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Introduction

There have been many advances in the management of patients suffering from traumatic injuries. However, trauma remains the leading cause of death in the civilian population younger than 44 years of age [1]. Uncontrolled hemorrhage, including non-compressible hemorrhage, accounts for approximately 40 % of trauma-related deaths [2], in addition to 20–40 % of deaths following hospital admission [3]. As hemorrhage continues, patients develop hypovolemic shock in addition to tissue injuries that lead to the activation of multiple factors resulting in acute traumatic coagulopathy. Trauma-induced coagulopathy in and of itself has been associated with an increase in mortality in the trauma population [4–7]. Recently, Pati et al.

described the endotheliopathy of injury and used plasma to reverse or prevent this systemic injury altogether [8]. In this chapter, we discuss the role of plasma in the resuscitation of the traumatically injured patient to combat acute traumatic coagulopathy, but more importantly to prevent it all together.

In 2012, the Department of Health and Human Services published data from a survey collected in 2011 describing the utilization of blood and blood products across the USA. 5,926,000 units of plasma were produced for transfusion in total. This included 2,802,000 units of plasma frozen within 24 h (FP24), 1,813,000 units of fresh frozen plasma (FFP), 560,000 units of liquid plasma (LQP), and 251,000 units from apheresis collection. The overwhelming majority of units were collected and produced by blood centers with less than 10 % derived from hospitals. Additionally, 8,195,000 units were produced for further manufacturing. In total, 3,882,000 units were transfused in 2011; a decrease of 13.4 % from 2008. The amount of FFP and FP24 transfused decreased over the 3-year period. However, the utilization of thawed plasma (TP) only became reportable in 2011. 1,181,000 units of TP were transfused, amounting to 30.4 % of all transfused plasma, and mostly being transfused at larger institutions. Finally, only 2000 units of LQP were transfused in 2011. The average cost of a unit of FFP and FP24 were \$57.91 and \$56.08 respectively [9].

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Plasma is the aqueous portion of blood that contains coagulation factors, fibrinolytic proteins, albumin, immunoglobulins, and up to 6000 individual proteins. It is derived from whole blood or apheresis collection. Once collected and produced it can be stored in the liquid state, frozen until needed for transfusion, or frozen then thawed and kept in the liquid state. The concentration of labile coagulation factors, namely factors V, VII, and VIII, are affected by the type of storage form plasma has undergone [10].

Types of Plasma

In order to achieve the more balanced transfusion goal set forth by multiple military and civilian studies an immediate and plentiful supply of plasma is necessary. This becomes difficult in centers where thawed plasma is unavailable and in austere environments where cold chain storage and transportation is a limiting factor. As a result, much research and development has gone into the production and distribution of plasma products suitable for human transfusion. In this section we discuss the different plasma products available for transfusion. The characteristics of the different plasma preparations available for transfusion are summarized in Table 20.1.

Fresh Frozen Plasma (FFP)

Fresh frozen plasma is prepared either by separating the red blood cells and platelets from whole blood with centrifugation or by apheresis. The plasma is then frozen at -18°C and stored until needed for transfusion. To be called FFP the freezing process must occur within 8 h of donor phlebotomy. FFP contains high levels of all coagulation factors including the labile factors V and VIII. Whole blood yields approximately 200–250 mL of FFP, where apheresis collection yields 400–600 mL. The components are diluted approximately 8–20 % by the anticoagulant, a mixture of citrate, phosphate buffer, and dextrose [10–12]. Normal levels of factors V and VIII are found in FFP [10]. However, different blood groups yield different concentrations of coagulation factors confounding efforts to standardize therapy. The variations in expression can be as much as a 30 % difference between blood groups. This is exemplified by blood group O level of factor VIII and von Willebrand factor being 30 % lower than other blood groups [11, 12].

FFP must be thawed in a water bath between 30 and 37 $^{\circ}\text{C}$ prior to transfusion, taking anywhere from 20 to 40 min. Furthermore, breakage of bags occurs in the water bath in approximately 10 % of cases, further delaying delivery to the bedside.

Table 20.1 Characteristics of differing forms of plasma for transfusion

	Derivation	Yield	Storage	Preparation time
Fresh frozen plasma (FFP)	Centrifugation of whole blood or apheresis	Centrifugation—200–250 mL Apheresis—400–600 mL	Frozen at -18°C within 8 h of phlebotomy	20–40 min water bath thaw
Frozen within 24 h (FP24)	Centrifugation of whole blood or apheresis	Centrifugation—200 to 250 mL Apheresis—400 to 600 mL	Frozen at -18°C between 8 and 24 h of phlebotomy	20 to 40 min water bath thaw
Thawed plasma (TP)	FFP or FP24 thawed and not transfused within 24 h	Centrifugation—200–250 mL Apheresis—400–600 mL	$1-6^{\circ}\text{C}$ for 4 days following thaw	Immediately available
Liquid plasma (LQP)	Centrifugation of whole blood	n/a	$1-6^{\circ}\text{C}$ for up to 30 days	Immediately available
Dried plasma	Lyophilization or freeze drying	200 mL	Sterile container	10 min reconstitution

This can lead to a significant time delay to transfuse a dying patient. Once thawed, FFP should be transfused within 24 h or relabeled as thawed plasma [10, 12].

American Association of Blood Banks (AABB) indications for FFP transfusion include [10, 12, 13]:

1. Preoperative or bleeding patients with multiple coagulation factor deficiencies (e.g., liver disease, DIC).
2. Massive transfusion with clinically significant coagulopathy.
3. Reversal of warfarin effects in patients who are bleeding or undergoing a procedure without enough time for vitamin K reversal.
4. Transient reversal of warfarin in patients who are bleeding or undergoing an emergent procedure.
5. Thrombotic thrombocytopenic purpura transfusion or plasma exchange.
6. Management of rare specific plasma protein deficiencies when recombinant products are not available.

The AABB also recommends against the utilization of FFP when a coagulopathy can be corrected by a more specific therapy, such as vitamin K, prothrombin complex, or specific coagulation factors. FFP is not the optimal therapy when complete reversal of warfarin is desired and should not be used in the absence of severe bleeding [13].

Plasma Frozen Within 24 h (FP24)

Plasma collected via phlebotomy or apheresis and frozen between 8 and 24 h following collection becomes labelled as plasma frozen within 24 h (FP24). When derived from whole blood, a unit of FP24 yields a volume of 200–250 mL. However, an apheresis unit of FP24 yields 400–600 mL. FP24 contains high levels of stable coagulation factors and slightly diminished levels of the labile factors V, VIII, as well as Protein C due to the delayed in freezing from donor collection time [10]. FP24 undergoes the

same thawing process as FFP and also must be transfused within 24 h of returning to the liquid state [14]. If not transfused by that time, it can then be relabeled as thawed plasma [10].

The indications and contraindications for FP24 utilization are identical to FFP (see section above). FP24 should not be used when the sole replacement of factors V and/or VIII is necessary [12].

Thawed Plasma (TP)

Thawed plasma (TP) is the liquid form of FFP or FP24 following a thaw at 30–37 °C. It is then stored at 1–6 °C to be used for up to 4 days following initial thaw. The levels of stable factors remain close to those of FFP and FP24 even at the 4-day point. However, there is a decline in the levels of labile factors, the most significant of which being factor VIII [10, 12].

AABB indications for transfusion of TP include [10, 12, 13]:

1. Preoperative or bleeding patients with multiple coagulation factor deficiencies (liver disease, DIC).
2. Massive transfusion with clinically significant coagulopathy.
3. Reversal of warfarin effects in patients who are bleeding or undergoing a procedure without enough time for vitamin K reversal.
4. Transient reversal of warfarin in patient who are bleeding or undergoing an emergent procedure.
5. Thrombotic thrombocytopenic purpura transfusion or plasma exchange.

Thawed plasma is not recommended for the management of specific coagulation factor deficiencies as the concentration of the factors in the product is variable [10].

Liquid Plasma (LQP)

Liquid plasma (LQP) is produced from whole blood no later than 5 days after expiration (21 days) and is never frozen [10–12, 14]. LQP is

kept at 1–6 °C and can be stored for up to 30 days. The primary indication for transfusion of LQP is the management of the acutely hemorrhaging patient requiring massive transfusion. Studies have shown that the initial and prolonged hemostatic profile of LQP, as determined by thromboelastography and calibrated thrombograms, is better than FFP or thawed plasma. Furthermore, the levels of coagulation factors remained $\geq 88\%$ of original levels out to 26 days, except for factors V and VIII [14, 15]. As discussed, the vitamin K dependent factors (factors II, VII, IX, and X) are relatively stable under approved LQP storage conditions. Therefore, LQP is currently indicated in patients on warfarin therapy who are suffering massive hemorrhage. The labile factors (V and VIII) deplete over time during storage, making LQP less effective in patients with these specific deficiencies [10–12].

The coagulation properties of LQP are superior to TP from FFP. Matijevic et al. analyzed the hemostatic potential of LQP as compared to TP derived from FFP. LQP had a superior capacity to form clot and generate thrombin. This phenomenon may be explained either by the presence of platelet microparticles in LQP not present in FFP, FP24, or TP, cold activation of coagulation proteins, the decline in protein S activity, or a combination thereof [14]. It is known that the freeze–thaw process required for FFP and FP24 degrades proteins; however, it is not understood why certain factors are less tolerant than others. By avoiding the freeze–thaw process the proteins remain functional longer to the point that 15-day-old LQP appears to function as well as 5-day-old TP [14].

Dried Plasma

Currently, the goal of transfusion in the patient requiring massive transfusion is a balanced resuscitation with a ratio of platelets–plasma–red blood cells (RBC) units of 1:1:1 [16–18]. Achieving this goal is often difficult in environments where a large and rapidly accessible supply of plasma is not available. As described previously, FFP and FP24 require frozen storage

and re-warming under very controlled conditions. Furthermore, TP and LQP require storage under refrigerated (4 °C) conditions. This makes the rapid (within minutes of requirement) administration of plasma difficult at most civilian institutions and nearly impossible for military personnel. These factors, along with data indicating improved survival with balanced resuscitation, led to the recent redevelopment of dried human plasma. Lyophilization, a low-pressure, low-temperature, low-humidity process to convert plasma into powder, is not a new concept as it was first developed and introduced into practice during World War II. Lyophilized plasma (LP) was widely used, and became the primary resuscitative fluid on the battlefield by the end of WWII. Nevertheless, the concept was abandoned following unacceptable rates of viral transmission in the survivors, until modern screening methods improved transmission rates significantly [2]. LP possesses the same viscoelastic coagulation parameters as fresh plasma. In an animal model, Shuja et al. found an insignificant decrease in the activity of factors II, VII, and IX [19]. The French military has utilized dried plasma and has maintained a hemovigilance program since 1994. No adverse effects of infectious transmissions have been reported with the transfusion of more than 1100 units [20]. In 2011, Martinaud et al. described the utilization of freeze-dried plasma (FDP) in French intensive care units in Afghanistan, while caring for casualties from all the coalition forces [21]. The process of preparing the FDP involves the centrifugation of plasma. The supernatant is then removed and frozen by slow rotation in an ice slurry. The product is then freeze-dried at $-8\text{ }^{\circ}\text{C}$ for 48 h removing much of the CO_2 , resulting in an alkaline product upon rehydration [19]. FDP was described as easy to use, reconstituting in medical water within 10 min to provide 210 mL of fluid with hemostatic and volume expansive properties. 236 units have been delivered and evaluated without a single adverse event reported [21]. Israeli Defense Forces (IDF) also utilizes FDP (from the German Red Cross) as the preferred resuscitation fluid in the military prehospital setting. Using these dried products facilitates

an environment of balanced transfusion from the point of initial resuscitation without playing “catch-up” while FFP thaws [22].

To date, dried plasma products are not approved for use in the civilian population within the USA [23, 24]. FDP from the French military has recently been approved by the Department of Defense, FDA and White House and is utilized by selected units of the US Special Forces. In addition to the French military and IDF, dried plasma products are utilized by the German and Norwegian militaries, Norwegian civilian emergency aeromedical services, and the US Army Special Operations Forces [22]. Further investigation for utilization in US civilian emergencies and ABO group universality are necessary as these products will allow plasma resuscitation to occur in environments not conducive to current plasma storage [23–25].

Current Practices in Civilian Trauma Centers

Spinella et al. recently performed a study on transfusion practices at Level I and II trauma centers using data from The American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP). These investigators report that the types of plasma used at these centers are as follows: 78 % thawed fresh frozen plasma/plasma frozen within 24 h, 16 % thawed fresh frozen plasma/plasma frozen within 24 h or liquid plasma, and 7 % (6 of 90) liquid plasma.

Why Do We Transfuse Plasma?

Patients in hemorrhagic shock suffer from a multitude of physiologic derangements. The early administration of blood products has been shown beneficial throughout the literature. However, the reasoning behind plasma transfusion is not as simple as previously thought. Trauma patients lose blood; therefore, giving blood back makes sense. However, reaching for packed RBCs first does not accomplish the goal which the trauma community is trying to achieve: restoration of

circulating volume. The transfusion of plasma will restore circulating blood volume while delivering coagulation factors to bleeding patients actively consuming coagulation factors. Early administration of plasma, in the prehospital setting, as well as in the emergency center, has been shown to improve acid-base status upon admission, decrease the total transfusion requirement in the first 24 h following admission, and reducing mortality risk [25–27].

A decade ago, military and civilian physicians transfused plasma in order to correct coagulopathy. With increasing clinical experience on earlier and balanced use of plasma, the prevention of trauma-induced coagulopathy and endothelial dysfunction became the intent for transfusion based upon laboratory-based measures of coagulopathy. With increasing research and understanding as to the endothelial injury associated with massive trauma, treating the endotheliopathy of trauma has also become a goal for plasma transfusion [28]. This evolution of thought has been derived from a greater understanding of how hemorrhagic shock systemically affects physiology. Restoration of circulating coagulation factors is not the sole purpose for transfusion of plasma in patients with hemorrhagic shock.

The endotheliopathy of trauma (injury) refers to the breakdown of the endothelial glycocalyx on the endoluminal surface of blood vessels increasing permeability and decreasing their integrity. It has been hypothesized that injury to the endothelial glycocalyx leads to interstitial edema, inflammation, and tissue hypoxia [29, 30]. For further description of the endotheliopathy of trauma please refer to Chap. 7. At the Texas Trauma Institute we have anecdotally observed a decrease in edema, as well as a paucity of abdominal compartment syndrome secondary to resuscitation with the initiation of blood product based resuscitation. Animal data suggests a decrease in inflammation with transfusion of plasma when compared to infusion of albumin, artificial colloid, and crystalloid in a hemorrhage shock model [31–35].

Projecting from the endoluminal surface of blood vessels is a complex network of soluble components creating an endothelial glycocalyx.

Multiple proteoglycans and glycoprotein comprise this network providing surfaces for interactions with glycosaminoglycans, neutrophil-endothelial cell interactions that occur with injury to the glycocalyx, hemostasis, coagulation, and fibrinolysis. The glycocalyx allows the plasma component of blood to interact with the vessel wall while maintaining a barrier to erythrocytes and leukocytes [31–33]. Kozar et al. demonstrated that the endothelial glycocalyx is injured during hemorrhagic shock, manifested by shedding into plasma of syndecan-1, one of the endothelial glycocalyx’s proteoglycans [36]. This had been previously demonstrated in models of ischemia and reperfusion. Furthermore, these authors demonstrated that the injured glycocalyx is partially repaired with the transfusion of plasma in comparison to the infusion of crystalloid solution [36–38]. In their study, significantly less volume was needed in the plasma

group to maintain mean arterial pressure. The intact glycocalyx was ablated by hemorrhagic shock and signs of early restoration of the glycocalyx were present in the plasma group in comparison to the crystalloid group. Shown in Fig. 20.1 are electron microscopy images of mesenteric venules showing the effects of shock and resuscitation on the endothelial glycocalyx along with its thickness. Furthermore, the authors investigated lung injury with respect to hemorrhagic shock based on alveolar thickness, capillary congestion, and cellularity. They found an increase in all three parameters in the shock model compared to sham. However, the infusion of crystalloid increased all three parameters above the model, while the plasma transfusion group had improvement of all three parameters, suggesting attenuation of lung injury [36]. These findings were also demonstrated by Pati et al.; however, they also demonstrated that the age of

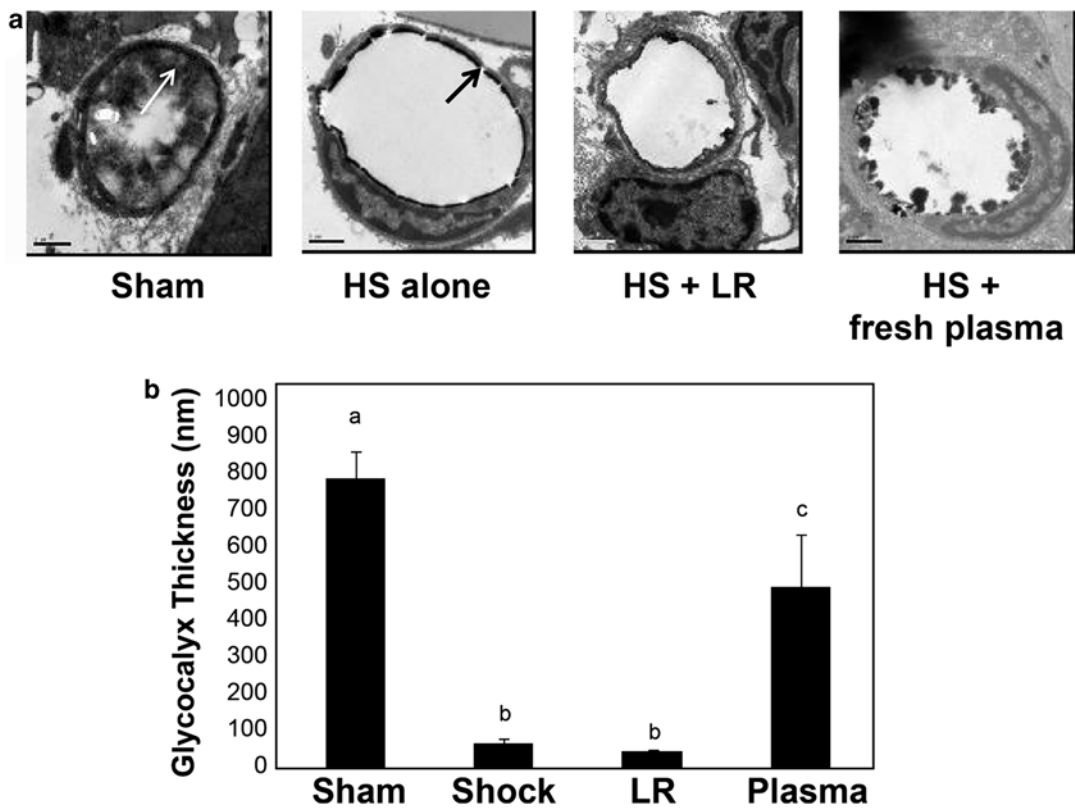


Fig. 20.1 Electron microscopy of mesenteric venules stained to reveal endothelial glycocalyx following hemorrhagic insult and resuscitation

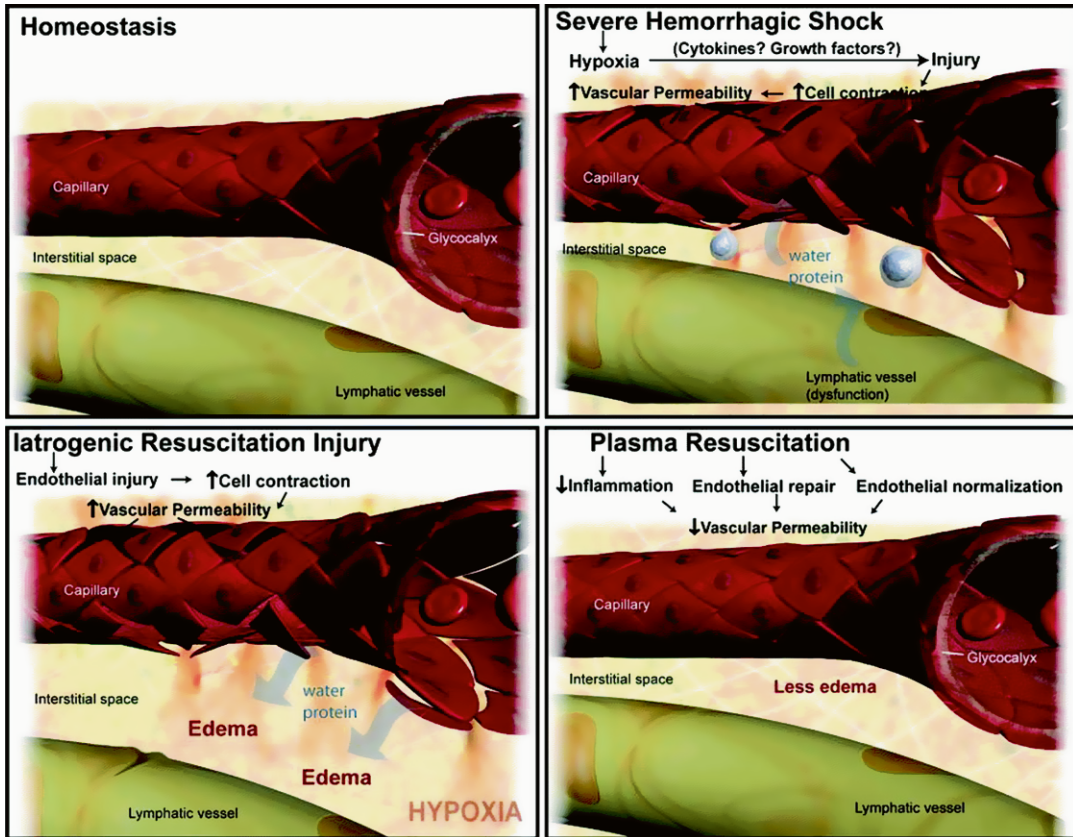


Fig. 20.2 Working biological model of the mechanism of action of fresh frozen plasma (FFP)

the plasma transfused also had an effect on this attenuation of lung injury (older plasma being less beneficial) [8]. Nevertheless, day 5 plasma stored at 4 °C remained superior to crystalloid infusion with respect to reparative capacity in the animal model [8]. This indicates that a component of plasma, in soluble form, interacts with the endothelial membrane to restore the endothelial glycocalyx. Figure 20.2 shows the vascular injury caused by hemorrhagic shock through hypoxia leading to cell contraction and decreased vascular permeability. Resuscitation with plasma decreases the inflammatory response, promotes endothelial repair, and leads to normalization of the endothelium. This leads to a decrease in vascular permeability; clinically seen as less edema.

In 2011, Haywood-Watson et al. found that patients arriving to a level 1 trauma center in hemorrhagic shock had an elevated level of the endothelial proteoglycan syndecan-1 [39].

The shedding of syndecan-1 was negatively correlated with pro-inflammatory cytokines INF-gamma, fractalkine, and IL-1beta, and positively correlated with IL-10, an anti-inflammatory cytokine [39]. This correlation suggests that syndecan-1 is not just a marker of endotheliopathy; it may be involved in the restoration of glycocalyx integrity as depicted in Fig. 20.3 [39]. Furthermore, Johansson et al. found an elevated admission syndecan-1 level in severely injured trauma patients to be associated with inflammation, coagulopathy, and increased mortality [40].

Protocols

The institution of exsanguination protocols at major trauma centers has been shown to improve survival [41, 42]. The original investigation did not specifically involve a balanced ratio resuscitation.

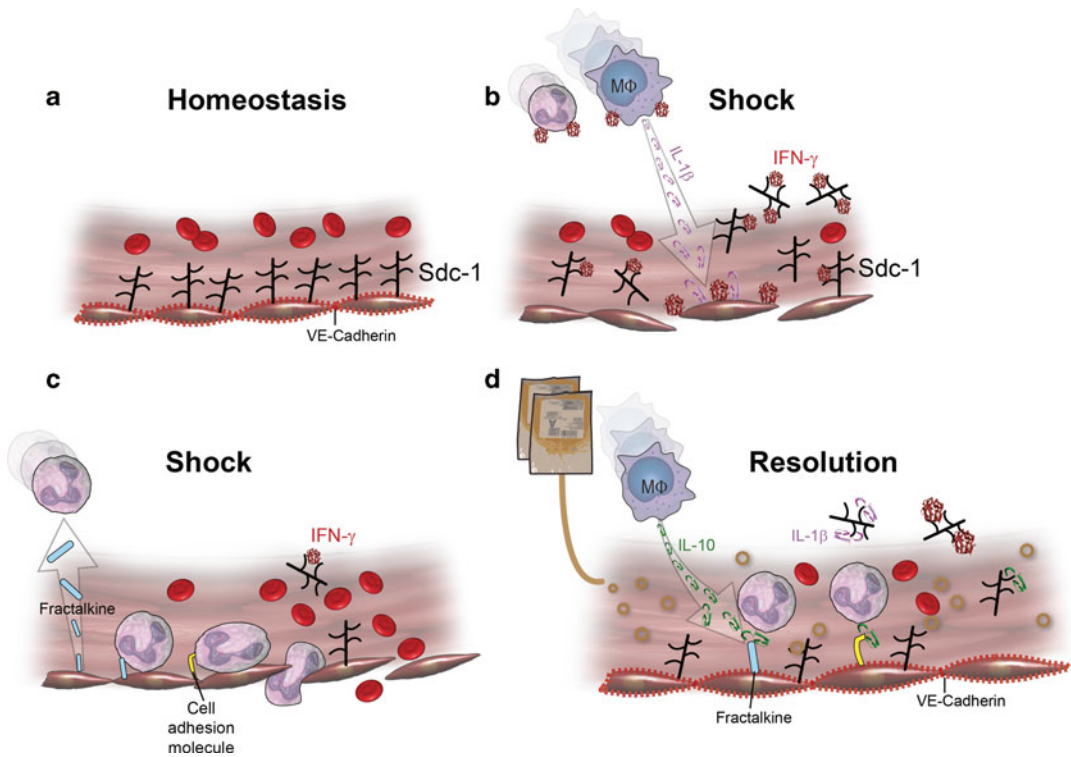


Fig. 20.3 Proposed model of syndecan-1 interaction with inflammatory cytokines after shock and resuscitation with fresh frozen plasma (FFP)

Simply by initiating a protocol for the delivery of blood products to the emergency center for an exsanguinating patient, mortality improved. The activation of a “massive trauma protocol” delivered blood component therapy to the emergency center without the request of specific components by the trauma team. This was also demonstrated in the military environment with improved survival in both Iraq and Afghanistan [43, 44]. Furthermore, a decrease in the total amount of blood products transfused was seen [41, 42, 45, 46].

The majority of trauma centers store uncross-matched RBCs in the emergency center. However, plasma often remains in the blood bank awaiting the activation of the massive transfusion protocol or a direct order from a physician. The lack of readily available plasma makes it difficult to achieve a high plasma–RBC ratio in an expedited fashion, which has been shown in multiple studies to decrease mortality [47, 48]. By implementing an emergency center thawed plasma protocol, with 4 units of thawed AB plasma stored in the

emergency center, the time to first plasma transfusion was improved by 46 min resulting in a decrease in 24-h transfusion of PRBCs, plasma, and platelets and a significant decrease in mortality [27]. Furthermore, a decrease in the rate of the activation of the massive transfusion protocol was seen following the implementation of the thawed plasma in the emergency center [27], as well as with attaining increased plasma–RBC ratios [49].

Recent Studies Involving Plasma

PROMMTT

The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study demonstrated that earlier transfusion of plasma, within minutes of identification of hemorrhagic shock, and achieving high early plasma–RBC ratios decreased 24-h and 30-day mortality.

This was evidenced by the three- to fourfold increased mortality risk associated with plasma–RBC ratios <1:2 [17, 28, 50]. Furthermore, gradual achievement of balanced transfusion ratios may not be as beneficial as early plasma transfusion [50]. Initiating plasma transfusion early also led to a decrease in the total amount of RBCs transfused during the initial 24 h following admission [50]. PROMMTT clearly showed that earlier plasma was associated with improved survival; however, few patients received consistent ratios. There was significant concern that higher ratios would lead to increased hypoxia, acute respiratory distress syndrome (ARDS) and transfusion related acute lung injury (TRALI). However, Robinson et al. showed that hypoxia was associated with excessive crystalloid infusion rather than plasma [51]. Lastly, it was clear from the PROMMTT data that the two ratios that clinicians were trying to transfuse were 1:1 and 1:2.

PROPPR

The PROMMTT study was followed by the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study which evaluated the effectiveness and safety of two transfusion strategies in patients with major trauma and severe bleeding. The PROPPR study was the first multicenter randomized trial comparing transfusion strategies with mortality as the primary endpoint. It provided evidence for the commonly held belief that balanced transfusion protocols were beneficial to severely injured patients with hemorrhagic shock. Although no significant differences in 24-h and 30-day mortality were found between the two transfusion ratios investigated (plasma–platelet–RBC ratio of 1:1:1 versus 1:1:2), the early availability of blood products transfused within minutes of arrival in a balanced (1:1:1) ratio achieved hemostasis more often and decreased hemorrhage-related deaths within the first 24 h following admission [18]. Furthermore, while the balanced transfusion group received significantly more plasma and platelets within the first 24 h, no difference was found in the rate of 23 prespecified complications including the

systemic inflammatory response syndrome (SIRS), ARDS, transfusion associated circulatory overload (TACO), TRALI, and allergic reactions. Consistent with the biology of bleeding patients, the median time to hemorrhagic death in PROPPR was 2.3 h. In a post hoc analysis, at 3 h after admission there was a significant mortality difference between the two groups [18].

Texas Trauma Institute: Resuscitation

The concept used at the Texas Trauma Institute at Memorial Hermann Hospital in Houston has been derived from the experiences gained on the battlefield, and supported by military and civilian studies. In the prehospital setting the emphasis centers on the cessation of bleeding. This occurs in parallel with hypotensive resuscitation utilizing liquid plasma and packed red blood cells. LQP and packed RBCs are utilized by our hospital-based helicopter program, Life Flight. Patients are identified as requiring a prehospital transfusion based upon the assessment of blood consumption (ABC) score. Over a 20-month study period, 942 units (244 RBCs and 698 plasma units) were placed on the Life Flight helicopters with a 1.9 % waste rate [26]. Once a severely injured patient reaches the trauma center, a rapid thromboelastograph (r-TEG), venous blood gas, and hemoglobin levels are drawn and immediately analyzed. In patients that have an ABC score <2 (1 point each for penetrating mechanism, systolic blood pressure <90 mmHg, heart rate >120 beats/min, and a positive focused abdominal assessment with sonography for trauma) or without substantial bleeding (<3 units/h), the r-TEG is used to guide blood product resuscitation [52]. Patients that are in shock, are hypotensive, or have an ABC score ≥ 2 are started on the massive transfusion protocol and receive 1:1:1 ratio-driven resuscitation [53]. The patient then either proceeds to the operating room or interventional radiology. The response to resuscitation is closely monitored. Once clinical bleeding has slowed considerably or ceased the resuscitation is converted to goal-driven resuscitation utilizing r-TEG [53].

Adverse Effects/Events

Of all transfusable blood products, plasma, specifically FFP, is considered the most hazardous according to multiple studies into the mid-2000s. However, the overall risk remains low. The major risks include TRALI, TACO, infectious disease transmissions, acute transfusion reactions, and leukocyte-associated reactions. However, most of these studies only evaluated some of the blood products that are infused, frequently not evaluating the effects of RBCs, platelets or crystalloids, all which have well described deleterious effects.

TRALI

Transfusion related acute lung injury manifests as hypoxia, pulmonary edema, pulmonary infiltrates with radiographic changes, fevers, and possibly hypotension within 6 h of plasma transfusion. The presentation is similar to ARDS; however, >80 % of patients typically recover within a few days of symptom onset and treatment is mainly supportive [54–56].

The UK hemovigilance Serious Hazards of Transfusion (SHOT) reports a TRALI risk of 1 in 63,940 transfused units, a 28.8 % decrease since 2008 [9, 57]. It is the most common cause of death from transfusion and is the most frequent serious complication of FFP transfusion [58]. In 2013, the FDA reported that TRALI represented 37 % of all fatalities secondary to blood transfusions for that year and 38 % from 2009 to 2013. Plasma, specifically FP24 was implicated in two of the 17 cases and a plasma product may have been implicated in four other cases that received multiple transfusions. Interestingly, no units of FFP were implicated in 2013. The number of cases of TRALI has significantly decreased over the study period following voluntary measures taken by the transfusion community [59]. The absolute numbers of TRALI are very low, a testament to the rigorous testing performed by the blood banking community.

TRALI is significantly associated with leukocyte alloantibodies found in the donor plasma. These specific antibodies are found exclusively

in post-partum female plasma and in male plasma from donors who have previously received a transfusion. Some authors believe TRALI to develop in two steps. A predisposing condition must be present that incites the release of cytokines leading to the attachment of neutrophils to the pulmonary capillary endothelium. The second step occurs with neutrophil priming, activation and pulmonary injury [13, 60]. In 2008, Eder et al. reported a reduction in the incidence of TRALI with the conversion to male-predominant plasma for transfusion [13, 61]. Unpublished data from the Texas Trauma Institute demonstrate that with the increase usage of plasma in resuscitating trauma patients the incidence of TRALI did not increase. There were nine incidences of TRALI related to plasma transfusion in over 180,000 units transfused. The incidence was approximately 1:20,000 units [62].

Further discussion amongst hemovigilance programs regarding standardization of the definition of TRALI versus TACO will improve the way health care workers identify and manage transfusion reactions [63, 64].

TACO

Transfusion associated circulatory overload occurs secondary to increased hydrostatic pressure resulting in pulmonary edema. This process can be indistinguishable from TRALI and the two entities may in fact co-exist [64]. In 2013, the FDA reported that TACO represented 34 % of transfusion related mortalities for that year. There has been an uptrend in mortality related to TACO over time. It is difficult to determine whether the uptrend is secondary to improved diagnostics or actual increase in incidence [59].

The incidence of TACO is not well described in the literature. Multiple retrospective reviews have reported an incidence of TACO from <1 % to 11 % [55, 64]. This range with multiple reports is secondary to the difficulty in determining the etiology of pulmonary edema as diagnostic evaluations for TACO are invasive and serologic tests for TRALI have yet to be validated. In Fig. 20.4, Gajic et al. designed an algorithm to determine the etiology of

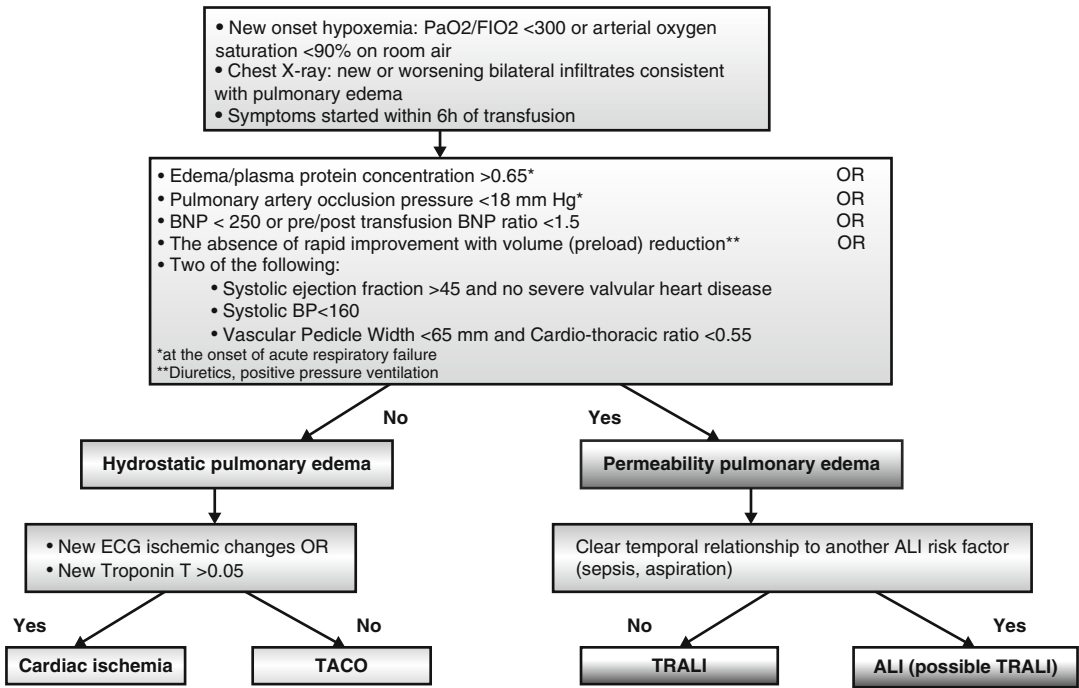


Fig. 20.4 Approach to post-transfusion pulmonary edema

post-transfusion acute pulmonary edema [64]. The algorithm is based on the European-American ARDS Consensus Conference definitions of TRALI and integrates specific laboratory values into the decision-making process. Frequently, TACO is a post-hoc diagnosis made once a patient responds to a specific therapy [55].

Infectious Disease Transmission

The transmission of infectious diseases has dramatically decreased with extensive donor screening and infectious disease testing. Nucleic acid testing sensitivity has improved leading to a decrease in transmission risk. This has led to an estimated risk of 1:1,467,000 for acquiring HIV, 1:1,149,000 for hepatitis C virus, and 1:280,000 donations for hepatitis B virus [58, 65, 66].

Outside the USA, many blood centers utilize donor retested plasma, pathogen inactivated plasma, and pathogen reduced plasma [67]. Donor retested plasma are units that are quarantined until the donor submits a subsequent donation which tests negative

for infectious disease [67]. Pathogen inactivated and pathogen reduced plasma are prepared via the addition of chemicals (solvent/detergent, methylene blue, amotosalen, riboflavin, and UV light) to prevent the transmission of lipid-enveloped viruses [68, 69]. Two companies leading this technology are Terumo Medical Corp. (Somerset, NJ) and Cerus Europe B.V. (Amersfoort, NL). The Cerus process was FDA approved in early 2015.

The freezing process during preparation of plasma inactivates bacteria. Furthermore, bacterial contamination with the production of endotoxin prior to freezing is unlikely [58]. The 2013 FDA report describes a single bacterial infection transmitted through plasma transfusion [59]. The process of removing cellular components via filters also removes cell-associated bacteria, most protozoa, and cell-associated viruses including malaria, CMV, and HTLV. Freezing does not remove the free viruses including Hepatitis A, B, and C, HIV 1 and 2, and parvovirus B19 [13, 58].

Currently, no screening protocol exists for the detection of prion diseases. Furthermore, modern techniques of decreasing infectious transmission

are ineffective against prion diseases. In the UK, three possible cases of variant Creutzfeldt–Jakob disease (vCJD) have been reported. Each case involved transfusion of non-leukocyte reduced red blood cells [70]. There have been no reported cases of prion disease transmission following plasma transfusion; however, animal studies have shown that it is possible [71].

Acute Transfusion Reactions

In 2013, the 17th Annual SHOT Report described just over 3000 acute transfusion reactions in over 13,000 transfusions. Three hundred and twenty incidents occurred in 2012 including allergic, hypotensive, and severe febrile reactions. Thirty-one cases were associated with transfusion of FFP, which included 13 anaphylactic/severe allergic reactions, 12 moderate allergic reactions, four hypotensive reactions, one febrile reaction, and one mixed febrile/allergic reaction. No deaths were related to any type of transfusion reaction [57]. Moderate allergic reactions present with an urticarial rash, wheezing, and other symptoms not severe enough to be termed anaphylactic and occur in 1–3 % of transfusions. Anaphylaxis includes bronchospasm, angioedema, severe hypotension, and cardiovascular collapse and is a rare occurrence [13, 55, 57, 58, 68].

Other than human immunoglobulin A (IgA) and haptoglobin, the proteins involved in acute transfusion reactions are unknown and generally unpredictable. For patients known to have an IgA sensitivity, plasma obtained from patient with IgA deficiency is available for transfusion [13, 72].

Leukocyte-Associated Reactions

Leukocyte-associated reactions following plasma transfusion are rare. The freeze–thaw process yields a small percentage of viable leukocytes prior to transfusion [73, 74]. The presence of viable leukocytes leads to the rare occurrence of febrile non-hemolytic transfusion reactions (FNHTR), transfusion-associated graft versus

host disease (TA-GVHD), and transmission of leukocyte viruses [68].

Following the freeze–thaw process nonviable leukocytes release mediators that may contribute to FNHTRs. These reactions are generally clinically insignificant and resolve quickly with supportive therapy [57, 68].

TA-GVHD requires viable leukocytes to be transfused and then engraft and proliferate in the host patient. This is a rare transfusion reaction amongst all blood components transfused and has yet to be reported with FFP transfusion. Therefore, irradiation of FFP is not currently recommended [68].

Future Endeavors in Plasma Resuscitation and Research

The utilization of plasma as the primary resuscitation fluid has been the subject of multiple retrospective studies, a large prospective observational study and a recent prospective randomized trial. The benefits of balanced transfusion with respect to hemorrhagic mortality in the trauma population have been reported. Current randomized studies are evaluating the utility of plasma in the prehospital area. Future investigations will likely include the utilization of dried plasma products in the US civilian population with the longer storage life and substantial logistic benefits.

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