Introduction

Early administration of plasma to the massively hemorrhaging patient combats trauma-induced coagulopathy, decreases total blood product usage, and improves survival rates. Uncontrolled hemorrhage still accounts for approximately 40% of trauma-related deaths, in addition to 20–40% of deaths following hospital admission [1, 2]. As hemorrhage continues, patients develop hypovolemic shock in addition to multiple systemic changes resulting in trauma-induced coagulopathy (TIC). TIC is strongly associated with mortality in the trauma population [3–6], but prevention is possible with early plasma-directed therapy. This approach also decreases total transfusion requirements, as hemostasis and thus homeostasis are more readily achieved. Similarly, endotheliopathy of injury can be reversed or prevented with early plasma administration [7]. Plasma also appears to have neuroprotective effects [8]. In this chapter, we discuss the role of plasma in the resuscitation of the traumatically injured patient.

Demographics and Usage

The most recent nationwide data regarding blood products in the United States are derived from the 2017 National Blood Collection and Utilization Survey (NBCUS). The survey has been conducted biennially since 1997 by the Centers for Disease Control and the Department of Health and Human Services. In the 2017 report, a total of 3,210,000 units of plasma were distributed and 2,318,000 transfused. This represents a 13.8% decrease from the previous NBCUS, a trend that has continued since 2011 [9, 10]. Improved utilization of the blood supply and more exacting guidelines regarding its use have been proposed as causes of this shift, a reversal of steady increases since the origination of the survey. The overwhelming majority of units were collected and produced by blood centers with less than 7% derived from hospitals. The median cost of a unit of plasma was $50–51, figures that are also declining [11].

Types of Plasma

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, plasma can be frozen for storage or kept nonfrozen for
immediate use. If frozen within 8 hours of phlebotomy, the product is labeled as fresh frozen plasma (FFP). If frozen after 8 hours from the time of phlebotomy but within 24 hours, it is labeled as plasma frozen within 24 hours (FP24). When FFP and FP24 are mobilized from the blood bank, they are thawed in a water bath to create thawed plasma (TP), which can be stored in liquid form for up to 5 days prior to transfusion. Liquid plasma (LQP) is derived from whole blood and is never frozen. The concentration of labile coagulation factors, namely, factors V, VII, and VIII, is affected by these various storage techniques, which will be further described in the next section.

Less commonly available products include “plasma, cryoprecipitate reduced” and “plasma frozen within 24 hours after phlebotomy held at room temperature up to 24 hours after phlebotomy.” Plasma, cryoprecipitate reduced is the supernatant plasma remaining after the removal of cryoprecipitate from thawed FFP, but this is generally used for transfusion or plasma exchange in cases of thrombotic thrombocytopenic purpura. These forms are mentioned here only for completeness. Dried plasma, typically lyophilized or freeze-dried from FFP and later reconstituted for transfusion, is not currently approved for use in the United States, although several products are available elsewhere in the world. The characteristics of the different plasma preparations typically available for transfusion are summarized in Table 21.1.

A 2013 survey on transfusion practices at Level I and II trauma centers using data from the American College of Surgeons Trauma Quality Improvement Program reported that the types of plasma used at 90 centers were as follows: 78% thawed FFP or FP24, 16% thawed FFP/FP24 or LQP, and 7% LQP [12].

### Fresh Frozen Plasma

FFP 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 or colder and stored until needed for transfusion. The freezing process must occur within 8 hours 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, whereas apheresis collection yields 400–600 mL. The components are diluted approximately 8–20% by the anticoagulant, a mixture of citrate, phosphate buffer, and dextrose [13, 14]. Normal levels of factors V and VIII are found in FFP [15]. However, different blood groups yield different concentrations of coagulation factors, confounding efforts to standardize therapy. This variance is greatest in blood group O, which provides 30% less factor VIII and von Willebrand factor than other blood groups [14].

| Table 21.1 Characteristics of differing forms of plasma for transfusion |
|---------------------------------|-------------------|------------------|------------------------|-----------------------------|
| Derivation                      | Yield             | Storage          | Preparation time       |
|---------------------------------|-------------------|------------------|------------------------|-----------------------------|
| Fresh frozen plasma             | Centrifugation of whole blood or apheresis | Centrifugation—200–250 mL Apheresis—400–600 mL | Frozen at −18 °C within 8 hours of phlebotomy | 20–40 min water bath thaw |
| Plasma frozen within 24 hours    | Centrifugation of whole blood or apheresis | Centrifugation—200–250 mL Apheresis—400–600 mL | Frozen at −18 °C between 8 and 24 hours of phlebotomy | 20–40 min water bath thaw |
| Thawed plasma                   | FFP or FP24 thawed and not transfused within 24 hours | Centrifugation—200–250 mL Apheresis—400–600 mL | 1–6 °C for 4 days following thaw | Immediately available |
| Liquid plasma                   | Centrifugation of whole blood | n/a              | 1–6 °C for up to 30 days | Immediately available |
| Dried plasma                    | Lyophilization or freeze-drying | 200 mL           | Sterile container      | 2–10 min reconstitution |
FFP must be thawed in a water bath between 30 and 37 °C prior to transfusion, a process requiring 20–40 minutes. Furthermore, breakage of bags occurs in the water bath in approximately 10% of cases, further delaying delivery to the bedside [16]. This can lead to a hazardous delay in transfusing a patient in extremis. Once thawed, FFP must be transfused within 24 hours or else relabeled as TP. American Association of Blood Banks (AABB) indications for FFP transfusion include: [15]

1. Preoperative or bleeding patients with multiple coagulation factor deficiencies
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 or in patients needing transient reversal
4. Thrombotic thrombocytopenic purpura transfusion or plasma exchange
5. Selected coagulation factor deficiencies for which no specific concentrate is available
6. 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 when other volume expanders would suffice.

Plasma Frozen Within 24 Hours

Plasma collected via phlebotomy or apheresis and frozen between 8 and 24 hours following collection becomes FP24. When derived from whole blood, a unit of FP24 yields a volume of 200–250 mL. 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, and protein C due to the delay in freezing from donor collection time [15]. FP24 undergoes the same thawing process as FFP and also must be transfused within 24 hours of returning to the liquid state. As with FFP, if not transfused by that time, FP24 can then be relabeled as TP. The indications and contraindications for FP24 utilization are identical to FFP (see the section above). FP24 should not be used when the sole replacement of factors V and/or VIII is necessary [16].

Thawed Plasma

TP is the liquid form of FFP or FP24 following a thaw at 30–37 °C if the unit is not used within 24 hours of thaw time. It is then stored at 1–6 °C to be used for up to 4 days following the initial 24 hours post-thaw period. The levels of stable factors remain close to those of FFP and FP24 even at the 5-day point after the time of thaw. However, there is a decline in the levels of labile factors, most significantly factor VIII [13]. Viscoelastic testing also indicates slower thrombin generation after 5 days of storage [17]. AABB indications for transfusion of TP differ slightly from those of FFP and FP24, including [15]:

1. Preoperative or bleeding patients with multiple coagulation factor deficiencies
2. Initial treatment in patients undergoing 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 or in whom only transient reversal is needed
4. Thrombotic thrombocytopenic purpura transfusion or plasma exchange.

Because labile factor concentration is variable, TP is not recommended for the management of isolated or specific coagulation factor deficiencies for which other products containing higher concentrations are available.
Liquid Plasma

LQP is produced from whole blood no later than 5 days after the 21-day expiration period of whole blood. It cannot be frozen. LQP is refrigerated at 1–6 °C for up to 30 days. The primary indication for LQP is massive transfusion, as the thawing time is inherently absent. Vitamin-K-dependent factors (factors II, VII, IX, and X) are relatively stable under approved 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 [14, 15].

The hemostatic profile of LQP, as determined by thrombelastography, calibrated thrombogram, and clotting factor activity, is better than FFP or TP. Furthermore, the levels of coagulation factors remain ≥88% of original levels out to 26 days, except for factors V and VIII [18]. LQP’s superior capacity to generate thrombin and form clot may be explained by the presence of platelet microparticles in LQP not present frozen plasma, cold activation of coagulation proteins, the decline in protein S activity, or a combination thereof. 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.

Dried Plasma

Although no dried plasma product is currently approved by the Federal Drug Administration for use in the United States [19–21], the earliest report of treating shock with dried plasma dates back to 1938 [22]. By the time of the United States’ entry into World War II, freeze-dried plasma was approved for use by the Council on Pharmacy and Chemistry of the American Medical Association. The kit designed for reconstitution contained the packages of dried plasma with bottles of sterile water [23]. Eventually, several million units were produced by the American Red Cross for distribution to Allied Forces. This method served as the standard for the resuscitation of war casualties through the war, until hepatitis transmission from the pooled transfusions was recognized [23, 24]. By the 1950s, the United States discontinued use, although the French Military Blood Institute (Centre de transfusion sanguine des armées (CTSA)) and German Red Cross (Deutsches Rotes Kreuz (DRK)) still produce dried plasma products. Numerous studies are underway to develop and approve a product for US military and civilian use, discussed at the end of this chapter.

In general, dried plasma is produced either by freeze-drying, also known as lyophilization, or by spray-drying. Lyophilization involves cryodesiccation, freezing the plasma under a vacuum to decrease the water content to 1–2%. In the French method (French lyophilized plasma, or FLyP), apheresis plasma from a maximum of 10 donors is pooled and leukoreduced. After photochemical viroinactivation, three liters of product is distributed into individual flasks, which are freeze-dried for 4 days [25, 26]. This process removes much of the bicarbonate in the solution. Lyophilized plasma is therefore alkalotic with a pH near 8, causing issues in animal studies but appearing well tolerated in humans [25, 27]. The German method of lyophilization licensed as LyoPlas N-w (German Red Cross Blood Service, West Hagen, Germany) sources plasma only from single donors, a change made in 2006 due to concerns over Creutzfeldt-Jakob disease transmission [28]. The other general method of production, spray-drying, atomizes LQP by using pressurized droplets exposed to heated gas in a drying chamber, followed by rapid cooling [29].

Although safety concerns led to the discontinuation of dried plasma in the United States after the Korean War, newer methods of viral detection and inactivation have vastly improved the safety profile of the donor pool. Transmission of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is calculated at one in two million units [30]. Solvent/detergent treatments bind lipid-enveloped viruses, and photochemical processes bind and inactivate non-enveloped viruses with any other free nucleic acids. A treatment including a prion reduction...
step, Octaplas LG (Octapharma, Lachen, Switzerland), now has FDA clearance [31]. These processes are examined in more depth in the section “Infectious Disease Transmission.”

Dried plasma possesses similar coagulation parameters as LQP and thawed FFP. In an animal model, Shuja et al. found an insignificant decrease in the activity of factors II, VII, and IX [26]. The German Red Cross Blood Service has reported minimal degradation of coagulation factor activity for factor V, factor XI, fibrinogen, protein S, antithrombin, and plasminogen. Only factor VIII and von Willebrand factor lost more than 10% activity, with the latter particularly affected by prolonged storage at room temperature. Cold storage for 24 months also showed retained coagulation factor activity with the same factor VIII and von Willebrand factor reduction of 20–25% [32]. While standard solvent/detergent processes can degrade coagulation factors significantly, newer methods preserve factor activity [31]. Additionally, minimal effect was seen with the reconstitution of dried plasma with acidic buffers to counteract the alkalotic dried form [27].

**Current Practices in Civilian Trauma Centers**

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 whole blood; therefore, giving whole blood or its components back makes sense. However, reaching for packed red blood cells (RBCs) first does not necessarily accomplish the goal that the trauma community is trying to achieve: restoration of circulating volume. The transfusion of plasma does restore circulating blood volume while delivering coagulation factors to bleeding patients actively consuming those 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 transfusion requirements follow-

ing admission, and reduce mortality risk [33–35]. These protective benefits can be synergistic with other therapies. When used to correct traumatic coagulopathy, combinations of FFP with tranexamic acid or prothrombin complex concentrate are superior in improving acidosis and coagulopathy than when these agents are given without plasma [36].

Restoration of circulating coagulation factors is not the sole purpose for the transfusion of plasma in patients with hemorrhagic shock. With increasing understanding of systemic endothelial injury associated with massive trauma, treating the endotheliopathy of trauma has also become a goal for plasma transfusion [37]. This evolution of thought has been derived from insights into how hemorrhagic shock systemically affects physiology.

**Endotheliopathy of Trauma**

The endotheliopathy of trauma refers to the breakdown of the endothelial glycocalyx on the endoluminal surface of blood vessels, increasing permeability and decreasing their integrity. Multiple proteoglycans and glycoproteins comprise this endoluminal network, providing surfaces for interactions with glycosaminoglycans, neutrophils, and a host of other particles. The glycocalyx normally allows the plasma component of blood to interact with the vessel wall while maintaining a barrier to erythrocytes and leukocytes [38]. It has been hypothesized that injury to the endothelial glycocalyx leads to interstitial edema, inflammation, and tissue hypoxia [39, 40]. Kozar et al. demonstrated that the endothelial glycocalyx is systemically injured during hemorrhagic shock, manifested by shedding of syndecan-1, one of the endothelial glycocalyx’s proteoglycans [41]. Patients arriving at trauma centers in hemorrhagic shock express elevated level of syndecan-1. Johansson et al. found an elevated admission syndecan-1 level in severely injured patients to be associated with inflammation, coagulopathy, and increased mortality [42].

These effects, fortunately, are reversible. The injured glycocalyx is partially repaired with the
transfusion of plasma, an effect not seen with crystalloid solution [38, 41, 43]. 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 [44–48]. Increases in alveolar thickness, capillary congestion, and cellularity were seen in a shock model compared to sham; the infusion of crystalloid worsened all three parameters, while the plasma transfusion group demonstrated improvement, suggesting attenuation of lung injury [49]. Shown in Fig. 21.1 are electron microscopy images of mesenteric venules showing the effects of shock and resuscitation on the endothelial glycocalyx. TP, even when stored at 4 \degree C for 5 days after thawing, remained superior to crystalloid infusion with respect to reparative capacity in an animal model [7]. LQP also blocks endothelial permeability as effectively as thawed FFP [50]. This indicates that a component of plasma, in soluble form, interacts with the endothelial membrane to restore the endothelial glycocalyx. Figure 21.2 shows the vascular injury caused by hemorrhagic shock through hypoxia leading to cell contraction and increased 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.

![Fig. 21.1](image)

**Fig. 21.1** Electron microscopy of mesenteric venules stained to reveal endothelial glycocalyx following hemorrhagic insult and resuscitation
Neuroprotective Benefits

Through the prevention and repair of endotheliopathy, in addition to other mechanisms still under study, plasma also confers neuroprotective effects in both animal models and human cohort studies. Transfusion of FFP in animal models of traumatic brain injury and hemorrhagic shock lessened the severity of injury based on the level of neurologic impairment and time to recovery. The purported mechanisms include improved cerebral perfusion, decreased excitotoxicity, and decreased mitochondrial dysfunction [51, 52]. Other porcine models demonstrated a reduction in the size of hemorrhagic lesions and intracranial swelling with plasma [8, 53]. Initial results from animal models using lyophilized plasma also show similar neuroprotection compared with FFP [54]. In humans, subgroup analysis of a large retrospective cohort found that early administration of plasma was associated with a survival benefit in patients with multifocal intracranial hemorrhage [55]. In another retrospective review, patients receiving prehospital TP had clinically significant improvement in neurologic outcomes versus patients receiving RBCs, based on Glasgow Outcome Scale-Extended and Disability Rating Score. The improvements extended to a median follow-up of 6 months [56].

The Underappreciated Benefits of Plasma

While attenuating or correcting trauma-induced coagulopathy through the restoration of clotting factors and endothelial protection are now considered primary mechanisms of action of plasma, it has other critical benefits. A single unit of plasma contains more than 400 mg of...
fibrinogen, helping to address hypofibrinogenemia and fibrinogen dysfunction during the resuscitation of hemorrhage. In addition, plasma, likely through its high citrate content, serves as a tremendous acid-base buffer in hemorrhagic shock patients with severe acidosis. Traverso and colleagues demonstrated to be the best buffer available for resuscitation, with a buffering capacity 50 times that of standard crystalloid products [57]. Finally, these patients have also lost tremendous circulating blood volume, and plasma acts as a volume expander with high oncotic pressures.

**Massive Transfusion Protocols**

The institution of exsanguination protocols at major trauma centers has been shown to improve survival [58, 59]. Notably, early investigations did not specifically involve a balanced ratio resuscitation. 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 [60, 61]. Furthermore, a decrease in the total amount of blood products transfused was seen [58, 59, 62, 63].

The majority of trauma centers store uncrossmatched 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 [64, 65]. At one center, storing 4 units of thawed AB plasma next to the trauma bays, the time to first plasma transfusion was improved by 46 min. The study showed a decrease in the 24-hour transfusion of RBCs, plasma, and platelets and a significant decrease in mortality. Furthermore, a decrease in the frequency of activation of the massive transfusion protocol was seen following the implementation of TP in the emergency center [35]. Early administration of plasma in a massive transfusion protocol attains increased plasma-RBC ratios, which may reduce requirements for massive transfusion as currently defined [66].

**Sourcing**

While type AB plasma is traditionally considered the “universal donor,” type A plasma has been used with increasing frequency as a safe alternative. Type A is more widely available, comprising 40% of the American population, as opposed to AB at 4%. This translates into 85% of trauma patients, those with A or O types, being able to receive A plasma with no additional risk [67]. In the remaining 15% of patients with type B and type AB, the risk of hemolytic reaction is limited by the generally low levels of secreted anti-B antibodies in most donors, especially in the United States [68]. To this end, some centers have started selecting for donors with low titers of anti-B antibody. This approach has been published with excellent safety records and no changes in mortality compared to AB plasma [67, 69–72].

**Key Studies Involving Plasma**

**PROMMTT**

The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study demonstrated that earlier transfusion of plasma, ideally within minutes of identification of hemorrhagic shock, achieved high plasma-RBC ratios and decreased 24-hour and 30-day mortality. This was evidenced by the three- to fourfold increased mortality risk associated with plasma-RBC ratios <1:2 [37, 73, 74]. Furthermore, gradual achievement of balanced transfusion ratios may not be as beneficial as early plasma transfusion. Initiating plasma transfusion early also led to a decrease in the total amount of RBCs trans-
fused during the initial 24 hours following admission [74]. 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 actually associated with excessive crystalloid infusion rather than plasma [75].

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 in hemorrhagic shock. Although no significant differences in 24-hour 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 hours following admission [76]. Furthermore, while the balanced transfusion group received significantly more plasma and platelets within the first 24 hours, no difference was found in the rate of 23 prespecified complications including 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 hours. In a post hoc analysis, at 3 hours after admission, there was a significant mortality difference between the two groups. There was also lower hemorrhage-related mortality in the 1:1:1 group.

PAMPer

The Prehospital Air Medical Plasma (PAMPer) trial compared prehospital plasma resuscitation with standard care (i.e., no prehospital plasma transfusion) in 501 patients from 2014 to 2017 across nine trauma centers. Also designed as a multicenter randomized trial, two units of TP (either group AB or group A with a low anti-B antibody titer) were carried by participating air transport teams. As with PROPPR, a mortality separation developed at the three-hour mark [77]. The plasma group exhibited lower mortality, and this effect persisted to 30 days (23.2% vs 33%). Only five patients experienced transfusion-related adverse events labeled as possibly related to the trial treatment, all of which were minor allergic or other reactions. PAMPer serves as the first randomized trial to show the benefits of plasma in a prehospital setting with no increase in multiorgan failure, TRALI, nosocomial infection, or transfusion-related reactions.

COMBAT

Published concurrent with PAMPer, the Control of Major Bleeding After Trauma (COMBAT) trial also compared prehospital plasma resuscitation to standard care. Notable differences include a single-center design at the Denver Health Medical Center using all ground-based paramedics, as well as the transfusion of FP24 rather than TP. Sixty-five patients transfused two units of thawed FP24 were compared to 60 patients receiving saline, which was dosed according to the perceived need for resuscitation. No differences were seen in mortality at 28 days or in safety outcomes [78]. The authors suggested that in a nonurban setting with longer transport times than in Denver, plasma may have benefits that were not demonstrated in their setting. Concerns have been raised regarding the confounding effects of time needed to thaw frozen plasma en route, when median transport times were only 16–19 minutes [79]. In COMBAT, only 32% of the plasma group actually received the protocolled two units during transport, as opposed to
PAMPPer, in which the plasma infusion was completed during air transport in 84.4% of the plasma patients with 89.1% receiving the planned two units. A combination of the COMBAT and PAMPPer data later revealed that prehospital transport times do in fact have a significant effect on overall survival [80]. Pooling the data sets of the 626 patients between the two trials showed that while patients receiving standard care had increased mortality in transports longer than 20 minutes, the plasma group did not share this increased mortality. The post hoc analysis concluded that prehospital plasma was associated with reduced mortality when transport times are prolonged, with the primary benefit being observed in blunt trauma patients.

A Clinical Protocol of Plasma-Focused Resuscitation

The concept used at the Red Duke Trauma Institute at Memorial Hermann Hospital in Houston has been derived from the experiences gained on the battlefield, supported by military and civilian studies. The aggressiveness of plasma use in Houston was further driven by their experience with TRALI being increasingly rare and more likely associated with excessive crystalloid use [81]. In the prehospital setting, emphasis centers on the cessation of accessible bleeding. This occurs in parallel with hypotensive resuscitation utilizing whole blood or 1:1 ratio plasma-RBC units (with plasma being given first). Patients are identified as requiring a prehospital transfusion based upon the assessment of blood consumption (ABC) score [82]. Patients receiving blood in the prehospital setting have automatic activation of the institution’s massive transfusion protocol (which often arrives at the trauma bay before the patient). 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), rapid thrombelastography (rTEG) is used to guide blood product resuscitation on arrival to the trauma bay. Patients demonstrating shock, profound hypotension, and/or ABC scores ≥2 are started on the massive transfusion protocol and receive initially whole blood and then 1:1:1 ratio-driven resuscitation with early administration of LQP. The patient then proceeds to either the operating room or interventional radiology as indicated. Once surgical bleeding is controlled, the resuscitation converts to a guided, non-fixed-ratio approach utilizing rTEG and clinical response [83].

Adverse Effects and 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 transmission, acute transfusion reactions, and leukocyte-associated reactions. It should be noted that RBCs, platelets, colloids, and crystalloids also carry well-described deleterious effects.

Transfusion-Related Acute Lung Injury

TRALI manifests as hypoxia, pulmonary edema, pulmonary infiltrates with radiographic changes, fevers, and possibly hypotension within 6 hours of 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 [84]. A consensus panel update in 2019 updated the 2004 definition and introduced the terms TRALI Type I (without an ARDS risk factor) and TRALI Type II (with an ARDS risk factor or with mild existing ARDS) [85]. TRALI remains a clinical diagnosis, though serologic testing is available.

TRALI is significantly associated with leukocyte alloantibodies found in donor plasma. These specific antibodies are found almost exclusively in postpartum female plasma and in 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 [86]. In 2008, Eder et al. reported a reduction in the incidence of TRALI with the conversion to male-predominant plasma for transfusion [87].

While it is the most common cause of death from transfusion and the most frequent serious complication of FFP transfusion, the absolute risk of TRALI remains low [88]. The UK hemovigilance Serious Hazards of Transfusion (SHOT) report included a single case of TRALI in the entire country in 2018 [89]. The estimated risk is approximately 1 in 64,000 transfused units. The FDA reported that the 56 reported cases of TRALI in the United States represented 30% of all fatalities secondary to blood transfusions from fiscal years 2013 to 2017. Plasma was implicated in four cases and a plasma product may have been implicated in 16 other cases that received multiple transfusions. No plasma-associated cases were reported for 2016 or 2017. The number of cases of TRALI has significantly decreased following voluntary measures taken by the transfusion community [90]. These measures include rigorous testing and safety procedures performed by the blood-banking community, as well as conversion to male-predominant plasma donors. At the caregiver level, the dramatic decrease in crystalloid use during the initial 24 hours of resuscitation of hemorrhage has been associated with marked reductions in its occurrence [75, 81].

Transfusion-Associated Circulatory Overload

TACO occurs secondary to increased hydrostatic pressure resulting in pulmonary edema. This process can be indistinguishable from TRALI, and the two entities may in fact coexist [91]. The FDA reported that TACO represented 18% of transfusion-related mortalities for the fiscal year 2017. 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 [90].

The incidence of TACO is not well described in the literature. Multiple retrospective reviews have reported an incidence of TACO from <1% to 11% [91, 92]. In Fig. 21.3, Gajic et al. designed an algorithm to determine the etiology of post-transfusion acute pulmonary edema [91]. 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 [92].

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 HCV, and 1:280,000 donations for hepatitis B virus [88, 93, 94].

Outside the United States, many blood centers utilize donor-retested plasma, pathogen-inactivated plasma, and pathogen-reduced plasma [95]. Donor-retested plasma are units that are quarantined until the donor submits a subsequent donation which tests negative for infectious disease. 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 [96, 97]. Two companies leading this technology are Terumo Medical Corp. (Somerset, NJ) and Cerus Europe B.V. (Amersfoort, Netherlands). The Cerus process was FDA approved in 2015.

The freezing process during preparation of plasma inactivates bacteria. Furthermore, bacterial contamination with the production of endotoxin prior to freezing is unlikely [88]. The most recent annual FDA report describes no bacterial infection transmitted through plasma transfusions [90]. The process of removing cellular components via filters also removes cell-associated bacteria, most protozoa, and cell-
associated viruses including malaria, cytomegalovirus, and human T-cell leukemia virus. Freezing does not remove the free viruses, including hepatitis A, B, and C, HIV 1 and 2, and parvovirus B19 [16].

Currently, no screening protocol exists for the detection of prion diseases, although techniques are being developed, such as protein misfolding cyclic amplification [98, 99]. Modern techniques of decreasing infectious transmission are ineffective against prion diseases. In the United Kingdom, three possible cases of variant Creutzfeldt-Jakob disease have been reported. Each case involved the transfusion of non-leukocyte-reduced RBCs [100]. There have been no reported cases of prion disease transmission following plasma transfusion; however, animal studies have shown it remains a possibility [101].

Febrile and Allergic Reactions

The 2018 SHOT Report documented 235 allergic, hypotensive, and severe febrile reactions. Only 11 cases were associated with plasma and/or cryoprecipitate, which were reported as a sum. These figures included five anaphylactic reactions. No deaths were related to any febrile or allergic reaction [89]. Moderate allergic reactions present with an urticarial rash, wheezing, and other symptoms not severe enough to be termed anaphylactic, and they occur in 1–3% of transfusions. Anaphylaxis includes bronchospasm, angioedema, severe hypotension, and cardiovascular collapse, a very rare occurrence [15, 89, 90, 92, 96].

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 patients with IgA deficiency is available for transfusion [102].

Leukocyte-Associated Reactions

Leukocyte-associated reactions following plasma transfusion are also rare. The freeze-thaw process yields a small percentage of viable leukocytes prior to transfusion [103, 104]. The presence of
leukocytes leads to febrile nonhemolytic transfusion reactions, transfusion-associated graft-versus-host disease, and transmission of leukocyte viruses [96]. Following the freeze-thaw process, nonviable leukocytes release mediators that may contribute to febrile nonhemolytic transfusion reactions. These reactions are generally clinically insignificant and resolve quickly with supportive therapy [89, 96]. Graft-versus-host disease requires viable leukocytes to be transfused and then engraft and proliferate in the host patient. This is a rare transfusion reaction among all blood components transfused and has yet to be reported with FFP transfusion. Therefore, irradiation of FFP is not currently recommended [15].

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, a recent randomized trial, and numerous other cohort studies. 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 arena. Future research may yield an approved dried plasma product that eliminates the logistic constraints of frozen and liquid plasma.

Rationale

In order to achieve a 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 TP is unavailable and in austere environments where cold chain storage and transportation is a limiting factor. As a result, much research and development have gone into the production and distribution of alternative plasma products suitable for human transfusion. Achieving the goal of 1:1:1 balanced resuscitation is often difficult in environments where a large and rapidly accessible supply of plasma is not available [105]. As described previously, FFP and FP24 require frozen storage and rewarming under very controlled conditions. TP and LQP require storage under refrigerated conditions with relatively short shelf lives. This makes the rapid (within minutes of requirement) administration of plasma difficult at most civilian institutions and sometimes impossible for military personnel.

Recent and Ongoing Studies Using Dried Plasma

These factors have led to the recent redevelopment of dried human plasma. As previously mentioned, lyophilized plasma is not a new concept, as it was first developed and introduced into practice during World War II. The French military has utilized lyophilized plasma with a well-documented hemovigilance program since 1994. No adverse effects of infectious transmissions have been reported with the transfusion of more than 1100 units [25]. In 2011, Martinaud et al. described the utilization of French lyophilized plasma intensive care units in Afghanistan while caring for casualties from coalition forces [106]. The product was described as easy to use, reconstituting within 10 minutes to provide 210 mL of fluid with hemostatic and volume expansive properties. A total of 236 units were delivered without a single adverse event reported. Israeli Defense Forces also utilize German LyoPlas N-w as a protocolized resuscitation fluid in the military prehospital setting. Using these dried products facilitates balanced transfusion from the point of initial resuscitation without playing “catch-up” after FFP thaws [107–109]. British helicopter transport has also shown decreased time to transfusion and the need for RBC transfusion in units carrying LyoPlas N-w [110].

French lyophilized plasma is approved by the Department of Defense, FDA, and White House for selected units of US Special Forces. In addition to the French, German, and Israeli militaries, dried plasma products are utilized in South Africa.
and by the Norwegian military and civilian aeromedical services [107]. Further investigation for utilization in US civilian emergencies and ABO group universality are necessary, which may allow plasma resuscitation to occur in environments not conducive to current plasma storage [19, 20, 33].

Multiple products are under development in the United States with this goal in mind. HemCon Medical Technologies, Inc. (Portland, OR) started development in 2008 of lyophilized plasma sourced from single donor FFP under contract from the US Army Medical Materiel Development Activity (USAMMDA) and US Army Special Operations Command [111]. At the same time, the Office of Naval Research funded Entegrion, Inc. (Research Triangle Park, NC) with the goal of producing a pooled AB spray-dried plasma product named Resusix. This product uses a solvent/detergent process from Octapharma (Lachen, Switzerland) that not only controls lipid-enveloped viruses but also removes immunogenic lipids, cellular debris, and proinflammatory microparticles. Resusix is currently in Phase II clinical trial development [112, 113]. In 2012, the Biomedical Advanced Research and Development Authority funded the development of spray-drying technology with Velico Medical Technologies (Beverly, MA). The product called FrontlineODP (OnDemandPlasma) employs a decentralized manufacturing model, which would allow greater flexibility in individual blood centers quickly preparing dried plasma [56]. In 2014, Vascular Solutions, a subsidiary of Teleflex Corp (Limerick, PA), was awarded the USAMMDA Cooperative Research and Development Agreement previously with HemCon. Their product, RePlas, started Phase I clinical trials in 2017 [31, 114]. Terumo BCT, Inc. (Lakewood, CO) is developing another decentralized lyophilized plasma production process [115].

Further efforts may yield a plasma product with all the advantages of early plasma transfusion in trauma without the logistic difficulties of frozen storage and transport, thawing delay, and short shelf lives after thawing. Dried plasma development, while currently focused on military and austere environments, may progress to replace FFP in a multitude of settings such as prehospital transport, smaller hospitals, and mass casualty responses.

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