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Recent advances in use of fresh frozen plasma, cryoprecipitate, immunoglobulins, and clotting factors for transfusion support in patients with hematologic disease

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ABSTRACT

Hematologic diseases include a broad range of acquired and congenital disorders, many of which affect plasma proteins that control hemostasis and immune responses. Therapeutic interventions for these disorders include transfusion of plasma, cryoprecipitate, immunoglobulins, or convalescent plasma-containing therapeutic antibodies from patients recovering from infectious diseases, as well as concentrated pro- or anticoagulant factors. This review will focus on recent advances in the uses of plasma and its derivatives for patients with acquired and congenital hematologic disorders.

Introduction

Hematologic diseases include a broad range of acquired and congenital disorders, spanning dysfunction of the bone marrow, red blood cells, leukocytes, and platelets. The plasma proteins of the coagulation system, the complement system as well as the immunoglobulins can also be affected. Finally, hematologic diseases affect the vascular endothelium from which blood arises during embryogenesis, and with which blood constantly interacts.

Unsurprisingly, a common component of treatment strategies for patients with hematologic disease involves replacement or enrichment of missing, dysfunctional or consumed constituents of blood through transfusion. This review will focus on the recent advances in the use of plasma and its derivatives, cryoprecipitate, immunoglobulin preparations, and individual clotting factors for patients with acquired and congenital hematologic disorders.

The use of plasma transfusion for treating patients with hematologic disease

Plasma is the aqueous component of blood and is separated from blood cells by centrifugation of whole blood units or apheresis. Plasma is a source of coagulation factors, albumin and immunoglobulins, as well as a large number of other proteins, lipids and other biological mediators. A variety of plasma products are currently available for transfusion including fresh frozen plasma (FFP), plasma frozen within 24 hours (PF24), thawed plasma (TP), liquid plasma (LP), and solvent-detergent plasma. FFP, PF24, TP, and LP have similar indications for use including in the management of preoperative or bleeding patients who require replacement of multiple factors (eg, liver disease, disseminated intravascular coagulation [DIC]); massive transfusion; urgent warfarin reversal; transfusion or plasma exchange in thrombotic thrombocytopenic purpura (TTP); congenital or acquired coagulation factor replacement when specific factor concentrates are unavailable; and rare specific plasma protein deficiencies [1]. In practice, FFP and PF24 are considered interchangeable, whereas TP and LP are not to be used to correct specific factor or plasma protein deficiencies when products containing higher concentrations of the required proteins are available. Solvent-detergent plasma is indicated in TTP and for replacement of multiple factors in acquired factor deficiency states including liver disease, liver transplantation, and cardiac surgery [2]. In addition, cryo-poor plasma is also a plasma-derived product wherein plasma is thawed at 1°C to 6°C to remove the precipitated fibrinogen, and it is indicated for transfusion or plasma exchange in patients with TTP or for providing limited clotting factors excluding fibrinogen, Factor VIII, Factor XIII, and vWF. These products differ in the content and activity of coagulation factors present in them and must be used within the stipulated shelf life.

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With the recent advances in transfusion medicine, the use of plasma components is anticipated to drastically decline in the near future. The current guidelines call for plasma transfusions in patients with coagulopathy only when a specific therapy or factor concentrate is not appropriate or is unavailable. Plasma use has been discouraged as a treatment to improve international normalized ratio (INR) for low-risk procedures. However, the use of FFP to treat the acquired coagulopathies of DIC and liver diseases may still be relevant, as the replenishment of coagulation factors in these patients could be critical to treat the endothelial dysfunction associated with these conditions [3-7]. At basal conditions, endothelial cells are nonthrombogenic and are a main source of the tissue factor pathway inhibitor. Endothelial cells exert control of coagulation at critical steps of the clotting cascade [8,9]. Thus, endothelial dysfunction in these patients disturbs the finely tuned coagulation and fibrinolysis equilibrium causing blood failure [10-12], and can hence be classified as an acquired hematologic disease. For these patients, plasma or whole blood transfusion offers clear advantages over the clotting factor concentrates to treat endothelial dysfunction by supplying the adequate coagulation factors and fibrinolytic proteins to re-establish endothelial hemostasis [3]. Randomized clinical trials are warranted for developing evidence-based treatment recommendations in patients requiring multiple factor replacement in liver failure or DIC or in treating complex disorders like endothelial dysfunction arising from a variety of conditions.

Further, patients undergoing massive transfusion could potentially benefit from the clotting factors available in plasma transfusion, and a high FFP to RBC ratio (ie, 1:1) is advocated [13]. However, massive transfusion is a rare scenario in primary hematologic disease. In acquired coagulopathies arising from trauma and in other settings, an equal ratio of FFP, platelets, and RBCs (1:1:1) is used to mitigate platelet dysfunction and to reinstate hemostasis in these patients [14]. Conversely, when trauma patients who did not require a massive transfusion were transfused with FFP, a dose-related increase in adult respiratory distress syndrome, multi-organ failure, pneumonia, and sepsis was reported [15].

Another major indication for FFP is during warfarin or related vitamin K antagonists (VKA) treatment, for patients who are bleeding or undergoing urgent invasive procedures and need only transient reversal of warfarin effect. VKAs are routinely used for the primary and secondary prevention of arterial and venous thromboembolism, in patients with prosthetic heart valves, atrial fibrillation, peripheral arterial disease, and antiphospholipid syndrome [16,17]. The major concerns of plasma treatment in these patients are the varying levels of coagulation factors which may result in a partial or insufficient reversal of INR [18], and the large volume required to reverse the coagulation defect which can lead to cardiogenic pulmonary edema [19]. FFP transfusion is also specifically associated with a noncardiogenic pulmonary edema known as transfusion-related acute lung injury (TRALI), which is linked to formation of alloantibodies in prior transfusions or pregnancy. The incidence of TRALI has declined since the introduction of risk mitigation strategies such as collection of plasma from male or never pregnant female donors [19,20]. The more recently developed 4-factor prothrombin concentrate complex (4F-PCC) is currently considered optimal for treating warfarin reversal compared to plasma as it corrects INR more quickly with a lower volume of product infused [21-25]. As a result, plasma use in this setting is relegated to when 4F-PCC is not available.

Finally, TTP patients constitute an important cohort receiving FFP or cryo-poor plasma transfusion or plasma exchange to replace the VWF-cleaving protease, ADAMTS13. This enzyme prevents the formation of small-vessel platelet-rich thrombi, and the resulting thrombocytopenia, and the microangiopathic hemolytic anemia that characterizes TTP. TTP can be either an acquired syndrome arising from an autoantibody against ADAMTS13 or a congenital syndrome, resulting from ADAMTS13 gene mutations. While acquired TTP still requires plasma exchange along with other treatments including rituximab, caplacizumab, and immunosuppressive agents to better manage the disease [26-28], a recombinant protein rADAMTS13 (BAX930) is currently underway in phase III clinical trials for use in congenital TTP patients [ClinicalTrials.gov Identifier: NCT03393975] [29]. This might be a significant breakthrough as these patients have a significant lifetime exposure to plasma that can cause severe complications such as allergic and anaphylactic reactions or volume overload, and infections from bloodborne pathogens [30].

In summary, FFP is recommended in patients with complex coagulopathies such as liver disease and DIC; however, there is little high-quality evidence to inform the optimal use of FFP in prophylaxis in these patients. Plasma has an established role in major hemorrhage and in TTP. Use of plasma is declining in warfarin reversal since the introduction of 4F-PCC. There are differing opinions about the efficacy of plasma transfusion to treat patients suffering from other hematologic diseases with no consistent evidence of significant benefit for prophylactic and therapeutic uses across a range of indications evaluated [31-35]. There is a pressing need for new clinical studies to evaluate the efficacy of plasma in non-bleeding patients to understand whether the risk is outweighed by the benefits.

Use of convalescent plasma

The plasma of patients recovering from acute viral diseases contains neutralizing antibodies that mediate immune clearance of viruses. Convalescent plasma has been safely used in a number of diseases including measles, influenza, Ebola, Severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome, and may affect the clinical course of infection [36-40]. Most recently, it has been used in patients with COVID-19 (SARS-CoV-2 virus) [38,41–43]. Evidence of efficacy has been variable by disease, and in general very few adequately powered clinical trials have been performed. Convalescent plasma is considered by the US Food and Drug Administration to be a licensed plasma product used for investigational purposes [44]. Collection, storage, and transfusion of convalescent plasma are all performed as is standard for other plasma products. Dosing strategies have varied based on the availability of neutralizing antibody titer assays for various infections. Most protocols have stipulated the transfusion of 1 to 2 standard plasma units (200-600 mL total, or 10-20 mL/kg in pediatric patients). Published reports indicate that risks of convalescent plasma transfusion are similar to those of standard plasma, and adverse events are uncommon [40,45,46].

The use of cryoprecipitate in treating patients with hematologic disease

Cryoprecipitate was routinely used in the 1970s-1990s for hemophilia A and various factor deficiencies. However, its use has become increasingly confined to the treatment of hemorrhage with the development of individual factor concentrates. It derives its name from its own collection process, whereby FFP is thawed at 1°C to 6°C permitting precipitation of its cold-insoluble proteins. Centrifugation allows separation of these proteins: fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin. A unit is typically stored at -18°C in 10 to 20 mL volumes of re-suspended plasma for up to 12 months [47]. After thawing, infusion is mandated within 4 hours [1,48]. While there are no definitive transfusion thresholds, general recommendations advise use when fibrinogen levels are less than 100 mg/dL in the setting of hemorrhage or DIC [47]. In the absence of bleeding or active

consumption, 1 unit of cryoprecipitate per 10 kg body weight typically raises the plasma fibrinogen concentration by approximately 50 mg/dL [49].

Its official name, cryoprecipitated antihemophilic factor, reflects its historical use to stop bleeding in patients with hemophilia A. Due to its high concentration of factor VIII, it significantly enhanced overall survival in patients with hemophilia A [47,50]. While the method for its acquisition was described in 1964, it was not approved for the use by the FDA until 1971 [51].

Until the early 1990s, most factor replacements were derived from human plasma. In 1992, the FDA-approved recombinant factor VIII [52]. Since then, individual factor concentrates have surpassed cryoprecipitate as front line for replacement therapies for hemophilia A, FXIII deficiency, hypofibrinogenemia and in von Willebrand disease. Moreover, clinical guidelines have recommended against cryoprecipitate for these conditions unless specific factor replacement products are unavailable [50]. This is because individual factor concentrates generally are associated with fewer transfusion reactions and episodes of TRALI, and lower infection risk compared to cryoprecipitate [50]. However, fibrinogen concentrate in the United States remains licensed only for congenital deficiencies and not acquired fibrinogen deficiencies [53]. As a result, cryoprecipitate is primarily used as a concentrated source of fibrinogen in the setting of acquired fibrinogen deficiencies: massive blood loss from trauma, hemorrhagic obstetric complications, liver transplant, and DIC [54]. Fibrinogen is the most abundant coagulation factor in plasma. However, it is highly susceptible to hemodilution from fluid resuscitation and blood loss, both of which are common in the setting of massive transfusion. It is the earliest clotting factor to become depleted in hemorrhage and thus is targeted for replacement in such patients [55]. Cryoprecipitate maintains a place in the setting of major hemorrhage from trauma. Trauma-induced coagulopathy is a phenomenon resulting in accelerated fibrinolysis, induced hypofibrinogenemia, and subsequent dysfibrinogenemia [56,57]. It heralds increasing transfusion requirements and mortality as acquired hypofibrinogenemia is associated with coagulopathy and inferior outcomes in hemorrhage control [55,58]. As a result, cryoprecipitate is still often integral in massive transfusion protocols as a fibrinogen source. It can be utilized when plasma fibrinogen is found to be less than 150 to 200 mg/dL or viscoelastic test values indicate a functional fibrinogen deficit [55,59]. A retrospective review of US Army combat soldiers who received massive transfusions (10 or more packed red blood cell transfusions in 24 hours) showed improved mortality with a higher ratio of cryoprecipitate to red blood cells [60]. While a limiting factor may be time-to-administration after thawing the product, early supplementation has been shown to be feasible in trauma patients [61].

Cryoprecipitate still has a role in obstetric hemorrhage when fibrinogen is found to be less than 100 mg/dL. However, many institutions are moving toward use of fibrinogen concentrate, given ease of use and limited infection risks with this product. Fibrinogen concentrate has been shown to be as efficacious as cryoprecipitate in correcting hypofibrinogenemia identified in major obstetric hemorrhage [62]. Given current guidelines indicating focus on single factor replacement, cryoprecipitate's role in obstetric hemorrhage may soon become historical or limited to resource-constrained settings.

Dysfibrinogenemia has been observed in various states of liver disease, ranging from cirrhosis, biliary obstruction, or acute and chronic liver failure [63]. Furthermore, when synthetic liver function is compromised in such disease states, fibrinogen synthesis is reduced. During liver transplant, the ischemic liver graft releases tissue plasminogen activator that disseminates into circulation after reperfusion. The ensuing fibrinolysis diminishes fibrinogen levels which may promote intraoperative hemorrhage. Thus, cryoprecipitate is advised in the setting of clinically significant bleeding after liver transplant with a target fibrinogen level of 150 to 200 mg/dL [64].

The consumptive coagulopathy that occurs from DIC is among the most common causes of acquired hypofibrinogenemia. DIC often results secondary to an underlining disorder such as malignancy (including due to treatment of acute lymphoblastic leukemia with asparaginase), infection, trauma, or complication of pregnancy. Cryoprecipitate is often provided to patients with fibrinogen levels below 100 to 150 mg/dL to mitigate hemorrhagic complications.

There are various genetic defects that result in undetectable circulating fibrinogen and a state of afibrinogenemia. Congenital hypofibrinogenemia is typically seen in heterozygous carriers of afibrinogenemia mutations [65]. International guidelines advise use of cryoprecipitate only if fibrinogen concentrates are unavailable [66,67].

The current FDA and AABB practice guidelines mandate that cryoprecipitate be transfused within 4 hours of thawing (or 6 hours if prepooled in a closed system prior to freezing) [48]. These current guidelines were established in the 1970s to ensure adequate FVIII levels for treatment of hemophilia A and reduced risk of bacterial growth. However, given that cryoprecipitate is now mostly limited to use in hemorrhage, recent studies have sought to expand this shelf life and expand availability in emergencies. It has been recently shown that refrigerated cryoprecipitate retains hemostatic function for 14 days after thawing. Moreover, the fibrinogen concentration was not significantly changed with storage at 4 weeks in room temperature or in a refrigerator for 5 weeks after thawing [68]. Even longer shelf life may be possible through use of lyophilization and pathogen reduction technologies.

The uses of immunoglobulins in hematologic diseases

Immunoglobulin therapy, commonly referred to as IVIG, requires extensive manipulation of plasma and is one of the most processed transfusion products used for the treatment of hematologic diseases. From collection to packaging, this product requires months of complex manufacturing steps to prepare it from the pooled plasma of many donors [69]. Additionally, the increased demand from both on- and off-label uses has contributed to the ongoing national shortage of this transfusion product [70].

The mechanism of action for this class of products depends on the hematologic condition for which it is used and the specific formulation. It can be used as a replacement therapy for primary or secondary immunodeficiencies or as a specific therapy for certain pathogens (ie, rabies, hepatitis B, etc.) when collected and used as "hyperimmune" globulin. Furthermore, immunoglobulins can occupy and saturate Fc receptors of the reticuloendothelial system, thereby reducing destruction of antibody-covered neutrophils, RBCs, or platelets, explaining their use in conditions like immune thrombocytopenic purpura (ITP). However, there is also evidence that infused immunoglobulins can affect the overall function of the immune system through its direct interaction with T- and B-cells [71], interference in the maturation and differentiation of dendritic cells [72], reduction in proinflammatory monocytes and their secreted cytokines [73], or the inhibition of the expression of the IgG receptor itself, and thus exert broad immunomodulatory effects [71].

Primary humoral immunodeficiency is a congenital loss of B-cell function resulting in lack of antibody production and loss of humoral immunity. These congenital diseases include congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies [74].

Secondary humoral immunodeficiency is an acquired loss of B-cell function secondary to autoimmune destruction and dysfunction or hematological malignancies. IVIG therapy can decrease the frequency of bacterial infections in hematological malignancies, like chronic lymphocytic leukemia and multiple myeloma, as well as cytomegalovirus, interstitial pneumonia, and graft-versus-host disease in allogeneic bone marrow transplant patients [69]. However, the frequency of severe bacterial infections, fungal, and viral infections, and mortality were not significantly reduced in chronic lymphocytic leukemia patients. Further analysis reveals that IVIG therapy increases treatment costs for relatively minor decreases in infection-free days. Moreover, the development of very effective anticytomegalovirus medications, more sophisticated graft-versus-host disease prophylaxis, and lack of survival advantage has reduced the use of this treatment for bone marrow transplant patients [75].

Use of IVIG in autoimmunity continues to generate mixed results. Immune thrombocytopenia (ITP) is the primary FDA indication for use of IVIG. This treatment combined with high-dose corticosteroids can rapidly increase platelet counts in hours to days when a rapid rise in platelets are needed. Moreover, the anti-Rh(D) immunoglobulin can be used in Rh (+) patients that do not have a concomitant hemolytic anemia. As for other autoimmune cytopenias (ie, refractory disease) associated with either pediatric, adult, or perinatal conditions, the evidence is not as strong and suggested use is limited. IVIG is also indicated for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) [76]. As for other systemic autoimmunity conditions, only dermatomyositis and severe, refractory juvenile idiopathic arthritis have convincing evidence supporting use. This is due to lack of trials with this treatment as well as breakthrough developments in biologic therapies [69].

Thrombosis is the major complication associated with use of IVIG and has resulted in an FDA "boxed warning." The risk factors for developing this adverse event include advanced age, prolonged immobilization, hypercoagulable conditions, history of arterial or venous thrombosis, estrogen use, indwelling central venous catheters, hyperviscosity, and cardiovascular risk factors [77]. Also, the rate of infusion and underlying hematological malignancy may affect this risk as well [78,79]. Furthermore, in 2010, an investigation into this risk showed that certain lots of IVIG were contaminated with kallikrein and Factor XIa, with Factor XIa deduced to be the major cause of impurity-driven thrombotic events [80]. Investigation into specific products associated with thrombosis revealed Octagam to be the offending agent, and it was removed from the market. Once the manufacturing process was improved, however, it was re-introduced with no increased rate of drug-induced thrombosis [81].

Renal dysfunction and acute kidney injury are also associated with IVIG use. Those at increased risk include those with preexisting chronic kidney disease, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving nephrotoxic drugs [82]. Sucrose-containing products seem to be the most closely associated with this adverse event. The mechanism is likely osmotic nephrosis, where tubular cells absorb the large sugar load, become vacuolated, swell, and develop tubular nephropathy [83]. This can be minimized through the selection of sucrose-free IVIG if available and if not, infusion of the product at $\leq$3 mg sucrose/kg/min or use of lower concentrated product (ie, 5%), dividing the dose to 500 mg/kg/day [84]. Case reports suggest that IVIG-induced hemolysis from a sucrose-free IVIG product led to pigment-induced nephropathy and may be an unrecognized cause of acute kidney injury as well [85].

The most common hematologic adverse event in use of IVIG is hemolytic anemia. The mechanism of action is the presence of anti-A and anti-B antibodies (isohemagglutinins) in the IVIG product. The major risk factors for developing this are high-dose infusions (>1 g/kg/day, doses >100 g), female sex, and non-O blood group [86]. Manufacturers have identified methods for reducing isohemagglutinins which may reduce these risks [87]. Other strategies available to clinicians to reduce hemolysis risk include switching brands or lots if possible as well as subcutaneous administration [88].

Recent data suggest potential new trends in use of IVIG. As indicated on the website clinicaltrials.gov, recent efforts in IVIG research are focused on exploring use of these products in infectious or autoimmune processes. Evidence of activity in mixtures of antibodies then stimulate efforts to isolate the specific therapeutic antibodies and targets and use these to manufacture disease-specific immune globulin or the development of monoclonal antibodies to specific targets. Regrettably, there have been no major developments in the recent past for the routine use of IVIG, but certain areas continue to be a focus for improving its utility. One such area is the use of subcutaneous immunoglobulins for maintenance therapy in CIDP as a well as other neuromuscular disorders like multifocal motor neuropathy [89]. Recent advances in Kawasaki's disease in children show that the addition of steroids to IVIG decreases development of coronary artery anomalies [90]. Promising data also exist for the use of IVIG to treat toxic epidermal necrolysis (TEN, or Stevens-Johnson Syndrome), but further randomized controlled trial data are needed [91].

The uses of clotting factor concentrate in hematologic diseases

Replacement of clotting factors

Hemophilia

A discussion of clotting factor therapies inevitably begins with hemophilia A (congenital Factor VIII deficiency) and hemophilia B (congenital Factor IX deficiency) as the classic cases of bleeding disorder mutations. These have been observed for centuries (if not millennia) [Reference: PMID 24513149], but identification of the responsible proteins did not occur until characterization of the coagulation cascade in the 1950s and 1960s [92]. Prior to that, factor replacement therapies were only achieved inefficiently by blood or plasma transfusions, but in the late 1960s and 1970s, cryoprecipitate, delivering a more concentrated dose of plasma factors, and Factor VIII and IX concentrates were available [93]. By the end of the 1990s, recombinant Factor VIII and IX were widely used, and further improvements were made by mitigating the immune response to transfused factors (which was also critical for acquired hemophilias) [93]. Multiple entries at clinicaltrials.gov demonstrate that new formulations of recombinant Factor VIII and IX are constantly being evaluated.

While the gains made over the past century have greatly improved longevity and quality of life for hemophiliacs, more recent advancements have focused on treating the diseases at their roots by gene therapy [94,95]. The methods and modalities by which gene therapy have been conducted have varied, ranging from viral vector delivery [96], stem cell transplant [97,98], CRISPR/Cas editing [99,100], and synthetic transgene development (all primarily in animal models to date) [101]. There are more than 30 active gene therapy trials for Factor VIII and IX replacement currently listed at clinicaltrials.gov.

Additionally, a unique alternative to factor replacement has emerged for Factor VIII: emicizumab, a bispecific chimeric monoclonal antibody, will mimic the cofactor activity of Factor VIII by co-locating Factor IXa and Factor X to catalyze clot formation [102-104]. This is a major advancement in the field since it is not affected by alloantibodies that commonly appear with repeated lifelong usage of factor concentrates and avoids usage of "bypass agents" like prothrombin complex concentrates or recombinant

Factor VIIa (each discussed below), both of which can result in complications for hemophilia A patients.

Fibrinogen

Fibrinogen plays a central role in hemostasis as the substrate by which clots are formed. Deficiencies of a congenital or acquired nature have significant morbidity and mortality effects, and therefore supplementation is required in these patients [105,106]. Plasma and cryoprecipitate have both been used as replacement therapies for decades, but neither of these is ideal, requiring large volumes (less so in cryoprecipitate), risking pathogen infection, and requiring lengthy thawing [107,108].

Alternatively, fibrinogen concentrate products are currently on the market with still others in development, although these are more expensive than plasma or cryoprecipitate [109]. These are currently indicated for congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Studies have shown that FC usage reduces bleeding and transfusion requirements [110].

However, fibrinogen concentrates are not indicated for acquired hypofibrinogenemia, bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest, dysfibrinogenemia, obstetric hemorrhage including postpartum hemorrhage in persons without congenital fibrinogen deficiency, perioperative or trauma-associated hemorrhage (without congenital fibrinogen deficiency). But several studies have been completed for the above off-label usages indications [111-113]; there are also currently multiple trials on clinicaltrials.gov recruiting for usage in pediatric cardiac surgery [NCT03884725, NCT04376762], traumatic brain injury [NCT03304899], severe traumatic hemorrhage (including pediatric and prehospital usage) [NCT04149171, NCT03508141], and acquired hypofibrinogenemia [NCT03444324]. Additional approved usages may appear in the near future. For purposes of severe bleeding, an interesting approach has been the implementation of liquid fibrin glue or stiff fibrin patches containing freeze-dried concentrates of fibrinogen, FXIII, fibronectin, and thrombin [114].

Prothrombin

Prothrombin is available in the form of a concentrate of multiple factors, referred to as prothrombin complex concentrate, and it exists in 2 forms: 3-factor PCC (3F-PCC) consisting of Factors II (prothrombin), IX, and X, as well as Protein C and S, and 4-factor PCC (4F-PCC) that also contains Factor VII [115]. Its indication is currently only for urgent reversal of the VKA warfarin in adults with acute major bleeding; however, multiple off-label uses exist including reversal of direct oral anticoagulants in major bleeding or surgery [116,117], treatment of bleeding in congenital deficiencies of any of the coagulation factors found in PCC (the vitamin K-dependent factors), prophylactic usage to reduce perioperative bleeding and reduce transfusion requirements [118-120], and in traumatic bleeding alongside FFP to correct coagulopathy [121-123]. Clinicaltrials.gov lists multiple ongoing studies investigating PCC for usage in reducing perioperative bleeding [NCT02740335, NCT04244981, NCT03341156] as well as treatment of coagulopathy and bleeding including the prehospital setting [NCT03981484, NCT04019015].

Factor V

Factor V is a component of the prothrombinase complex that increases the rate of conversion of prothrombin to thrombin, rapidly resulting in clot formation upon activation. Factor V deficiency (Owren's disease) is rare and acquired Factor V deficiency is even rarer, resulting in increased bleeding risk [124]. Treatment of these patients is through supplementation with plasma, as no Factor V concentrates exist currently. Alternatively, platelet transfusion has been shown to be effective in treating Factor V deficiency due to the presence of activated Factor V in platelets. A new plasma-derived Factor V concentrate is currently under investigation but not yet in clinical trials [125,126]. More common are mutations such as Factor V Leiden which result in resistance to degradation and increased risk of thrombosis, but these patients are treated with anticoagulants rather than additional clotting factors [127]. A mutant Factor V, resistant to cleavage by Protein C is under investigation to treat severe bleeding [128-131].

Factor VII

Factor VII is activated when blood is exposed to tissue factor found in the extravascular space, resulting in downstream cascade activation of the tissue factor-activated pathway (AKA extrinsic pathway). A recombinant activated Factor VII (rFVIIa) has been available for several years, with FDA-approved indications of usage for treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors (or acquired hemophilia) [132,133], congenital Factor VII deficiency [134], and Glanzmann's thrombasthenia with refractoriness to platelet transfusions [135]. Due to several severe adverse thrombotic events associated with rFVIIa shown in trials, off-label usage of the drug (such as in traumatic hemorrhage) has greatly diminished from its initially perceived potential [136]. However, warnings and precautions have been issued by the FDA to prevent or reduce the risk of thrombosis for vulnerable populations, especially considering interactions with other procoagulant drugs. Multiple reports have demonstrated the safety of rFVIIa when used appropriately [137-140], and clinicaltrials.gov lists at least one study currently evaluating rFVIIa in hemorrhagic stroke [NCT03496883], so rFVII clinical development is likely to continue.

Factor X

Factor X is critical for efficient conversion of prothrombin to thrombin in the clotting cascade, and supplementation with Factor X concentrates or PCCs as described above is indicated in FX-deficient patients for prophylactic reduction of spontaneous bleeding, control of bleeding episodes, and perioperative management of bleeding in mild or moderate FX deficiency. Clinicaltrials.gov indicates that a study of FX concentrates in severe Factor X deficient patients undergoing surgery will be completed by 2021 [NCT03161626].

Factor XI

Factor XI is responsible for downstream activation of Factor IX in the contact activation pathway, and deficiency in this protein is rare (known as hemophilia C), sometimes resulting in abnormal bleeding. A plasma-derived concentrate has existed for over 2 decades now with a good safety profile for its limited patient population [141]. Expansion of extracorporeal life support system usage has demonstrated that Factor XI concentrate exacerbates the already prevalent clot formation in the bypass circuit [142].

Factor XII

Factor XII deficiencies are rare and have little impact on the patient [142]. No treatments are necessary.

Factor XIII

Factor XIII is responsible for crosslinking and stabilizing clot formation, and deficiency in this protein, while rare, results in bleeding disorders that require replacement. Both plasma-derived and recombinant Factor XIII are prescribed for routine prophylactic treatment and perioperative management of bleeding. Factor XIII is difficult to measure by current methods [143], but at least one study has been planned on clinicaltrials.gov to evaluate the level of Factor XIII in trauma to determine the need for acute supplementation [NCT03634215].

ADAMTS-13

ADAMTS-13 is a metalloproteinase responsible for maintaining von Willebrand factor at appropriate multimeric lengths. Severe deficiency in this enzyme's function results in TTP [144], an emergent condition requiring plasma exchange in both acquired TTP (to remove ADAMTS-13 autoantibodies) or congenital TTP (to provide limited but sufficient levels of ADAMTS-13) [145]. Plasma exchange is an invasive procedure that has many adverse effects, particularly for pediatric patients, but newly developed recombinant ADAMTS-13 has provided a safe and sustainable alternative [29,146]. Prophylactic and therapeutic trials are ongoing.

Replacement of anticoagulant factors

Antithrombin

Produced by the liver, antithrombin (AT) is a vitamin K-independent glycoprotein that blocks coagulation by irreversibly inactivating various enzymes of the coagulation cascade, most notably Factor Xa and thrombin. AT deficiency can be acquired or congenital and results in insufficient endogenous anticoagulation and subsequent predisposition to increased thrombosis [147]. Acquired AT deficiency can occur as a result of increased consumption (eg, DIC, AML), decreased synthesis (eg, liver disease), or can be drug-induced (eg, L-asparaginase, heparin). In the United States, 2 AT concentrates exist—Thrombate III (Grifols/Talecris), a pooled lyophilized product derived from human plasma and ATryn (Ovation), a recombinant AT product derived from transgenic goats [148]. AT concentrates have been proven safe and effective in patients with AT deficiency and acute VTE [149,150]. Thrombate III is FDA-approved to treat hereditary AT deficiency and for the treatment and prevention of thromboembolism that arises from surgical or obstetrical procedures [151], whereas ATryn is used in hereditary AT-deficient patients for the prevention of perioperative and peripartum thromboembolic events [152].

AT concentrates have also found success off-label for treatment and prevention of veno-occlusive disease [153,154] and for extracorporeal membrane oxygenation patients [155,156].

Recombinant human-soluble thrombomodulin

Akin to thrombomodulin, recombinant human-soluble thrombomodulin (rhTM) binds thrombin via a functional extracellular domain, activates protein C, and thwarts excessive coagulation [157]. rhTM has been assessed as a novel therapeutic agent for management of DIC. Several studies in Japan have evaluated the usefulness of rhTM in sepsis-induced DIC patients [158-161], but results have been conflicting. One multicenter retrospective study evaluating rhTM administration in DIC patients showed no reduction in mortality, and a meta-analysis of RCTs generally supported this conclusion [159,161]. Contrastingly, results from a multicenter retrospective study showed improvement of survival outcomes in sepsis-induced DIC patients who received rhTM [160]. In the United States, a randomized, double-blind placebo-controlled phase 3 clinical trial evaluating high-risk patients (ClinicalTrials.gov Identifier: NCT01598831) recently reported no significant reduction in 38-day mortality of sepsis-associated coagulopathic patients who received rhTM (ART-123) over placebo [162]. Studies evaluating sepsis-induced DIC patients with severe respiratory failure (eg, ARDS) have also been performed with both positive and negative correlations in reducing mortality [161,163]. Further study of this product is required to determine its role in treatment of coagulopathy.

Protein C

Produced by hepatocytes, protein C is a vitamin K-dependent anticoagulation factor that becomes activated by thrombin [164]. Activated protein C along with its cofactor, protein S, targets Factors Va and VIIIa for inhibition to downregulate thrombin generation. The recombinant human activated protein C, Xigris (Eli Lilly), was FDA-approved for treatment of severe sepsis but later withdrawn from the market after clinical trials failed to confirm survival benefit for patients with severe sepsis and septic shock [165-167]. The human Protein C Concentrate, ceprotin (Baxter Healthcare Corp.), is currently FDA-indicated for use in patients with severe congenital Protein C deficiency to prevent and treat venous thrombosis and purpura fulminans [168].

Protein S

Protein S has multiple functions including as a cofactor for protein C inactivation of Factors Va and VIIIa. Protein S deficiency is a rare disorder resulting in an increased risk of thrombosis [169,170]. Acute treatment with heparin and prophylactic treatment with warfarin are common after the first thrombotic incident, but lifelong usage of warfarin is not without risks [171]. There are currently no protein S concentrates available. Direct oral anticoagulants have been used successfully in cases where warfarin is ineffective or side effects become too burdensome [172,173], but no randomized controlled trials have been conducted to validate their true effectiveness [174].

C1 inhibitor

Hereditary angioedema is a congenital deficiency or dysfunction of C1 esterase inhibitor (C1-INH). While C1-INH is a complement factor rather than a coagulation factor, its loss directly affects high-level elements of the contact-activated (intrinsic) pathway, including Factor XII, kallikrein, and high molecular weight kininogen (whose cleavage product is bradykinin). Prophylactic and acute treatment of the disease has included the prominent antifibrinolytic tranexamic acid, although this is an off-label use of the drug reserved for those who cannot tolerate the androgens danazol and stanozolol which are effective treatments with a number of significant side effects [175,176]. In acute flare ups, plasma has been given to restore C1-INH, but this is less than ideal as it contains the panoply of proteases that can serve to exacerbate the attack [177,178]. Therefore, more recently developed therapies such as icatabant (a bradykinin receptor antagonist), ecallantide (a kallikrein inhibitor), and plasma-derived or recombinant C1-INH are currently used with safer profiles for hereditary angioedema patients [179-181]. New alternatives include the monoclonal antibody lanadelumab which functions by directly blocking bradykinin [182]. A multitude of other inhibitors, antibodies, and other drugs are currently under investigation.

Alpha-2 antiplasmin

Initiation of fibrinolysis is orchestrated by the generation of plasmin from plasminogen. The fibrinolysis process must be properly regulated to prevent excess bleeding and tissue damage. In combination with plasminogen activator inhibitor and thrombin activatable fibrinolysis inhibitor, α_2-antiplasmin (α_2-AP) serves as a major regulator of fibrinolysis by acting on plasminogen [183]. α_2-AP has most recently been utilized for reduction of bleeding secondary to thrombolytic therapy without affecting thrombolysis [184]. Additional efforts to produce variants of α_2-AP for therapeutic benefit are also under evaluation [183,184].

Conclusions

Plasma and its derivatives are widely used in a variety of congenital and acquired hematologic disorders. Major trends in use of these products can be identified. Plasma and cryoprecipitate use are becoming most frequent in the management of bleeding or complex coagulopathies like DIC, or less frequently, liver disease, since these disorders affect a large number of plasma proteins,

and specific therapies are lacking. Plasma use is decreasing for the purpose of warfarin reversal, prophylaxis prior to procedures and in replacement of coagulation factors or other plasma proteins as concentrates become available. Plasma use in TTP also may eventually decrease if ADAMTS13 products are successfully developed. Immunoglobulin therapy remains a bedrock of treatment of humoral immunodeficiency states, ITP and CIDP, and off-label use is common in other autoimmune disorders. Use of IVIG may decrease as more targeted immunotherapies are developed. Significant advances have been made to replace many pro- and anticoagulant factors as well as other plasma proteins. As development efforts continue in these areas, recombinant products or engineered proteins such as bi-specific antibodies will continue to displace plasma concentrates. Further early stage work is needed to optimize therapies and inform randomized trials for complex conditions like DIC and trauma-induced coagulopathy.

Conflicts of interest

The authors declare no conflicts of interest.

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