Typically, RhIG is administered to RhD negative pregnant women at 28 weeks of gestation to prevent alloimmunization. It is also administered if any feto-maternal hemorrhage is suspected due to trauma or other pregnancy complications. Following delivery, the infant is tested for blood type and Rh status. No RhIG administration is needed for a mother of a RhD negative infant. However, if the infant is Rh positive, the number of infant cells is quantified in the maternal blood and an appropriate dose of RhIG is calculated and administered. In most cases, the mother only requires a single dose of 300 µg of RhIG. It is recommended that RhIG be given to Rh negative women with Rh positive infants within 72 hours after birth. However, it has been shown that partial protection is afforded by giving RhIG up to 13 days after birth (59). When RhIG is administered to Rh negative women at 28 weeks and postpartum, the risk of Rh alloimmunization decreases to 0.1% (60).

Most RhIG comes in doses of 50 and 300 µg. A 300 µg dose is considered sufficient to neutralize or protect against 15 mL of the fetus/newborn's RBCs or 30 mL of whole blood. The incidence of fetal maternal hemorrhage that exceeds 30 mL is 0.25%; thus, a 300 µg dose of RhIG is sufficient in most cases (58). It is the standard of care to screen for fetal maternal hemorrhage and quantitate the hemorrhage if necessary. Several methods are available for this purpose including, the rosette test, the Kleihauer-Betke (KB) test, and flow cytometry (61). The rosette test is a commonly used screening test, however, it does not work if the mother is a D variant as the test will be falsely positive. If the rosette test is negative, the standard practice is to administer 300 µg dose of RhIG. In positive results, a more quantitative test such as the KB test is then used (61). Flow cytometry can be used as both a screening test as well as a quantitative test (62).

Although platelets do not contain Rh antigens, platelet products can contain a few RBCs. It has been reported that each whole blood derived (WBD)-platelet contains <0.5 mL of cells and apheresis platelets (AP) contain <0.001 mL of red cells (63). Thus, transfusion of platelet products from an RhD positive donor has the risk of causing D alloimmunization in a RhD negative recipient. In some cases, blood banks may suggest RhIG when a platelet unit from an Rh positive donor(s) is released for transfusion to a Rh negative recipient. The development of an anti-D antibody following transfusion of a platelet product from a RhD positive donor depends upon a variety of factors, including the recipient's immune system as well as the dose of RBCs in the unit. Recipients who have hematologic malignancies have been reported to have lower rates of alloimmunization following transfusion with RhD positive platelets (64-66). Infants also have a lower rate of alloimmunization following administration of Rh positive platelets due to an immature immune systems not fully competent to produce alloantibodies; thus, infants have a lower rate of alloimmunization following administration of Rh positive platelets. Notably, alloimmunization with subsequent development of anti-D has been documented following WBD-platelets (67). Some medical providers do not recommend administration of RhIG to women past childbearing age following administration of Rh positive products (68).

Alloimmunization to RhD following plasma transfusion is rare; however, several cases of alloimmunization have been reported (69-71). Notably, due to the rarity of alloimmunization in this context, RhIG is likely not necessary and is rarely used under these conditions.

RhIG administration typically causes minimal adverse reactions. Itching, headaches, chills, fever, dizziness, tenderness and swelling at the site of administration, diarrhea, nausea, vomiting, arthralgia, myalgia, and sweating have been reported. As described above, IM reparations of RhIG contain small amounts of IgA and have been reported to cause anaphylaxis (72). Many years ago, RhIG was linked to HCV transmission (73); however, there have been no recent reports of transmitted infectious diseases. In addition to being used in pregnancy, IV RhIG is also used in some patients with ITP who are RhD positive. Following administration in RhD positive individuals, severe hemolysis, anemia, renal insufficiency, DIC, and death have been reported in some cases (74).

Convalescent plasma (CP) and hyper-immunoglobulin (Hyper-Ig)

Convalescent blood products were first described as being of benefit during the Spanish Influenza of 1918. Retrospective analysis of CP usage during the Spanish Influenza pandemic showed that the mortality was reduced to 16% in individuals receiving CP as compared to 37% in control cases (75). Notably, the mortality was lower (19%) in patients that received CP early (prior to 4 days of pneumonia complications) as compared to 59% mortality in those that received plasma after 4 days (75). CP has been used and studied to treat various infections including Ebola, middle eastern respiratory syndrome (MERS), H1N1, severe acute respiratory syndrome (SARS), and SARS-CoV-2 COVID-19 (76-86). During pandemics, large amounts of CP are needed for both direct patient infusion and to make hyper-immunoglobulin products.

CCP was FDA approved as an emergency investigational new drug on March 24, 2020 to treat critically ill COVID-19 patients (87). The FDA has recommended a titer of >1:320 in CCP. The first study to show improvement in patients treated with CCP was done in China. In this study, 5 patients with rapid progression of severe pneumonia were mechanically ventilated and were receiving steroids and antiviral medications. They received CCP between days 10 and 22 of hospital admission and showed improvement via normalized temperature, improved PaO2/FiO_2, and improved sequential organ failure assessment (SOFA) score (88). Another study of 6 patients in China who received CCP showed improved viral clearance and longer survival times but no improvement in mortality (89). Similarly, another study in China showed that 10 patients with severe COVID-19 who were treated with CCP early in disease course (average of 16.5 days after onset) had a substantial improvement in symptoms and decreased requirements for ventilatory support (78). CCP has also shown some benefit when given late in disease course. Ye *et al.* showed that 6 patients in China who were treated with CCP >4 weeks after disease onset and trials of other clinical regimens had clinical improvement and decreased ICU need (90). Libster *et al.* performed a randomized, double-blind, placebo-controlled trial of CCP in older adult patients with COVID-19 within 72 hours after the onset of mild symptoms (91). The primary end point was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. They found that 13/80 patients (16%) who received CCP developed severe respiratory disease as compared to 25/80 patients (31%) who received placebo (RR, 0.52; 95% CI: 0.29 to 0.94; P=0.03), with a relative risk reduction of 48% (91). A recent randomized, multicenter single-blind trial compared 257 emergency room patients presenting with one or more high risk factors for severe COVID-19 and receiving CCP to 254 patients with similar characteristics receiving placebo and found that disease progression was similar in the two groups (92). There were no differences in secondary outcomes (worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause) (92). The patients in this study received CCP later (within 1 week of symptom onset) as compared to other trials showing improvement in outcome (91,92).

Prior to the COVID-19 pandemic, was the H1N1 pandemic in 2009. During this pandemic, Baxter BioLife plasma centers collected plasma from convalescent donors as well as self-identified donors who were vaccinated against H1N1 to make a hyper-immunoglobulin product. They collected 15,000 units of plasma which was found to have 16-fold increased hemagluttination inhibition titers as compared to normal source plasma (93). This group found that 54% of self-identified vaccinated donors, 37% of self-identified convalescent donors, and 10% of control donors had titers against H1N1 greater than 64 (94). Notably, 80% of control donors had titers <16 as did 47% of convalescent donors and 40% of vaccinated donors (94). Thus, a higher titer final product could have been produced by eliminating plasma from donors with lower antibody titers. Baxter BioLife did not test each plasma product for influenza antibodies. In another study of hyper-immunoglobulin therapy for H1N1, 17 patients received hyper-Ig and 18 patients received regular IVIG (95). The two groups had similar viral loads prior to therapy. By day 7, the hyper-Ig group had significantly lower viral load as compared to the IVIG group (P=0.02) (95). Notably, hyper-Ig treatment of patients prior to day 5 was associated with reduced mortality (OR 0.14, P=0.04) (95).

In 2019-2020, several plasma manufacturers including CSL, Octapharma and Takeda joined efforts to collect CCP to make a COVID-19 hyperimmune globulin product for clinical trials. This alliance was named the CoVIg-19 Plasma Alliance. Another large plasma manufacturer, Grifols, collaborated with the US FDA, National Institutes of Health (NIH), and the Biomedical Advanced Research Development Authority (BARDA) to develop a COVID-19 hyperimmune globulin product. The CoVIg-19 Plasma

Alliance solicited convalescent donors and either required proof of previous COVID-19 positive test (either positive COVID-19 AB or COVID-19 PCR) provided from the donor or positive COVID-19 AB test at the testing center. Qualified donors were offered COVID-19 AB testing at various plasma collection centers. Each convalescent donor donation was tested for COVID-19 AB. Donors whose COVID-19 AB level fell below a positive value were then removed from the convalescent donor program. Hyper-immunoglobulin products were then produced and tested in clinical trials by selecting certain high titer donor plasma units. The COVID Hyper-Ig products produced by the Plasma alliance, Grifols, and Emergent BioSolutions were studied in a phase 3 clinical trial. This trial sought to study the safety, efficacy, and tolerability of a combination of remdesivir and hyper-Ig to treat sick patients with COVID-19. Approximately 600 adult COVID-19 patients were enrolled in the US and 10 other countries on 5 continents (96). Patients were enrolled if they had been hospitalized and symptomatic with COVID-19 for 12 or less days without life-threatening organ dysfunction or organ failure. This study sought to examine if the hyper-Ig could reduce the risk of COVID-19 disease progression when added to standard of care or remdesivir. Analyses of the study outcome and data is ongoing; however, it did not meet its endpoints (96). Notably, there were no safety concerns with the hyper-Ig product studied (96).

Overall, studies of CP use in infectious viral diseases have shown that it is helpful and improves outcomes. A meta-analysis of 40 studies of CP use in infectious diseases showed that CP use reduced mortality, promotes antibody production, decreases viral load, and shortens disease course. Moreover, there was a very low incidence of adverse events (97). Studies with CCP and other convalescent plasmas have shown that treatment of patients earlier in disease course is associated with improved outcomes as compared to treatment later (98). Notably, Hegerova *et al.* compared a cohort of 20 patients with COVID-19 to retrospectively matched controls and found that patients who received CCP before day 7 had a mortality rate of 0% as compared to 10% mortality in patients who received CCP later in the disease course (99). The success of CP early in disease course is thought to be attributable to the fact that viremia peaks during the first week in most viral illnesses and most people develop a primary immune response by 10–14 days followed by clearance of the virus (82). A retrospective multicenter randomized trial of CCP in the US examined 39 patients that were transfused with 2 units of ABO matched CCP with anti-spike titers >320. Patients receiving CCP were more likely than controls to not have an increased supplemental oxygen requirement by day 14 (OR 0.86) (100). Notably, survival only improved for nonintubated patients (HR 0.19) (100). Protection offered by CP is thought to last weeks to months (78,79,101).

Albumin

Albumin is the most abundant protein in human plasma and comprises ~50% of the total protein (102). Albumin is also responsible for a large portion of the plasma's oncotic pressure (102). The albumin content in the human body is 4–5 g/kg with 1/3rd being intravascular and 2/3rd being extravascular (102). Albumin is synthesized primarily by the liver at a rate of 9–12 g/day and has a half-life of 2–3 weeks (102). In addition to exerting oncotic pressure, albumin also binds other molecules, ions, and drugs. Hence, it serves to buffer hydrogen ions, transport hormones, bind bilirubin, bind and transport drugs such as lithium, and contribute to the redox potential of plasma (103). Albumin is clinically used for many diverse situations such as for fluid resuscitation in burn patients, replacement fluid in therapeutic plasma exchange (TPE), and to maintain oncotic pressure in patients with third spacing due to protein loss.

The clinical use of albumin has had some controversy. In 1998, a meta-analysis reviewed the use of albumin in 40 years of randomized controlled clinical trials (RCTs) and found that there was an increase in mortality associated with its use (104). Other meta-analyses including studies that employed newer albumin preparations did not support this finding (105,106). In 2005, a large RCT compared 4% albumin to normal saline in critically ill patients and found that mortality was equivalent in both groups (107).

There are several different manufacturing processes to generate albumin from human plasma. Some involve 30% ethanol fractionation, anion exchange chromatography, diafiltration, cation exchange chromatography, gel filtration chromatography, and/or pasteurization (103). These differences in manufacture lead to differences in the albumin products and different associated adverse events (108,109). It is also believed that different manufacturing processes affects the capacity of albumin to bind drugs and fatty acids (110-112). Manufacturing differences are thought to result in differences in the effects of albumin on microcirculation as well as inflammatory marker upregulation (113,114). Different preparations of albumin have also been shown to

have heterogeneity in relation to their oxidation status with up to 57% having oxidation at Cys34 which reduces the antioxidant capacity of albumin (115).

Compared to crystalloids (saline and Lactated Ringers solution), colloids (albumin and hydroxyethyl starch) are superior at maintaining intravascular volume. Crystalloid have been shown to be associated with decreased intravascular volume and increased pulmonary and peripheral edema as compared to colloid use in severely ill and hypovolemic patients (116,117). Notably, administration of colloids and crystalloids was equivalent in septic patients, with both groups developing equivalent edema due to capillary leakage (118). The SAFE study looked at the impact of albumin as compared to normal saline on organ function and mortality in patients with severe sepsis (119). This study found no difference in renal or other organ failure. Moreover, it found that the unadjusted relative risk of death for albumin versus saline was 0.87 for patients with severe sepsis (119). In subgroup analysis, trauma patients given albumin were found to have higher mortality (P=0.04) (119). This difference was attributed primarily to traumatic brain injury (TBI) patients where albumin administration was associated with a higher 28-day mortality (P=0.009) (119). Interestingly, a follow-up study on these TBI patients found that they continued to have higher mortality at 25 months (120). Thus, the use of albumin contributed to the decrease in mortality risk in non-TBI patients but increased mortality for TBI patients. The FEAST trial looked at mortality after fluid bolus in African children with severe infection. The children were randomized to boluses of 5% albumin, normal saline, or no bolus. There were no differences between the normal saline and albumin groups in terms of 48-hour mortality, 4-week mortality, neurologic sequelae, or increased intracranial pressure or pulmonary edema (121). Thus, albumin appeared to be as safe as normal saline. In the ALIAS (Albumin in Acute Ischemic Stroke) part 1 and 2 trials, investigators evaluated whether 25% human albumin improves clinical outcomes after acute ischemic stroke beyond standard of care using similar protocols. The part 1 trial ended prematurely due to safety concerns, and the part 2 trial terminated early because of futility, since there was a statistically significant effect of albumin over saline administration. These studies found that treatment with 25% albumin was not associated with improved outcome at 90 days but was associated with increased intracerebral hemorrhage and pulmonary edema (122). Rochwerg *et al.* performed a meta-analysis looking at the effect of replacement fluid choice in sepsis patients on renal replacement therapy and found that there was no difference between fluid resuscitation with albumin and crystalloid (OR 1.04) (123). There were no significant differences between balanced crystalloid and saline (OR 0.85) or albumin (OR 0.82) (123). Xu *et al.* looked at whether albumin reduced mortality when used for the resuscitation of adult patients with severe sepsis and septic shock compared with crystalloid (124). They found that albumin use was associated with a trend toward decreased 90-day mortality in sepsis patients (OR 0.88; P=0.08) and that that the use of albumin significantly decreased 90-day mortality in septic shock patients (OR 0.81; P=0.03) (124). Use of albumin for resuscitation also slightly improved the outcome in sepsis patients (OR 0.81; P=0.09) (124). Thus, albumin use in sepsis patients may be slightly advantageous. Overall, additional studies are needed to clarify the risks and benefits of albumin in these patient populations.

Albumin is available in two formulations, an iso-oncotic preparation (4–5%) and a hyper-oncotic preparation (20–25%). The 4–5% albumin is frequently used as a replacement fluid in TPE. Albumin is used to in hypovolemia, hypoalbuminemia, burns, cirrhotic ascites, and respiratory distress syndrome (125). Since albumin is derived from human plasma, it has risks of transmission of infectious diseases. With comprehensive donor screening and product manufacturing processes, the risk of disease transmission, however, is very remote.

Albumin infusion has been associated with allergic reactions that in some cases may progress to severe anaphylaxis. Adverse reactions normally resolve when the infusion rate is slowed down or the infusion is stopped. In case of severe reactions, the infusion should be stopped and appropriate treatment should be initiated. Thus, epinephrine should be available to treat any acute hypersensitivity reaction. The amount of electrolytes in the 20–25% and 4–5% albumin preparations differs between the 2 preparations, with the hypertonic albumin having less electrolytes. Thus, the patient's electrolyte status should be monitored with albumin infusion. Infusion of large amounts of either albumin solution can result in changes in coagulation test results as well as hematocrit. Thus, with large volume albumin replacement, RBC or plasma transfusions may be necessary. Lastly, monitoring of blood pressure and pulse, central venous pressure, pulmonary artery occlusion pressure, and/or urine output may be helpful with administration of 20–25% albumin. Notably, 20–25% albumin should not be diluted with water for

injection as this can cause hemolysis.

C1-esterase inhibitor

C1-esterase inhibitor is used to treat patients with a deficiency of this protein who have hereditary angioedema (HAE). People with HAE can have attacks of nonpruritic, nonpitting SQ or submucosal angioedema that causes pain and/or disability. C1-esterase inhibitor is approved for use in routine prophylaxis and acute treatment of angioedema attacks in adults, adolescents and pediatric patients (6 years of age and older) with HAE. In addition to plasma derived C1-esterase inhibitor, several other treatments are available for treatment and prophylaxis of HAE including lanadelumab (a monoclonal antibody against plasma kallikrein), recombinant C1-esterase inhibitor, icatibant (a B2 receptor antagonist), and ecallantide (a plasma kallikrein inhibitor) (126). C1-esterase inhibitor is manufactured from source plasma that is thawed and then depleted of cryoprecipitate. The cryoprecipitate-depleted plasma is then further purified using chromatography, ammonium sulfate precipitation, pasteurization, and filtration (32,126-128). Infusion of plasma-derived C1-esterase inhibitor is most frequently associated with headache, nausea, rash, vomiting, and fever (47). Hypersensitivity reactions and arterial/venous thromboembolism are also possible. Using current manufacturing processes, Simon *et al.* have estimated the risk of one vial of C1-esterase inhibitor to contain one infectious virus particle of either HIV, HCV, or HBV to be 1 in 333,333 years (126).

α1-antitrypsin

α1-antitrypsin is used to treat individuals with hereditary deficiency who have emphysema. The severity of α1-antitrypsin deficiency has been shown to be related to the development of emphysema; an α1-antitrypsin level >11 μM/L has been found to be protective (129). The first plasma-derived α1-antitrypsin product was approved by the FDA i 1987 (130). Notably, α1-antitrypsin products have been used in individuals with α1-antitrypsin deficiency to prevent and treat emphysema, panniculitis, asthma, and vasculitis (131). Additionally, they may be beneficial in patients with α1-antitrypsin deficiency after lung transplantation (132).

α1-antitrypsin is produced from Cohn fraction IV precipitate using chromatography and heat treatment (24,133-135). Viruses are removed and inactivated using pasteurization and filtration (136). α1-antitrypsin is administered IV; however, only ~2% of the administered drug is delivered to lung tissue (133). Several studies have shown that the α1-antitrypsin infusion increases pulmonary antiprotease activity as demonstrated by the correlation between serum α1-antitrypsin concentration and lung anti-elastase activity as well as decreases in some inflammatory markers and markers of tissue damage (137-139). Several studies have shown a decrease in the rate and severity of exacerbations following treatment with α1-antitrypsin as well as decrease in lung density decline (140-143). Notably, some studies did not find a protective effect for α1-antitrypsin therapy (144).

The rate of adverse events with α1-antitrypsin is quite low. A 7-year observational cohort study of 747 participants receiving α1-antitrypsin showed an overall rate of 0.02 per patient-month, and in 83% of patients, no events were reported (145). The most common side-effects included chills, urticarial rashes, fatigue, nausea and vomiting. To date, no deaths have been reported related to plasma-derived α1-antitrypsin administration and there have been no reported cases of infectious viral transmission (146).

Plasma-derived clotting factors

Plasma-derived clotting factor replacement therapy is available for Factors VIII, IX, XIII, von Willebrand factor (vWF), II (prothrombin/thrombin), VII, and X. Factors II, VII, IX, and X along with protein C (PC) and protein S (PS) are manufactured as the prothrombin complex concentrate (PCC). When a proportion of factors II, VII, IX and X are activated, the complex is called activated PCC (aPCC) and it does not contain proteins C or S. Antithrombin concentrates are also available. In addition to plasma-derived factor concentrates, recombinant factors VIII, IX, vWF, and antithrombin are also commercially available. Despite the availability of recombinant factors, plasma-derived clotting factors are still used. Many years ago, these products were associated with transmission of infectious diseases such as HIV and HCV; however, the manufacturing process has changed and the products are now safer with equivalent risk of infectious disease transmission compared with recombinant products (1,147-149). It has been argued by some that plasma-derived products are more efficacious and cost-effective than recombinant products in regards to inhibitor development, immune tolerance induction in patients with factor VIII (FVIII) inhibitors , and factor IX (FIX) replacement therapy (150,151).

Plasma-derived coagulation factors production involves collection of source plasma as described above. The plasma is then subjected to immunoaffinity chromatography using monoclonal antibodies for high-purity FVIII concentrates followed by solvent/detergent treatment or pasteurization (152). These manufacturing steps have significantly reduced the transmission of lipid-enveloped viruses such as HIV, HBV, and HCV by clotting factor concentrates (153). Heat treatment of the product serves to eliminate non-enveloped viruses such as HAV and Parvovirus B19 (152).

Treatment with FVIII replacement therapy is associated with inhibitor development, particularly in patients with severe hemophilia A. This is a very serious complication as it typically renders the patient refractory to replacement therapy and subject to bleeding. Inhibitor development is seen with both plasma-derived and recombinant FVIII products and is seen in 25–30% of previously untreated patients (PUPs) within the first 10–11 days of FVIII exposure or within the first 50 exposures (154,155). A randomized trial, the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) showed a 2-fold higher risk of inhibitor development in children treated with recombinant FVIII compared with plasma-derived FVIII (155-158). This difference in rate of inhibitor development is thought to be due to the presence of vWF in plasma-derived products (159). The presence of vWF is thought to affect the immune recognition, processing and presentation of FVIII. vWF also protects FVIII from clearance by antigen-presenting cells. Moreover, surface bound FVIII-vWF complexes may regulate the internalization of FVIII. FVIII binding to vWF is dependent on sulfation of Tyr1699 in the light chain of FVIII, and incomplete sulfation of this residue has been suggested to occur in several recombinant FVIII products resulting in a loss of vWF binding (159). There are currently no plasma-derived products that contain only vWF without FVIII. However, there is a recombinant vWF product available in the US.

The first plasma-derived FIX concentrate became available in 1992. It was chromatographically purified using monoclonal antibodies followed by ultrafiltration and thiocyanate treatment (152). Highly purified FIX is used to treat hemophilia B.

Antithrombin

Antithrombin is a serine proteinase inhibitor (SERPIN) that inhibits a variety of coagulation enzymes including FXa, thrombin, FIXa, FXIa, FXIIa, and FVIIa in the presence of heparin (160). Antithrombin prefers inhibition of FXa and thrombin. Patients deficient in antithrombin are predisposed to clotting. A common situation where antithrombin is decreased is when a patient is on extracorporeal membrane oxygenation (ECMO) where the circuit is anticoagulated with heparin (161). Frequently, these patients are very ill and require supplementation with antithrombin to maintain proper circuit anticoagulation. Acquired antithrombin deficiency may also occur in patients on cardiopulmonary bypass (CPB) due to hemodilution, consumption of antithrombin by the circuit, and utilization of large doses of heparin (162,163). Lastly, antithrombin levels are frequently decreased in sepsis (164,165). During sepsis, acute phase reactants are increased and antithrombin production is downregulated (165). The degree of antithrombin deficiency has been found to correlate with severity of illness and outcome (165). Interestingly, a meta-analysis of several studies of antithrombin replacement in sepsis found a non-significant trend toward improved 28-day survival (45% for antithrombin replacement versus 35% without) (166). However, the KyberSept study did not find any difference in 28-day mortality in patients with sepsis and antithrombin deficiency who either received or did not receive antithrombin replacement (167,168). Notably patients with severe sepsis in the KyberSept study who did not receive concomitant heparin did have an improved outcome and survival benefit (169). Currently, both plasma-derived antithrombin and recombinant antithrombin products are available for use as replacement therapy.

It has been debated as to whether antithrombin use is associated with an increased risk of bleeding. Niebler *et al.* found that there was no increased frequency of bleeding when antithrombin was administered to pediatric patients on ECMO (170). However, in patients with hereditary antithrombin deficiency, there is a 5% incidence of hematomas (47). A recent study by Mattke *et al.* looked at the effect of 562 doses of antithrombin concentrate on plasma antithrombin levels. They found that current antithrombin dosing guidelines overestimate the effect of a dose of antithrombin on the plasma antithrombin level in critically ill children and result in under-dosing (171). They recommend that age, disease state and ECMO/CPB use be taken into consideration (171). The most common adverse reactions to plasma-derived antithrombin are dizziness, chest discomfort, nausea, dysgeusia, and cramping pain (47).

Factor XIII

Factor XIII (FXIII) is a plasma protein responsible for the cross-linking of fibrin to stabilize the clot. A deficiency of FXIII results in unstable clots that rapidly degrade. Congenital deficiency of FXIII is rare, with an estimated rate of 1 per 2–5 million people (172,173). Acquired FXIII deficiency is more common than congenital deficiency and is categorized as either immune or non-immune mediated (174). Individuals with severe deficiency of FXIII are at risk for development of intracranial hemorrhage, spontaneous abortion, poor wound healing, and spontaneous bleeding episodes (175-177). As in von Willebrand Disease (vWD), treatment with cryoprecipitate and/or plasma is not recommended due to the risk of infectious disease transmission as well as transfusion reactions including transfusion related acute lung injury (TRALI).

Human plasma-derived FXIII products are manufactured using purification and heat-treatment to reduce infectious disease transmission. Studies have shown that long - term administration of plasma-derived FXIII concentrate every 28 days is a well - tolerated and effective way to prevent spontaneous bleeding in children and adults with congenital FXIII deficiency and that prophylactic treatment with FXIII concentrate prior to surgery was effective for prevention and/or treatment of perioperative bleeding (178,179). It has been recommended that the FXIII level be maintained at 5–10% in congenital FXIII deficient individuals (180). The most common adverse reactions reported following administration plasma-derived FXIII products were joint inflammation, hypersensitivity, rash, pruritus, erythema, hematoma, arthralgia, headache, elevated thrombin-antithrombin levels, and increased lactate dehydrogenase. Serious adverse reactions reported include hypersensitivity, acute ischemia, and neutralizing antibodies against FXIII (47).

PC

PC is a vitamin K-dependent protein involved in anticoagulation. Once activated (APC), it combines with PS to cleave and inactivate FVa and FVIIIa. Plasma-derived PC has been approved for patients with congenital PC deficiency for the prevention and treatment of venous thrombosis or purpura fulminans (181). Replacement with plasma-derived PC is recommended following diagnosis of congenital PC deficiency particularly if there is active purpura fulminans. The typical half-life of PC is ~10 hours; however, during increased consumption, the half-life may decrease to 2–3 hours (182). Thus, frequent monitoring is needed following administration. Plasma-derived PC has been successfully administered IV as well as SQ (183,184).

Plasma-derived PC was thought to be useful in sepsis. Patients with sepsis have been shown to have decreased antithrombin, PC, and PS activity (185,186). In several studies, decreased PC was associated with increased risk of death in sepsis (187-189). Pappalardo *et al.* conducted a double-blinded, placebo-controlled, RCT to determine if PC improves clinically relevant outcomes in adult patients with severe sepsis and septic shock (190). Notably, this study was stopped early due to futility for the outcomes of prolonged intensive care unit (ICU) stay and/or 30-day mortality. The rate of prolonged ICU stay was 79% (15 patients) in the PC group and 67% (12 patients) in the placebo group (P=0.40) (190). The ICU mortality was 79% (15 patients) in the PC group versus 39% (7 patients) in the placebo group (P=0.020) (190). Lastly, the 30-day mortality was 68% in the PC group as compared to 39% in the placebo group (P=0.072) (190). PC did not improve any measured outcome in this study and the investigators concluded that PC use in sepsis should be discouraged. Moreover, a meta-analysis by Martí-Carvajal *et al.* which looked at the clinical usefulness of recombinant APC in patients with sepsis, found that APC did not significantly affect all-cause mortality at day 28 [780/3,435 (22.7%) versus 767/3,346 (22.9%); RR 1.00] (191). Moreover, APC did not significantly affect in-hospital mortality [393/1,767 (22.2%) versus 379/1,710 (22.1%); RR 1.01] and was associated with an increased risk of serious bleeding [113/3,424 (3.3%) versus 74/3,343 (2.2%); RR 1.45] (191). Based upon these findings, it was concluded that APC should not be used to treat septic patients. Notably, all clinical trials involving APC were stopped and APC was withdrawn from the market. Thus, at present, PC use is limited to congenital PC-deficient patients.

The most common reported adverse reactions following PC administration are rash, itching and lightheadedness. To date, there has been no reported bleeding, inhibitor formation, or infection transmission with plasma-derived PC (192). As with all proteins derived from human plasma, there is a risk of hypersensitivity/allergic reactions with plasma-derived PC administration. The only available plasma-derived PC product contains heparin. Thus, patients receiving this therapy should be monitored for heparin-induced thrombocytopenia and if it is suspected, PC use should be discontinued (47). Lastly, the currently available

preparation of plasma-derived PC contains >200 mg of sodium. Consequently, patients on a low sodium diet and/or patients with renal impairment should be monitored more closely (47).

PCC

PCCs are approved for warfarin reversal. Off-label uses of PCC include bleeding in patients with liver failure or pre-procedure prophylaxis for elevated INR. aPCC is used to treat hemophilia A patients with FVIII inhibitors (alloantibodies) or acquired hemophilia (autoimmune condition). There are two forms of PCC: 3-factor PCC and 4-factor PCC. The 3-factor PCCs contain mainly factors II, IX, and X and only small amounts of FVII. The 4-factor PCC contains factors II, VII, IX and X as well as proteins C and S. Thus, the 4-factor PCC is viewed as superior to 3-factor PCC in reversing warfarin anticoagulation (193-197). Interestingly, in a meta-analysis of 18 studies involving 654 elderly patients presenting for emergent warfarin reversal, the INR was corrected in 75% of patients following 3-factor PCC and in 92% of patients after 4-factor PCCs (198). PCCs are infrequently used for trauma related bleeding as there is concern that the prothrombotic effects could last for days and increase the risk for thrombosis in this setting (199). PCCs are used off label in other settings including surgical bleeding. A recent review of 861 cardiac surgery patients found that PCC use was safe and reduced blood product use (OR 2.22) with no differences in other outcomes (200). However, there was a trend toward increased risk for renal replacement therapy in the PCC group (OR 0.41) (200). A recent pilot randomized controlled trial looked at PCC versus FFP for patients with bleeding related to cardiac surgery and found no increase in thromboembolic events related to PCC use (201). They did see an increase in serious adverse events (13 versus 5) related to FFP use (201). Thus, PCC use appears to be safe and efficacious.

PCCs are manufactured from human plasma that has been frozen and thawed to generate cryoprecipitate and cryoprecipitate-poor plasma. The plasma coagulation factors are then purified from the cryoprecipitate-poor fraction. Production of PCC involves viral inactivation using solvent-detergent, pasteurization, nanofiltration, and vapor-heated treatment. The factors in each PCC product are quantitated as international units (IUs) per 100 IU of FIX. The concentration of various clotting factors (factors VII, II, and X) and anticoagulant proteins (C and S) vary from product to product. Both 3- and 4-factors PCC have been used to reverse warfarin/Coumadin; however, due to the lack of FVII in 3-factor PCC, the PT/INR values may not fully correct (202,203). 4-factor PCCs are FDA approved for the urgent reversal of acquired coagulation factor deficiency in adults caused by vitamin K antagonist therapy with bleeding or in need of urgent surgery or invasive procedure (204-208).

The alternative for use in vitamin K antagonist therapy reversal is plasma. Plasma is much less expensive; however, larger volumes are needed, transfusion will take much longer, and there are additional risks of transfusion reactions and disease transmission with plasma use. Importantly, whether plasma, 3 factor or 4 factor PCC are used for vitamin K antagonist therapy reversal, IV vitamin K should be administered. This will help lower the PT/INR. Notably, IV vitamin K needs approximately 12 hours prior to observation of clinical efficacy. PO vitamin K is less reliable due to inefficient and unreliable absorption (209,210).

In addition to vitamin K antagonist reversal, PCCs have been used off-label to treat coagulopathies in patients on ECMO, CPB, and in surgeries such as cardiac surgery and liver transplantation (211-217). PCCs are also frequently used in trauma patients as well as in patients with intracranial hemorrhage (218-220). PCCs have also been used in the reversal of direct oral anticoagulants (DOACs) such as direct thrombin (dabigatran) and FXa inhibitors (rivaroxaban, apixaban, edoxaban) (221-223). Specific reversal agents have been FDA-approved for reversal of the DOACs: idarucizumab is available to reverse dabigatran and Andexanet alfa is available to reverse the direct FXa inhibitors including rivaroxaban, apixaban, and edoxaban (224). PCCs are associated with increased risk of thromboembolism (225,226). The thrombotic risk is increased with repeated dosing of PCCs as well as with larger doses of PCCs (221,226). Care should be taken in use of PCCs particularly when used off-label.

Fibrinogen concentrates

Fibrinogen concentrates were first licensed over 50 years ago (227). Fibrinogen concentrates are used to replace/supplement fibrinogen in individuals with congenital afibrinogenemia, congenital dysfibrinogenemia, as well as in acquired dysfibrinogenemia and fibrinogen deficiency. Acquired dysfibrinogenemia and fibrinogen deficiency are significantly more common than the congenital forms.

Acquired fibrinogen defects and deficiency can result from a prosthetic heart valve, ECMO, cardiopulmonary bypass, DIC, or miscellaneous other causes. During bleeding where patients are transfused with predominately RBCs, fibrinogen is the first clotting factor to reach critically low levels (228). Low fibrinogen levels have been shown to be associated with increased bleeding risk perioperatively (229). Decreased fibrinogen levels in patients has primarily been replenished using plasma or cryoprecipitate; however, there are disadvantages to using these products including risks of disease transmission (230,231). Fibrinogen concentrates are predominantly used to control bleeding and to decrease the use of allogeneic blood products during treatment of acquired bleeding in a variety of clinical settings, including surgery, trauma, liver transplantation, and obstetrics (215,232-242). Several studies have indicated that fibrinogen concentrates reduce the need for allogeneic blood transfusion (243-245). This is highlighted by a recent study in infants less than 12 months old who had cardiac surgery with CPB, showed that infants who received fibrinogen concentrates had a median of 4 units of blood components as compared to 5.5 units in infants who did not receive fibrinogen concentrates (246). Fibrinogen concentrates have also been shown to be effective in trauma settings (247). In this setting, they have an advantage of being ABO-universal and easily and readily available for transport in the field. Sanders *et al.* found that fibrinogen concentrates were helpful adjuncts to remote damage control resuscitation (247). Innerhofer *et al.* conducted a single center study looking at trauma induced coagulopathy (TIC) with randomization to receiving either FFP or coagulation factor concentrates (primarily fibrinogen concentrate). They found that coagulation factor concentrates/fibrinogen concentrate was superior to FFP for correction of TIC as defined by rotational thromboelastometry EXTEM coagulation time >90 s or FIBTEM amplitude at 10 min <9 mm (248). Thus, fibrinogen concentrates are helpful in a variety of clinical settings.

Currently, there is a lack of agreement as to what fibrinogen value should trigger fibrinogen replacement. Additionally, it is unclear if fibrinogen concentrates and cryoprecipitate are equivalent in replacing fibrinogen during trauma and further studies are needed. Many of these studies are complicated by various forms of bias and further studies are needed. There are several fibrinogen concentrates currently available that are produced from pooled donor plasma that is pasteurized, purified, virally inactivated, and lyophilized (148,249). The different fibrinogen concentrates are prepared similarly; however, there are differences in the manufacture of each product that result in clinical differences in the preparations. Notably, the albumin concentration is different in the preparations as it is used as a stabilizer in manufacturing for some fibrinogen concentrates (250). The different preparations of fibrinogen concentrates have been shown to behave differently in models of dilutional coagulopathy (251,252). Notably, depending upon the diluent used, two fibrinogen concentrates were noted to have different thrombin times as well as different thromboelastography coagulation time and MCF (251,252). One of the available fibrinogen concentrates has been shown to have elevated fibronectin levels as compared to the other preparations (252). Similarly, other preparations were shown to have elevated vWF and/or FXIII compared to the others (250,252). The exact clinical significance of these differences in albumin, fibronectin, vWF, and FXIII levels is not clear. There have been 28 reports of spontaneous thrombotic events that may be related to administration of fibrinogen concentrates over a 27-year period (253). Thus, the possible incidence of associated thrombotic event is 1:23,300 doses of fibrinogen concentrates. Further studies are needed to assess the possible clinical differences between the various fibrinogen concentrates.

Fibrin sealants

Fibrin sealants are comprised of fibrinogen and thrombin and can polymerize into fibrin. In the presence of small amounts of calcium and FXIII, thrombin converts fibrinogen into insoluble fibrin which is then cross-lined and stabilized by FXIII. Fibrin sealants are FDA approved to be used as a topical agent that can function as a hemostat, sealant, or adhesive. A hemostat is an agent that causes blood to clot and does not work unless blood is present. A sealant is an agent that creates a barrier to flow of liquid but does not actively cause blood to clot. An adhesive is an agent that can glue tissues to one another and decrease blood loss. Fibrin sealants have been used for fistula closure, seroma reduction, anastomosis construction, early drain removal, and adhesion prevention (254,255). Fibrin sealants have been used to facilitate attachment of cartilage, dermis, mesh, nerves, pleura, and stem cells as well as used as a drug delivery system to release antibiotics, chemotherapeutic drugs, growth factors, and local anesthetics (256-264). Fibrin sealants can also facilitate tissue engineering by

functioning as a growth medium, helping with gene transfer, organizing tissues into body organs, and facilitating cell growth for graft viability (254,265-268).

There are several limitations that restrict more widespread use of fibrin sealants: (I) difficulty in reconstitution and preparation into an applicator; (II) education as to which fibrin sealant is optimal for a given application; and (III) cost. Fibrin sealants have been studied extensively in a variety of settings including abdominal, cardiovascular, dental, head and neck, obstetric and gynecological, oncological, ophthalmological, orthopedic, plastic, thoracic, urologic, and vascular surgery, in addition to neurosurgery.

Fibrin sealants are associated with a risk of allergic reaction or anaphylaxis. Each fibrin sealant on the market is manufactured slightly differently. Some fibrin sealants contain bovine thrombin which has been associated with complications including antibody development to FV and/or FII and may lead to abnormalities in coagulation (47). These complications are seen in some patients because the antibodies formed against bovine FV and FII antigens are capable of cross-reacting, neutralizing, and inactivating human FV and FII. These complications are more likely to occur with repeated use of bovine thrombin. Moreover, patients with known antibodies to bovine thrombin should not be re-exposed. The majority of fibrin sealants are comprised of pooled human fibrinogen and thrombin. Notably, there have not been any cases of hepatitis or HIV viral transmission associated with fibrin sealant use in more than 20 years; however, there have been a few cases of parvovirus B19 transmission (269,270).

Plasma-derived fibrinogen and thrombin components of the fibrin sealants are obtained from pooled human plasma that has been viral screened using both serology and PCR testing methodologies as well as viral reduction methods. During the manufacture of the concentrated fibrinogen and thrombin components, the plasma and proteins undergo filtration, heat treatment (dry or vapor heating, pasteurization), solvent/detergent cleansing, precipitation, pH treatment, and chromatography (266,267,271). Following this extensive purification process, the product has a low risk of viral and infectious disease transmission.

Fibrin sealants should only be applied topically and never injected intravascularly as this could cause thrombosis, hypotension, and death. Fibrin sealants should also not be allowed to enter a cell saver or cardiopulmonary bypass (CPB) circuits because of the risk of thrombosis (267). Application of too much fibrin sealant increases infection risk, reduces healing, and increases risk of air emboli from the gas-driven sprayers supplied by the product manufacturers. The increased risk of infection is the result of the fibrin protein providing a growth medium for bacteria (254). Biodegradation of the fibrin sealant typically occurs over a period of 10–14 days (267).

Platelet-rich plasma (PRP)

PRP has become increasingly popular over the last few years. PRP can be used as a bioactive scaffold in cell-based therapy and tissue engineering (272). PRP contains cytokines, growth factors, and many other plasma proteins. Platelets contain many proteins including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), matrix metalloproteinases 2 and 9, interleukin-8, and insulin-like growth factors (IGF-1 and IGF-2). These growth factors have been shown to be involved in stem cell homing; cell migration, proliferation and differentiation; macrophage activation; angiogenesis; and collagen/matrix synthesis (273,274). PRP is produced from autologous whole blood collected and centrifuged to separate out the RBCs. Whole blood collected in EDTA and citrate has been used for preparing PRP; however, EDTA use has been linked to an increase in damaged platelets (275). There are several commercially available closed systems for isolating PRP (276). These systems vary principally in their ability to concentrate platelets and centrifugation time. Thus, the different systems yield PRP with variations in platelets, WBCs, and growth factors (277,278). The commercial PRP preparation systems range in cost from approximately $175–1,150 per kit as compared to manual preparation which is estimated to cost approximately $4 (not including labor) (272). In the manual preparation, approximately 20 mL of whole blood is mixed with 2 mL of anticoagulant and centrifuged. In this first soft spin, RBC are easily removed as they go toward the bottom/outer most layer. The upper layer and buffy coat are then transferred to another tube and centrifuged again at a higher rate of speed. The platelets will pellet at the bottom and the platelet poor plasma is removed. The platelets are resuspended in a small volume of plasma yielding PRP (278,279). When prepared manually, the centrifugation protocol has been shown to greatly impact the quality of the PRP in the absence of anticoagulants. Notably, the contact of blood with the wall of the vacutainer can activate

platelets (280). Additionally, the centrifugation force, angle, and duration also impact the quality (280). PRP can be treated with calcium or thrombin to yield activated PRP (281). In some studies, activated PRP was useful in allowing platelets to be activated and facilitating adhesion to titanium surfaces and release of growth factors (282).

PRP uses include wound healing, hair restoration, skin and face rejuvenation, musculoskeletal regeneration, hand rejuvenation, and breast augmentation to name a few (281). Notably, PRP has been used in the fields of oral surgery, plastic surgery, dermatology, and orthopedic surgery. PRP use is somewhat controversial and still being studied. Many of the studies performed looking at the role of PRP in the processes described above are not well designed and also provide low level evidence for the therapeutic efficacy of PRP in these processes. An additional problem is that there is great variability in PRP preparations (272,283). In an attempt to standardize PRP and facilitate interpretation of clinical studies, PRP classification systems have been introduced. One system categorizes PRP based upon cellular content and fibrin architecture into 4 categories: pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte-and-platelet-rich fibrin (L-PRF) (284,285). In another attempt to better categorize various PRP preparations, DeLong *et al.* introduced the PAW classification system. The PAW classification system is comprised of: P—the absolute number of platelets; A—method used for platelet activation; W—presence or absence of white blood cells (286). More standardization is still needed to improve clinical studies and result interpretation.

PRP is relatively safe with risk mainly being associated with sterility and efficacy. Risks due to intrinsic factors include lower efficacy due to donors being on certain medications or thrombocytopenia and exacerbation/metastasis of tumor(s). PRP use is contraindicated for repair of small bone defects in patients with tumors in surrounding areas as the use of PRP is believed to cause tumors to increase in growth due to the presence of angiogenic factors (287). Extrinsic risks include bacterial contamination of the PRP product and irreversible inactivation of platelets. Lastly are risks associated with clinical characteristics of the patient/donor. The PRP product may have lower efficacy due to the underlying characteristics of the patient/donor such as a diabetic donor/patient (288). Contraindications for PRP include presence of tumors or metastatic disease, active infection, thrombocytopenia, anemia (hemoglobin <10 g/dL), pregnancy, and breastfeeding (288,289).

Pharmacovigilance

The PDMP products described above have active pharmacovigilance and risk management programs to monitor and ensure safety of the product. Associated pharmacovigilance procedures and policies ensure patient safety and promote regulatory compliance with pertinent standards. The Global Pharmacovigilance and Risk Management System collects all adverse reaction reports associated with PDMP use. It continuously monitors the data to enable early detection of any possible risks associated with PDMPs.

The field of blood product derivatives is ever changing with new product developments as well as ever increasing demand. New uses for several plasma proteins are currently being studied and more PDMPs are expected to the marketplace in the next 10 years. To meet the demand for PDMPs, increased plasma resources are needed. Many countries are working to become more self-sufficient in plasma collection either via source or recovered products. Notably in the case of CP to for viral pandemics, recovered and/or vaccinated donors will always be needed. The recent COVID-19 pandemic has challenged the PDMP market by both decreasing donors of source and recovered plasma as well as allowing us to learn more about CP use through large studies.

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