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Adverse Effects of Plasma Transfusion

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Abstract

Plasma utilization has increased over the last two decades, and there is a growing concern that many plasma transfusions are inappropriate. Plasma transfusion is not without risk, and certain complications are more likely with plasma than other blood components. Clinical and laboratory investigations of the patients suffering reactions following infusion of fresh frozen plasma (FFP) define the etiology and pathogenesis of the panoply of adverse effects. We review here the pathogenesis, diagnosis, and management of the risks associated with plasma transfusion. Risks commonly associated with FFP include: (1) transfusion related acute lung injury; (2) transfusion associated circulatory overload, and (3) allergic/anaphylactic reactions. Other less common risks include (1) transmission of infections, (2) febrile non-hemolytic transfusion reactions, (3) RBC allo-immunization, and (4) hemolytic transfusion reactions. The affect of pathogen inactivation/reduction methods on these risks are also discussed. Fortunately, a majority of the adverse effects are not lethal and are adequately treated in clinical practice.

Keywords

Plasma; Transfusion reaction; Anaphylactic reactions; Anti-IgA; TRALI; Allergic reactions; TACO

Introduction

Fresh frozen plasma (FFP) utilization has increased steadily over the past two decades. In 1991, 2.3 million units of FFP were transfused in the US versus 3.9 million in 2001.[1] By 2008, 4.5 million units of FFP were transfused, an 11.8% increase from 2006.[2] In addition, FFP use in the US appears to be disproportionately higher than in other developed countries.[1] In the UK, there has been little change in FFP usage over the past decade, but this is in contrast to decreasing red cell utilization.[3] Indications for FFP transfusion, which are reflected in national and local plasma guidelines, are included in Table 1.[4–7] Studies show that FFP is commonly requested for non-bleeding patients with abnormal coagulation studies. Approximately, 30–50% of FFP transfusions are prophylactic with or without a planned procedure. [3,8–10] Despite this common practice, there is little evidence to show that either 1) prophylactic plasma transfusion is beneficial or 2) modest elevations in INR/PT predict bleeding and correct with plasma transfusion.[3,11–17] Furthermore, multiple studies have shown that a large proportion (up to 50%) of FFP transfusions do not follow guidelines.[3,7,18,19] For pediatric patients, a recent study showed an unchanging rate of FFP use in Children's Hospitals over an eight year period even though FFP is no longer recommended in many clinical scenarios.[20] Recently, a panel of experts convened by AABB

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to develop evidence based guidelines for plasma transfusion concluded that current evidence supports the use of plasma for massive transfusion and warfarin related intracranial hemorrhage, but for most other scenarios additional studies are required to establish guidelines.[21] In light of increased FFP utilization, paucity of good data for certain indications, and the high rate of inappropriate transfusions, it is crucial that clinicians understand the risks of FFP transfusion. The incidence of adverse events to plasma found in hemovigilance reports varies widely,[22–25] and these data are limited by passive reporting and in many countries non-mandatory reporting. In France, where reporting is mandatory, the incidence of adverse events to plasma was 1:1700 units in 2010.[22] In a recently published study of 31,329 plasma transfusions in a large U.S hospital, a reaction rate of 1:360 plasma units transfused was reported, but some FFP transfusions were excluded from the analysis.[26] Risks commonly associated with plasma transfusion include transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and allergic transfusion reactions (ATR) while more rare complications include infectious disease transmission, leukocyte-associated risks, and red-cell alloimmunization. Recent studies have also commented on FFP transfusion and overall morbidity and mortality. Here we review the aforementioned risks associated with FFP, including pathogen inactivated/ reduced plasma (PRP). In this review, FFP refers to plasma frozen within 8 or 24 hours of collection. The described complications also apply to thawed plasma, which is often used in the trauma setting.

Transfusion Related Acute Lung Injury (TRALI)

In 2003, TRALI emerged as the leading cause of transfusion related mortality reported to the United States Food and Drug Administration (FDA).[27] FFP was the most frequently implicated blood product, and the United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance data from 2003 showed that TRALI risk per component was 6.9 times higher for FFP than for red cells.[28,29] TRALI is characterized by acute hypoxemia and noncardiogenic pulmonary edema during or within 6 hours of transfusion (Table 2). [27,30,31] Most patients recover in 3 days with respiratory support, but 5–25% of cases are fatal.[32,33] The primary mechanism of TRALI is the accumulation and activation of neutrophils within the pulmonary endothelium. Recent studies indicate that platelets may also play a role.[34] In the threshold model of TRALI, recipient and transfusion factors must act together to overcome a certain threshold and induce TRALI.[35,36] This model incorporates the "two-hit" hypothesis for TRALI: the first hit being a recipient factor which primes neutrophils on the pulmonary endothelium and the second hit being a mediator within the transfused component which activates primed neutrophils and induces a permeability edema.[37] A list of recipient risk factors for TRALI can be found in Table 3. The first described transfusion mediator of TRALI was leukocyte antibodies. In 1985, a study of 36 cases of TRALI demonstrated antibodies to human leukocyte antigens in 89% of cases, mostly of donor origin.[44] Since then multiple studies have supported the role of donor derived HLA and HNA (human neutrophil antigen) antibodies in TRALI.[45–49] When leukocyte antibodies are transfused into a patient with the cognate antigen, neutrophils within the pulmonary microvasculature agglutinate and release enzymes, reactive oxygen species, and inflammatory mediators which injure the pulmonary endothelium.[47,48] HLA Class II antibodies are implicated more frequently than Class I antibodies, and can indirectly activate primed neutrophils via monocyte activation and cytokine release (i.e. TNF-alpha and IL1 beta).[29,50–55] Interestingly, in a recent study, little or no risk was associated with HLA Class I antibodies.[38] HNA antibodies, specifically against HNA 3a, have also been shown to be potent mediators of TRALI.[55,56] An active surveillance study of TRALI in two US hospitals found that the quantity of strong cognate HLA-Class II antibodies and volume of HNA antibodies in blood products were predictive risk factors of TRALI.[38] Of note, numerous look-back studies of donors with leukocyte antibodies have demonstrated that the majority

of transfused patients do not develop TRALI even when the cognate antigen is expressed.[57–63] Furthermore, occasionally the implicated donor's leukocyte antibodies do not express specificity for recipient antigens, or donor leukocyte antibodies are not detected at all.[44,45] For these cases, a non-immune mechanism for TRALI has been described in which bioactive substances that accumulate during storage of cellular components (i.e. lysophosphatidylcholine, nonpolar lipids, and CD40 ligand) can provide the "second-hit" to induce lung injury in primed patients.[64–67] Additional studies, however, are needed to further characterize this non-immune pathway for TRALI. Ultimately, the literature supports that the majority of severe and fatal TRALI cases are in fact antibody-mediated.[28,49] A systematic review of studies reporting on TRALI and donor antibodies demonstrated that 1) the odds ratio for developing TRALI was 15 for patients who received a transfusion from a donor who tested positive for leukocyte antibodies, compared to donors who tested negative, and 2) leukocyte antibodies contributed to ~80% of all TRALI cases.[68] The increasing incidence of TRALI led blood collecting facilities to implement policies to prevent antibody mediated TRALI from high risk products (plasma and platelets).[69] Since most donors implicated in TRALI were multiparous women and approximately 17% of female donors have leukocyte antibodies (risk of antibodies increases with more pregnancies), the main strategy used to mitigate TRALI was to decrease or stop production of transfusable plasma from all females or females with pregnancy history.[49,70] Alternatively, for products typically in short supply, i.e. AB plasma and platelets, a strategy of testing female donors with pregnancy history for HLA antibodies has also been employed to limit donor loss.[71] Over the last few years, multiple publications have documented a decrease in TRALI after implementation of these strategies. Data from the American Red Cross and SHOT demonstrated a TRALI incidence of 1:51,000–65,000 plasma units issued pre-mitigation versus 1:250,000–317,000 post-mitigation.[29,72] German and Canadian hemovigilance systems also showed a decrease in the number of reported TRALI cases,[73,74] and a comparative cohort study from the Netherlands showed a 33% reduction of TRALI cases after implementation of a male-only plasma strategy.[75] A retrospective study of plasma transfusion in three US hospitals showed a 0.0084% risk of TRALI from plasma transfusion (47,756 units transfused) in the 16 months preceding implementation of low-TRALI-risk plasma versus 0% risk in the 16 months post-implementation (52,230 units transfused).[76] Finally, in the only large active surveillance study of TRALI, TRALI incidence went from 1:4000 blood products transfused pre-mitigation to 1:12,000 post-mitigation.[38] As expected, rates with active surveillance were higher and likely better represent true incidence. The consistent downward trend seen over these various reports strongly suggests that TRALI mitigation strategies contributed to the decrease in TRALI. Ultimately, there are now fewer fatal and non-fatal TRALI cases caused by plasma transfusion, and plasma safety with regards to TRALI risk has significantly improved.

Transfusion associated circulatory overload (TACO)

TACO is similar to TRALI since it is also characterized by acute respiratory distress, hypoxia, and pulmonary edema temporally associated with transfusion. However, TACO is a hydrostatic not permeability edema. Despite these different mechanisms, there is no distinct clinical finding or test that can differentiate TACO from TRALI. Nevertheless, a few features can aid the diagnosis (Table 4).[77] Most patients rapidly improve with diuresis, but the mortality rate has been reported as 5–15%.[84] Older age, younger age, and pre-existing cardiac and/or renal dysfunction are known risk factors.[77,85] Until recently, TACO has received little attention in the literature. However, in 2010, TACO was the second leading cause of mortality in the U.S, and TACO cases reported to SHOT increased from 18 in 2008 to 34 in 2009 and 40 in 2010.[86,87] The reported incidence of TACO ranges from <1% of transfusions to 8% of transfusions depending on patient population and identification method (passive or prospective observation).[78,88–90] Although TACO has

been reported after even a single unit of red cells,[89,90] greater transfusion volume is a risk factor for TACO independent of cardiovascular risk factors as was reported in a recent prospective cohort study.[88] Other risk factors included greater plasma volume transfused, FFP ordered for anticoagulant reversal, positive fluid balance, and increased infusion rate.[88] Regarding infusion rate, a rate of 1ml/kg of body weight per hour is often cited for patients at risk for TACO, but there is a lack of data on appropriate infusion rates in this setting.[91,92] Plasma transfusion is a risk factor for TACO since large volumes are usually needed in adults. The recommended dose of plasma for adults is 10–15ml/kg for coagulation factor replacement, and some data suggests this may even be insufficient.[7,93] Narrick and coworkers recently evaluated the rate of TACO with plasma transfusion in a large US hospital using both passive reporting and active surveillance. The rate of TACO with passive reporting over a 7 year period was 1 in 1,566 plasma units transfused, however, during a 1 month period of active surveillance a rate of 1 in 68 was observed.[26] In summary, although TACO is a potentially avoidable complication, more studies are needed to further assess patient risk factors and recommend effective preventive strategies, such as appropriate infusion rates and diuretic use in susceptible patients.

Allergic/Anaphylactic Transfusion Reactions

The incidence of allergic transfusion reactions (ATR) has been estimated at <1% to 3% of all transfusions.[94,95] Fortunately, most ATR are mild and limited to urticaria, pruritis, and/or flushing. Anaphylactic reactions are characterized by systemic symptoms of bronchospasm, angioedema, and/or hypotension and estimated incidence ranges from 1:18,000 to 1:172,000 transfusions.[96] Allergic/anaphylactic reactions are commonly associated with FFP and platelet transfusions,[87] and the rate of ATR to FFP found in two retrospective studies was 1:591 and 1:2,184 plasma units transfused.[26,94] In general, the offending plasma proteins/ antigens to which patients react are not easily identifiable, excepting haptoglobin and human immunoglobulin A (IgA).[97,98] Reports of rare cases of anaphylaxis after transfusion of methylene blue-treated plasma are mentioned below.

Antibodies to human IgA were first identified in 1968 as high-titered (>1:1000) IgG antibodies, reacting with a panel of purified IgA monoclonal myeloma proteins of both IgA1 and IgA2 subclasses, and termed “class-specific” anti-IgA.[99] Such antibodies cause dramatic anaphylactic reactions mediated by complement activation to small amounts of plasma containing IgA proteins.[99] The argument that the anaphylaxis is mediated by IgE antibodies was conclusively refuted by studies performed by Homburger et al.[100] The correlation of anaphylactic reactions with class-specific anti-IgA is so compelling that such patients must be managed with 1) cellular products extensively washed to remove residual plasma and 2) plasma products from IgA-deficient (IgA-D) donors.[101] Responding to this clinical need, the first registry of IgA-D donors was established in San Francisco in 1975. Analysis of sera from 73,569 blood donors revealed IgA-D in 113 (1:650) samples, all with normal IgG and IgM levels. Of these, 30 sera had low levels of IgA, while the remaining 83 had no IgA detectable by a more sensitive hemagglutination inhibition assay.[102] Class-specific anti-IgA was detected in 13 IgA-D donors and only two had any known history of parenteral injection of plasma proteins. Because isoimmunization to IgA in intrauterine life has been reported,[103] it is not surprising that class-specific anti-IgA antibodies occur in the serum of IgA-D donors without any parenteral exposure to IgA. Passive transfusion of high-titer anti-IgA provoked no clinical reaction in the recipients.[102] This observation of passive transfusion of high-titer anti-IgA to normal patients without provoking a reaction is now affirmed by a larger study carried out by Robittaille et al.[104] Currently, the American Rare Donor Program (a joint program with the American Red Cross and AABB) has an active registry of IgA-D donors in the U.S. and can provide IgA-D products to recipients nationwide who meet certain clinical and laboratory criteria.[105,106] Additional registries

exist in Europe, Australia, and most recently in China.[107] Depending on the screening method/s used, the prevalence of IgA-D varies widely, e.g. highest in Portugal (1:327) and lowest in Japan (1:31,800).[107,108] While many published reports continue to document the consistent picture of the anaphylactic reactions caused by class-specific anti-IgA,[109] how to manage patients with anaphylactic transfusion reactions is laid out in a clinically useful form by Sandler.[101] In contrast with the high-titered class-specific anti-IgA causing serious anaphylactic reactions, low-tittered (1:128) antibodies reacting with some of the proteins of either IgA1 or IgA2 subclass are termed anti-IgA of "limited specificity".[98,110,111] These antibodies are characteristically associated with milder allergic reactions.[99]

Genetic deletions resulting in deficiencies in other plasma proteins can also result in sensitization and induce anaphylaxis upon exposure to that protein within a blood product. Shimada and coworkers identified 7 out of 4138 Japanese patients with haptoglobin deficiency, six of whom had severe anaphylactic reactions after transfusion of a small volume of blood product.[112] Haptoglobin IgG and IgE antibodies were detected in the patients' sera, and the authors concluded that both antibody types may have played a role in inducing the reaction. Ultimately, the authors reported that, "haptoglobin deficiency is an important risk factor for anaphylactic reactions in Japan". Although less clear cut, another described case of a protein deficiency which may have induced a transfusion reaction is a patient who had 1) absence of complement component C4 with anti-C4 antibodies (with Chido and Rogers specificity) and 2) adverse reactions to plasma transfusions.[113]

The potential risk of food allergies as a cause of ATR has also been postulated by Erick,[114] and anaphylaxis from passive transfer of a peanut allergen in transfused platelets was recently documented by Jacobs et al.[115] Selective protein deficiencies in recipients, however, do not account for most anaphylactic and allergic transfusion reactions. Furthermore, passive transfer of food allergens likely does not contribute to most ATRs although this is harder to prove. Evidence to support the role of passive IgE-mediated transfer in ATR is not established, but one recent study did not show a significant difference in IgE levels in apheresis platelets implicated in allergic reactions versus control platelets.[116,117] Recent studies published by Savage and coworkers have tried to better characterize mechanisms and risk factors for allergic transfusion reactions with apheresis platelets. One study demonstrated that certain agonists of basophils and mast cells, such as C5a, brain-derived neurotropic factor, and CCL5 (RANTES), were found in greater concentration in the supernatant of apheresis platelet implicated in ATR than control units.[118] However, it is unclear if these agonists are associated with ATR due to FFP. Another study, observed 1,616 ATR among 93,737 transfusions (1.72% incidence) and found that 30% of recipients with an ATR had an ATR rate > 5%, which was greater than the overall incidence. Furthermore, these 30% of patients accounted for 62.1% of all the ATR.[119] Thus, certain patients are more prone to ATR. In fact, atopic predisposition in the recipient has been shown to be a risk factor for ATR to platelets.[117] Recipients with ATR had a higher total IgE and aeroallergen-specific IgE than matched controls.[117] Savage et al also showed that certain donors donated platelet products that resulted in an ATR rate of 5.8%, which was greater than overall incidence of ATR in the study (1.72%).[119] Thus, certain donor factors also play a role. Yet, interestingly, in 630 instances where split apheresis platelets were given to 2 patients in which one had a reaction, there were only 6 instances where the patient who received the split product also had a reaction.[119] This further supports the importance of recipient factors. Thus, the mechanism of ATR likely entails a two-event model where both recipient and donor factors must be present. Another possible mechanism for ATR which has been proposed involves the possible activation of anaphylatoxins in the recipient upon infusion of negatively charged platelet microparticles, which are abundant in FFP and platelet units.[96] Understanding the mechanism of ATR is important in order to recommend appropriate preventive measures. Currently, pre-

medication of patients with an anti-histamine prior to transfusion is a common practice, but two randomized controlled trials indicated that anti-histamine pre-medication did not decrease the incidence of ATR.[120,121] Although most ATR do not have major clinical sequelae, prevention is important since these reactions cause patient discomfort/anxiety and incur extra cost due to reaction workup and product wastage.

Infectious Risks

Risk of infectious disease transmission has been dramatically reduced in the last two decades due to extensive donor medical screening and infectious disease testing. Improvements in test sensitivity, such as nucleic acid testing (NAT), have significantly contributed to this decreased risk. In the United States, the estimated risk for acquiring HIV, HCV, and HBV through transfusion is 1:1,467,000, 1:1,149,000, and 1:280,000 donations, respectively.[122,123] To further enhance plasma safety, many blood centers, mainly outside the US, use 1) donor retested plasma (FFP-DR) or 2) pathogen inactivated/reduced plasma (PRP). With FFP-DR, FFP is quarantined until the donor gives a subsequent donation which tests negative for infectious disease.[124] PRP offers good virus protection and can be prepared from solvent/detergent (S/D) treatment of pools of plasma or treatment of single donor units with methylene-blue (MB), amotosalen, or riboflavin and UV light. S/D treated plasma prevents transmission of lipid-enveloped viruses (HIV, HCV, HBV), but does not protect against non-enveloped viruses such as HAV or parvovirus B19 (B19). Transmission of these two viruses is prevented by testing plasma units for HAV and B19 by NAT, dilution through pooling, and neutralization with antibodies present in the pool.[125] Pathogen inactivation/reduction is also not effective against prions, and currently there are no donor tests for prion screening. Creutzfeld Jacob disease (CJD) is the best known prion disease in humans but is most likely not transmitted through transfusion.[126] However, there have been four possible cases of transfusion transmitted variant CJD (vCJD) in the UK, all associated with transfusion of non-luekocyte reduced red cells between 1996 and 1999.[127] Universal leukoreduction has been implemented in Europe which decreases the risk of vCJD transmission but does not completely eliminate it.[128,129] Although there have been no reported cases of transmission via plasma transfusion, animal studies show that plasma can contain the infective prion.[130] In the US and other non-UK countries, donors with prion related risk factors are permanently deferred. In the UK, all children up to age 16 receive plasma imported from areas with low bovine spongiform encephalopathy incidence to reduce vCJD risk and MB treated to reduce other infectious risks.[129,131] Finally, bacterial contamination of plasma is rare due to frozen storage but is still reported. Five cases of bacterial contamination of FFP were reported in Canada from 2002 to 2003 and five cases in Germany from 1997 to 2007.[132,133] Organisms identified included species of *Staphylococcus, Klebsiella, Propionibacterium, and Psuedomonas*. Waterbaths used to thaw plasma are a potential source of contamination, and pseudomonas has been cultured from frozen products thawed in contaminated waterbaths.[134,135] Care must be taken to properly clean and sterilize waterbaths regularly, and plasma should be transfused as soon as possible after thawing. Malaria from transfusion of previously frozen plasma does not occur, and as discussed below, such is also the case for CMV transmission.

Leukocyte-Associated Risks

Leukocyte-associated complications, such as febrile non-hemolytic transfusion reactions (FNHTR), transfusion-associated graft versus host disease (TA-GVHD), white blood cell (WBC) alloimmunization, and transmission of leukotropic viruses (i.e. CMV, HTLV), are not typically associated with plasma transfusion since FFP is considered non-cellular. However, several studies have shown significant numbers of WBCs contaminating plasma units (1–3 x 10^6 WBCs per unit) pre-freeze, although only a small percent of viable leukocytes remain after the freeze-thaw process.[136–139] Destruction of WBCs during freeze-

thaw can release bioactive mediators which may mediate FNHTR.[140] In 2010, the rate of FNHTRs reported to SHOT for plasma was 0.9 per 100,000 units.[87] One retrospective study in a large US hospital reported the rate of FHNTR to plasma transfusion as 1:4,476.[26] Typically, FNHTR are clinically insignificant and resolve quickly. TA-GVHD, on the other hand, is usually fatal and is caused by viable lymphocytes within a transfused product which engraft and proliferate within the transfusion recipient. Fortunately, TA-GVHD is rare and has never been reported with FFP. It has been estimated that TA-GVHD can occur with as few as 80,000 transfused lymphocytes, but a thawed plasma unit is unlikely to contain that number of viable lymphocytes.[139,141,142] Therefore, irradiation of FFP is not currently recommended.[142,143] WBC alloimmunization is a potential risk of plasma transfusion since both dead and viable WBCs within FFP express HLA antigens.[139] Regarding CMV transmission, two studies did not detect CMV within frozen plasma units supporting that CMV transmission is highly unlikely.[144,145] Pre-storage leukoreduction of whole blood prior to component preparation decreases the number of residual leukocytes in FFP and further prevents these unlikely complications.

RBC allo-immunization

The UK, Germany, and Council of Europe require that a single plasma unit contain less than 6.0×10^9 RBCs/L before freezing.[146] In the US, there is no standard for acceptable RBC concentration in plasma units. Residual RBCs and RBC fragments within plasma units can potentially cause red cell allo-immunization, and identification of anti-D, -E, -Jka, and -Fya after plasma transfusion has been reported.[146–149] After the freeze-thaw process, most RBCs are fragmented which decreases their immunogenicity.[4] Since the complication of red cell alloimmunization is rare, there is currently no requirement to provide D-negative plasma to D-negative patients.

Hemolytic Transfusion Reactions

To prevent hemolytic transfusion reactions (HTR), transfusion services provide ABO-compatible FFP to patients. However, occasionally ABO-compatible plasma is unavailable due to inventory limitations or incompatible plasma is erroneously provided due to specimen/patient identification errors. Fortunately, a severe HTR with a unit of ABO-incompatible plasma is less likely than with a unit of ABO-incompatible red cells since the clinical effect of transfusing a small volume of isohemagglutinins relative to an adult recipient's red cell volume is usually insignificant.[141] Nevertheless, transfusion of an ABO-incompatible plasma unit may cause a HTR, especially if the donor has high titer isohemmagglutinins. There have been multiple case reports of HTR after transfusion of a single unit (~200ml) of ABO-plasma incompatible platelets (i.e. Type O platelet to a Type A patient).[149–151] Thus, even small volumes of ABO-incompatible plasma can potentially cause a HTR, and transfusion of ABO-incompatible FFP should be avoided. Guidelines for FFP use in the UK recommend that if ABO-compatible FFP is not available, FFP of a different ABO group may be used if it does not contain high titer anti-A or anti-B. The UK Blood Services tests donations for "high titer" antibodies.[4] Donations with low titers are labeled to indicate a low risk of causing hemolysis, however, hemolysis can still occur with these units.[4]

Pathogen-Inactivated/Reduced Plasma (PRP)

S/D-treated plasma and MB-treated plasma are widely used in Europe. In the US, S/D plasma is FDA licensed but is not generally available.[152] Pathogen inactivation/reduction methods can cause some loss of coagulation factors.[125] Compared to standard FFP, MB-plasma has lower Factor VIII and fibrinogen levels, and S/D plasma has reduced activity of von Willebrand Factor, Factor VIII, and Protein S.[153,154] The reduced activity of protein S in S/D-plasma may be associated with venous thromboembolism (VTE). One study reported

VTE in 7 of 68 TTP patients receiving plasma exchange with S/D plasma.[154] Although VTE may be a risk of S/D plasma, other benefits besides viral protection include a lower rate of allergic reactions, febrile reactions, and TRALI.[155,156] Klein et al reported an overall reaction rate per unit of S/D plasma transfused as 0.66% and most complications were minor (i.e. hives, chills).[157] Another study, however, reported no reactions to S/D plasma after transfusion of 5,064 S/D units to 894 recipients,[158] and Norway's hemovigilance system reported 14 adverse events with transfusion of 47,690 S/D-treated plasma units (1:3,400) in 2008.[159] Overall, reactions to S/D plasma appear less common than standard FFP, and most notably there have been no documented cases of TRALI (meeting consensus criteria) associated with S/D plasma despite transfusion of approximately 10 million units. The decreased incidence of TRALI may be explained by in-vitro studies which show that HLA antibodies are undetectable in S/D plasma units likely due to dilution of antibodies by pooling large volumes of plasma and/or neutralization of HLA antibodies by soluble HLA antigens in the plasma pool.[125,155,160,161] Similarly, pooled S/D-treated plasma products may cause fewer allergic reactions due to dilution of ATR mediators. Removal of platelet microparticles may also contribute to a decreased risk of ATR with S/D-treated plasma.[95] With regards to MB plasma, there have been three recent reports of anaphylactic reactions from the residual MB in MB-treated plasma.[162,163] Although this is a rare complication of MB plasma, it should be considered when a patient has an ananphylactic reaction during or after MB plasma transfusion. Finally, S/D plasma (but not MB plasma) contains no residual cells or cell fragments preventing leukocyte-associated risks and red cell alloimmunization.[4,164]

Transfusion Associated Morbidity and Mortality

Plasma transfusion has been associated with increased morbidity in different patient populations. In trauma patients who survive their initial injury, one study showed a 2.1% and 2.5% increased risk of multi-organ failure (MOF) and acute respiratory distress syndrome (ARDS), respectively, for every unit of FFP given.[165] Another study in non-massively transfused trauma patients (<10 RBC units within 12 hours of admission) similarly found increased complications with increasing volumes of plasma transfused. Patients transfused with > 6 plasma units had a 12-fold increase in ARDS, 6-fold increase in multi-organ dysfunction syndrome, and 4-fold increase in pneumonia and sepsis.[166] In addition, FFP transfusion has been associated with MOF in pediatric liver transplant patients, and ALI/ARDS in critically ill adult patients.[167,168] Plasma transfusion has also been associated with nosocomial infection in surgical and trauma patients,[166,169,170] and Puetz et al found that the rate of venous thrombosis in children who received FFP was greater than 10 fold higher than the rate seen in all hospital admissions.[20] With regards to mortality, plasma transfusion has been associated with improved survival in trauma patients. Two recent reviews summarized the findings of eleven retrospective studies evaluating the effects of aggressive plasma transfusion on mortality in massively transfused trauma patients.[171,172] Most studies showed improved survival with increased plasma to red cell ratios, but the optimal ratio varied between studies. Although this evidence supports increased plasma use in massive transfusion, prospective randomized controlled trials are needed to prove the efficacy of this practice. For civilian trauma patients not massively transfused, Inaba et alreported no improvement in survival with plasma transfusion whereas Spinella et al showed decreased mortality with increased plasma to red cell ratios for combat-related injuries with or without massive transfusion.[166,173] Studies have associated plasma transfusion with increased mortality in non-trauma settings. Church and coworkers described a dose-dependent association between FFP and increased mortality in children with acute lung injury.[174] Interestingly, recent studies have shown increased mortality or morbidity with transfusion of ABO-compatible but non-identical plasma. A large retrospective study in Sweden showed that exposure to ABO-compatible but non-identical

plasma was associated with increased 14 day mortality following transfusion, especially in group O patients receiving AB plasma.[175] However, the association was not dose dependent. Another studydid not show increased mortality with transfusion of ABO compatible, non-identical plasma, but did report increased complications including ARDS and sepsis.[176] Plausibility exists since soluble donor antigens in plasma may result in formation of immune complexes with recipient antibodies causing immune modulation. Although the described studies suggest an association between plasma transfusion and morbidity/mortality, which help guide further study, proving a cause-effect relationship remains a challenge as is discussed in a recent article on establishing causation in transfusion medicine.[177]

Conclusion

The risks associated with plasma transfusions have changed over the years. Risk of infectious disease transmission has been significantly reduced with donor testing and pathogen reduction strategies bringing non-infectious complications to the forefront. Hemovigilance systems play an important role in helping to identify areas of concern so that appropriate mitigation strategies can be developed. Early in the last decade, hemovigilance systems revealed TRALI to be a major cause of transfusion associated morbidity and mortality from plasma transfusion. Knowledge of TRALI's pathogenesis led to policy changes for plasma collection that evidence indicates has decreased the risk of TRALI from plasma transfusion. With risk of TRALI from plasma transfusion now decreased, more focus is being placed on TACO for which plasma transfusion appears to carry a greater risk. However, more studies are needed to better understand TACO in order to make appropriate recommendations for prevention. The same can be said for allergic reactions. Although plasma transfusion is safer today than in the past, zero-risk is not attainable and clinicians must be aware of the potential hazards that accompany the transfusion of plasma. Finally, a recent review by Vamvakas and Blajchmandescribed different strategies to reduce transfusion related mortality one of which was "avoidance of unnecessary transfusions through evidence-based transfusion guidelines".[178] Unfortunately, much of the current practice of plasma transfusion is not based on sound evidence. Clinical trials looking at restrictive versus liberal plasma transfusion, similar to those done with red cell transfusions, are needed in many settings for which plasma is currently transfused. Ultimately, better evidence based guidelines for plasma transfusion will increase transfusion safety by minimizing inappropriate transfusion.

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ABBREVIATIONS

ALI	acute lung injury
ATR	Allergic/anaphylactic transfusion reactions
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft
NT-proBNP	N-terminal pro-brain natriuretic peptide
PaO2/FiO2	Partial pressure of oxygen in arterial blood divided by fraction of inspired oxygen
TACO	transfusion associated circulatory overload

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Table 1

Indications for plasma transfusion

1	Treatment of multiple coagulation factor deficiencies in patients with bleeding or before an invasive procedure.
2	Immediate reversal of warfarin or correction of vitamin K deficiency in patients with bleeding or before an emergency invasive procedure.
3	Disseminated intravascular coagulopathy or consumptive coagulopathy in patients with bleeding.
4	Dilutional coagulopathy (i.e. massive transfusion).
5	Plasma exchange in thrombotic thrombocytopenic purpura (TTP).
6	Treatment of coagulation factor deficiencies for which concentrates are unavailable.
7	Management of rare protein deficiencies

Table 2

TRALI Consensus Criteria (adapted with permission[30])

TRALI Criteria[†]	
1	Acute onset
2	Hypoxemia: PaO2/FiO2 ≤ 300 or SpO2 < 90% on room air or other clinical evidence of hypoxemia
3	Bilateral infiltrates on frontal chest radiograph
4	No clinical evidence of circulatory overload
5	Occurs during or within 6 hours of transfusion
6	No pre-existing ALI before transfusion
7	No temporal relationship to an alternative risk factor for ALI[*]

[†]Criteria 1–4 are consistent with the American-European Consensus Conference Definition of Acute Lung Injury. Definition of hypoxemia expanded for TRALI.

[*]Alternative risk factors for TRALI include but are not limited to aspiration, pneumonia, sepsis, multiple fractures, pancreatitis, shock, and cardiopulmonary bypass. If criteria 1- 6 are met but there is a temporal association with another ALI risk factor, case is categorized as “Possible TRALI”.

Table 3

Recipient Risk Factors for TRALI (adapted with permission[35]).

Risk factor	OR	Patient cohort	Author
Chronic alcohol abuse	5.9	Hospitalized patients	Toy et al[38]
Positive fluid balance pre-transfusion	1.15		
Mechanical ventilation *	3.6		
Shock pre-transfusion	4.2		
Current smoker	3.4		
Liver surgery (transplant)	6.7		
[IL-8] pre-transfusion, per 10-fold increase	3.0		
End-stage liver disease	31.7†	Patients with GI bleeding	Benson et al[39]
Emergency CABG	17.6	ICU patients	Vlaar et al[40]
Hematologic malignancy	13.1		
Massive transfusion	4.5		
Mechanical ventilation	3		
Sepsis	2.5		
History of heavy alcoholism	2.7†	ICU patients	Gajic et al[41]
Sepsis	2.6†		
Liver disease	2.1†		
Patient age	n/a	Cardiac surgery patients	Vlaar et al[42]
Time on cardiopulmonary bypass	n/a		
None identified	n/a	Liver transplant patients	Benson et al[43]

Patient risk factors for TRALI identified in clinical studies published after 2004 are listed. All studies used the Consensus Criteria to diagnose TRALI. Adjusted odds ratios (†calculated by Sachs UJ) are included. Toy et al controlled for transfused cognate strong HLA class II antibody and HNA antibody in a multivariate model.

*Peak airway pressure >30 cm H_2O within 12 hours after intubation and before transfusion

Table 4

Features to distinguish TRALI from TACO (Adapted with permission[77])

Feature	TRALI	TACO
Body temperature	Increase may occur	No change
Blood pressure	Hypotension	Increase in systolic blood pressure
Systolic ejection fraction	Decreased or Normal (>45% and no severe valvular disease)[78]	Decreased
Chest x-ray	Bilateral infiltrates	Bilateral infiltrates Enlarged heart (vascular pedicle width >70mm and Cardiothoracic ration >0.55)[78]
Ratio of Pulmonary Edema/Fluid Protein Concentration[79,80]	≥ 0.75 (Exudate)	≤ 0.65 (Transudate)
BNP	<200 pg/ml or	>1200 pg/ml or Pre/Post transfusion BNP ratio of ≥ 1.5[81]
Clinical Exam	Rales on auscultation	Peripheral edema, distended neck veins, rales and S3 may be heard on auscultation
Pulmonary artery occlusion pressure	≤ 18 mm Hg	>18 mm Hg
Response to diuretic	Minimal	Significant
White count	Transient leucopenia	Unchanged
Leukocyte antibodies	Cognate donor leukocyte antibodies support the diagnosis of TRALI	Donor leukocyte antibodies may or may not be present

When confronted with a patient who develops hypoxemia and pulmonary edema within 6 hours of transfusion, the best strategy is to evaluate the above features to determine which diagnosis is most supported. Note, although the TRALI consensus criteria states that circulatory overload must be excluded to diagnose TRALI, TACO and TRALI may co-exist. Elevated post-transfusion BNP (and/or NT-proBNP) has been shown to be a useful adjunct marker for TACO.[81,82] A post-transfusion to pre-transfusion ratio of greater than or equal to 1.5 with post-transfusion BNP ≥ 100 pg/mL has a sensitivity and specificity of 81% and 89%, respectively, for TACO.[81] However, one study found that BNP had limited diagnostic value in distinguishing etiology of pulmonary edema post-transfusion in critically ill patients.[83]