Blood Products

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Background

Perioperative hemorrhage, anemia, thrombocytopenia, and coagulopathy are common in the surgical intensive care unit (ICU). Indeed, it is suggested that between 5 % and 7 % of cardiac surgical patients lose more than 2 L of blood in the first 24-h postoperatively [1]. Similarly, it has been estimated that 1.5 % of patients undergoing pancreatoduodenectomy experience hemorrhage requiring at least four units of red blood cell (RBC) transfusion [2], and up to 9 % of patients undergoing orthotopic liver transplant experience abdominal bleeding requiring radiologic intervention or re-laparotomy [3]. Accordingly, anemia is frequently observed on admission to the ICU, with a substantial proportion of the remaining patients becoming anemic during their admission [4]. In addition, around 40 % of critically ill patients have thrombocytopenia or other derangements in coagulation parameters at some point during their ICU stay [5–7]. Thus it is not surprising that blood product transfusion is common practice in the ICU. Indeed for decades, RBC, plasma, and platelet transfusions were given seemingly ubiquitously to alleviate their respective laboratory derangements. While these blood products clearly play a life-sustaining role in the setting of major trauma or life-threatening hemorrhage, in an era of evidence-based medicine, the safety and efficacy of transfusion in hemodynamically stable patients has been increasingly called into question.

Though a degree of clinical equipoise persists, a substantial and growing body of evidence supports the notion that liberal transfusion of blood products portends an increased risk for adverse patient outcomes, including in-hospital and 30-day mortality, infection, ARDS, and multi-organ dysfunction [8–10]. This, coupled with the known intrinsic risks of blood product transfusion (discussed below), has resulted in refinement of transfusion recommendations—with a shift toward more conservative practice. Despite this, the ICU remains one of the highest utilizers of blood products in the hospital [4, 11]. In the United States, an estimated 24,000,000 blood products are transfused each year [12], with approximately 40 % of critically ill patients receiving at least one unit of RBCs [4], and one out of every two patients receiving at least one allogeneic blood product during their ICU admission [11]. Concerningly, evidence suggests that many of these blood product transfusions are being given outside of published guidelines—for example, for the correction of stable asymptomatic anemia, or for correction of abnormal coagulation parameters in the absence of bleeding [13]. Improving the appropriateness of blood product transfusion in the ICU will require careful assessment of the known risks and benefits. In this chapter, we outline the contemporary evidence-based indications for blood product transfusions, their efficacy and risks. In addition, we describe recent changes with regard to massive transfusion as well as upcoming blood product alternatives.

Red Blood Cell Transfusion

Red blood cells (RBC) are the most frequently transfused blood product around the world [14, 15]. They are obtained from either whole blood donation or apheresis and can be stored for a maximum of 42 days from the time of collection at 4 °C [16]. Here, we discuss the temporal trends in clinical practice, indications and efficacy for RBC transfusion.

Past and Current Practice

Historically, the decision to transfuse RBCs has been driven by the assumption that higher hemoglobin (Hb) levels resulted in an increase in the oxygen carrying capacity of the blood and thus improved oxygen delivery to the tissues [17]. Until recently, commonly sought RBC transfusion

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thresholds aimed to maintain hemoglobin ≥ 10 g/dL and hematocrit (Hct) ≥30 % [18]. Whilst this mechanism of increasing oxygen delivery has physiologic rationale, the impact on patient-important outcomes has since come under significant scrutiny.

In the 1980s, the acquired immunodeficiency syndrome epidemic and concern for transfusion-transmitted infections incited a re-examination of the risk-to-benefit ratio of RBC transfusion in the perioperative setting [19]. While advances in donor screening and blood product testing have substantially mitigated concerns regarding transfusion-transmitted disease, the debate about RBC safety is ongoing—primarily driven by questions of efficacy and other patient-important outcomes. In 1999, the Transfusion Requirements in Critical Care (TRICC) randomized trial compared a liberal (transfusion trigger, Hb < 10 g/dL) versus restrictive (transfusion trigger, Hb < 7 g/dL) transfusion strategy and concluded that in-hospital mortality was significantly reduced in the restrictive group [20]. While this study failed to demonstrate a statistically significant difference in 30-day mortality for "all comers," subgroup analysis of 30-day mortality in those with lower APACHE II scores (<20) and <55 years of age was significantly reduced in the restrictive group [20]. Importantly, no adverse effects of the restrictive strategies were observed, however noticeably fewer RBCs were utilized [20]. This study was pivotal to modern transfusion practice, and subsequently leads to the generation of guidelines purporting a transfusion trigger of Hb < 7 g/dL. Similar studies have replicated these findings in a variety of patient populations including cardiovascular [21] and orthopedic surgery [22] as well as gastrointestinal bleeding [23], each concluding that either liberal transfusion did not confer a morbidity or mortality benefit, or that restrictive transfusion actually resulted in a higher probability of survival at 6 weeks, less bleeding, and fewer complications relative to the liberal transfusion group [21–23]. In addition, a number of observational studies support restrictive transfusion, noting that RBC transfusions may be associated with worse clinical outcomes [4, 24]. These studies hypothesize that restrictive transfusion strategies result in reduced exposure to the potentially harmful effects of transfusion therapies, and as such result in a reduced incidence of adverse events when compared to liberal transfusion.

Since the landmark results of the TRICC study, Carson and colleagues have conducted two systematic reviews—a decade apart—on each occasion supporting use of restrictive transfusion triggers [15, 25]. Over this time period, some authors have reported subsequent reductions in RBC utilization in the critically ill [9, 26]. Conversely however, in 2004, Corwin et al. [4] reported that "*Transfusion practice in response to anemia has changed little over the last decade*" suggesting ongoing inappropriate utilization of blood products in the critically ill.

Current Indications and Guidelines

Multiple iterations of transfusion guidelines are available in today's literature [15, 27–29] and while these recommendations have evolved over time, the one key consistent message is that in most cases, the decision to transfuse should not be solely based upon an arbitrary hemoglobin-based transfusion trigger. Rather, consideration of patient-specific symptoms and risks is paramount, and clinical judgment should be exercised with each blood product that is administered. In modern medical practice, efforts to minimize unnecessary RBC transfusion are hinged upon three key points; first recent evidence supports the notion that restrictive transfusion practice in hemodynamically stable patients is at least as safe and effective as liberal transfusion practice, and possibly superior. Second is the increasing awareness of the risks of transfusion, and third relates to the scarcity of RBCs, resource utilization, and the associated healthcare costs.

In 2009, the Society of Critical Care Medicine and the Eastern Association of Surgery for Trauma developed joint clinical practice guidelines for RBC transfusion [11]. Considering all available literature at that time, the single most irrefutable indication for RBC transfusion remains acute hemorrhage with hemodynamic instability, inadequate oxygen delivery or shock. Outside of the setting of acute hemorrhage, conservative transfusion practices (RBC transfusion only when Hb falls < 7 g/dL) are recommended for most critically ill patients with stable anemia, including those presenting with trauma, requiring mechanical ventilation or with known stable coronary disease. Furthermore, in all situations, it is recommended that only single unit transfusion takes place before reevaluation of the need for additional RBC transfusion. Notably, these guidelines recognize a possible exception to this standard of care. For patients with acute myocardial ischemia, it is suggested that transfusion for a Hb < 8 g/dL may be beneficial. Of note, given the lack of clinical trials focusing specifically on the effects on anemia in acute myocardial ischemia, this recommendation was considered level 3 evidence [11]. Recent studies focusing specifically on the issue of transfusion in cardiac disease have taken place with conflicting results [30–32]. This is discussed in more detail below—exceptional circumstances. However, the authors do highlight that RBC transfusion should not be considered as an absolute method to improve tissue oxygen delivery in the critically ill. With regard to sepsis and neurologic injury, the authors note that current data are insufficient to provide level 1 recommendations.

The above recommendations were further echoed in the 2012 clinical practice guidelines published by the American Association of Blood Banks (AABB) [15]. These authors again endorsed restrictive transfusion strategies, such that transfusion may be considered when the Hb level is <7 g/dL. Conversely, they also report the exception that in

postoperative surgical patients, transfusion should be considered at Hb < 8 g/dL or less in the presence of symptoms such as chest pain, orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, or congestive heart failure. The latter recommendation was largely informed by the results of the FOCUS trial [31] in which the authors examined the role of a more liberal threshold-based transfusion practice (<10 g/dL) versus symptom-driven (transfusion permitted if symptomatic with Hb < 8 g/dL) transfusion in patients with known cardiovascular disease who were undergoing surgery. These authors found no benefit from liberal (Hb < 10 g/dL) versus restrictive (Hb < 8 g/dL or symptomatic) practice, however they refrained from making any specific recommendations regarding transfusion thresholds in the setting of an acute coronary syndrome.

Exceptional Circumstances

Sepsis

Following publication of the early goal-directed therapy (EGDT) guidelines by Rivers et al. [33], motivation to administer RBC transfusion increased. Specifically recommendations were to transfuse RBCs to maintain a hematocrit > 30 % or to achieve a central venous oxygen saturation > 70 %, in addition to fluid resuscitation, use of inotropic agents, respiratory support, and invasive cardiopulmonary monitoring [34]. While these international guidelines are broadly endorsed for the management of early sepsis, this study was not designed to specifically evaluate the risks and benefits of transfusion. Additionally, since RBC transfusion was just one of several interventions, the attributable benefit is unclear. Indeed, specific guidance on the administration of RBC transfusion has been removed from the most recent iteration of the surviving sepsis guidelines [35]. Moreover, data exist to suggest an immunomodulatory effect of RBC transfusion [36], which may potentially propagate sepsis. Indeed, a recent systematic review noted a significant reduction in healthcare-associated infections in patients receiving a restrictive transfusion strategy [37]. To this end a recently completed multicenter randomized trial—Protocolized Care for Early Septic Shock (ProCESS) [38]—compared patient outcome with EGDT-driven care protocols versus protocolized standard therapy which did not require transfusion versus standard care. These authors concluded that need for organ support, mortality at 90 days and 1 year were comparable between all three groups. The recently published Transfusion Requirements in Septic Shock (TRISS) trial failed to support the need for more liberal RBC transfusion practices in those presenting with septic shock [39]. In lieu of further clinical data, the recommendation that each patient be assessed individually based upon symptoms and clinical need remains paramount, over arbitrarily defining a numeric transfusion trigger.

Cardiac Disease

In patients undergoing surgery, concern exists that coronary artery disease may render the myocardium more susceptible to the adverse effects of anemia and impaired oxygen delivery when compared to patients without coronary artery disease. Unfortunately, evidence relating to the optimum transfusion practice in this subgroup of patients remains limited. As such, guidelines for RBC transfusion in this specific population remain somewhat imprecise, particularly in the setting of acute coronary syndromes (ACS). The generally accepted threshold in clinical practice is to transfuse these patients if their hemoglobin falls below 8 g/dL [32]. To date, the strongest evidence specifically evaluating the role of transfusion in patients with cardiac disease comes from the FOCUS, TRACS, and MINT trials. In 2006, the FOCUS trial [31] found no benefit from liberal (Hb < 10 g/dL) versus restrictive (Hb < 8 g/dL or symptomatic) in terms of mortality, independent walking, or myocardial infarction. Similar notions were endorsed by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists in their 2011 guideline [27]. Although their threshold was set at 6–7 g/dL, they again emphasize that patients' clinical condition should be the most important component of the clinical decision to transfuse, and that these decisions will often be multifactorial.

Importantly, neither of these publications evaluated or commented on the safety of transfusion thresholds in patients experiencing ACS. Interestingly, patients enrolled in the TRICC study [40] were evaluated for cardiac events, including myocardial ischemia, unstable angina, pulmonary edema, and cardiac arrest. Evaluation of the entire cohort indicated that there was no evidence for an increase in adverse cardiac events in the restrictive group; however, subgroup analysis of patients with ischemic heart disease suggested a non-significant trend toward increased mortality at 30 and 60 days in the restrictive group [40]. This study was unfortunately underpowered to evaluate such an association, however these findings raised significant concern to warrant further investigation. In 2008, a single-center observational study published data relating to their experience of transfusion in ACS [32]. After careful adjustment for confounding variables, the authors concluded that transfusion appeared to be protective in the setting of a nadir Hb < 8 g/dL but harmful if nadir Hb was > 8 g/dL [32]. Following this observation, the TRACS study was established to evaluate the safety of restrictive perioperative RBC transfusion following elective cardiac surgery. These authors concluded that restrictive transfusion was noninferior when compared to liberal perioperative RBC transfusion [21]. In an effort to further clarify the optimal RBC transfusion threshold in the setting of ACS, Carson et al. conducted a pilot study (Myocardial Ischemia and Transfusion—MINT) addressing this very issue [30].

Though underpowered, the authors again noted a trend toward reduction in the composite outcome, death, myocardial infarction, or unplanned revascularization in patients transfused to a hemoglobin goal of >10 g/dL [30]. The findings of the MINT trial support both the feasibility and need for a large-scale randomized clinical trial in this area. In view of the ongoing clinical equipoise surrounding ACS, and in the absence of a randomized clinical trial, using a transfusion trigger of 8 g/dL would appear reasonable in these patients.

Acute Brain Injury

Historically, patients with acute neurologic injuries were therapeutically hemodiluted in an attempt to reduce blood viscosity and promote cerebral perfusion [41]. This practice has changed considerably since a 2004 systematic review revealed no benefit from hemodilution [42]. Subsequently, Naidech and colleagues described an association between increased cerebral infarction and death in anemic patients with neurologic injury [43], promoting adoption of a more liberal transfusion practice aiming to keep Hb > 10 g/dL. The primary hypothesis underpinning this observation was that the adverse outcomes associated with anemia were secondary to impaired oxygen delivery to the brain. Indeed, this theory appeared to be supported by a number of prospective observational studies [44, 45] demonstrating that brain tissue oxygenation was markedly improved after RBC transfusion. However, these investigations have numerous notable limitations and perhaps more importantly, no effects on neurologic outcomes were observed. Therefore, the clinical implications of these findings remain a matter of debate.

With this in mind, in 2006, Pendem et al. conducted a literature review seeking to clarify how existing transfusion thresholds may be applied to the neurologically critically ill [46]. Available literature at this time lead the authors to conclude that while an "*optimal transfusion thresholds in neurological critically ill patients are not known, there is little reason to suspect that transfusion-restricted protocols would be detrimental*" [46]. Similar conclusions were confirmed 2 years later by Leal-Noval and colleagues who sought to identify the optimal hemoglobin level in "neurocritical" patients [47]. Interestingly, their findings lead them to conclude that both "*severe anemia and red blood-cell transfusion may negatively influence outcomes*" and that "*Acceptance of lower hemoglobin concentrations may be justified by avoiding negative transfusion effects*" [47]. These authors refrained from defining an optimal transfusion trigger. More recently, Warner et al. conducted a retrospective review of transfusion in traumatic brain injury [48]. These authors concluded that in addition to the Glasgow coma score, RBC transfusion and transfusion volume were significantly associated with adverse long-term functional outcomes [48].

Summarizing the conclusions of contemporary literature surrounding appropriate and safe RBC transfusion practice, we endorse the use of restrictive transfusion strategies. However, we encourage further research into certain high-risk populations in whom an optimal transfusion threshold has not yet been clearly defined—including patients with sepsis, acute coronary syndromes, and acute brain injury.

Efficacy

Recent recognition that restrictive transfusion practice appears to be comparably safe, if not superior, to liberal transfusion practice has generated the question: does RBC transfusion lead to the expected physiologic result? Notably, few studies have been able to demonstrate improved clinical outcomes with RBC transfusion [8]. Though the underlying rationale for RBC transfusion relates to an improvement in oxygen delivery and more importantly tissue oxygenation [17], the theoretical association with the later remains largely unproven. A leading theory regarding the lack of improved tissue oxygenation with RBC transfusions relates to impact of RBC storage—a topic that remains actively debated [49–52].

Several observational studies have documented a multitude of adverse outcomes associated with the age-related functional and morphologic changes in RBCs—collectively termed the "red cell storage lesion" [53, 54]. It has been postulated that a rapid decline in S-nitrosohemoglobin concentrations, with resultant reduction in red cell deformability, can result in microcirculatory occlusions and subsequent tissue ischemia [55]. Meanwhile, others have suggested an immunomodulating effect of RBCs may be causal [36]. Additional adverse biochemical effects associated with RBC storage include reductions in ATP and 2,3-DPG [56, 57]. While there is little debate regarding these and numerous other time-dependent changes in both the RBCs themselves as well as the storage supernatant, the clinical impact of these changes remains unclear. Although observational data clearly suggest an association between prolonged storage and adverse recipient outcomes [58], these findings have not born out in the available, albeit small clinical trials [59]. More importantly, several recent multicenter clinical trials have failed to confirm the clinical significance of the RBC storage lesion. Nonetheless, the absence of strong data suggesting efficacy, combined with the known risks associated with RBC transfusion (discussed in detail below) suggest that a restrictive RBC transfusion practice is prudent until further data become available.

Plasma Transfusion

Plasma is the acellular, fluid portion of human donor blood and can be obtained from whole blood donation or by apheresis. It contains near-normal levels of most plasma

proteins including both the procoagulant and anticoagulant components of the coagulation cascade as well as albumin, immunoglobulins, and a variety of acute-phase proteins [28]. Plasma also contains fats, carbohydrates, and minerals in concentrations similar to those in the circulation of donors at the time of product collection. Of note, multiple plasma products are available in clinical practice including fresh frozen plasma (FFP), plasma frozen within 24 h (FP24), thawed plasma, jumbo plasma, and cryoprecipitate-reduced plasma. Although FFP remains the most commonly transfused plasma product in the United States, FP24 and thawed plasma now constitute a substantial proportion of the plasma units transfused as well [14]. FFP is frozen within 8 h of collection, stored at between −18 °C and −30 °C [60], and can be used up to 1 year after donation. Once thawed, it can be stored refrigerated for up to 5 days. FP24 extends the interval for freezing to 24 h. Here, we discuss the temporal trends in clinical practice, indications, and efficacy for FFP transfusion.

Past and Current Practice

Historically, plasma was frequently used in clinical practice as a volume expander. However, with the availability of more cost-effective alternatives (e.g. crystalloids and colloids) as well as our improved understanding of the risks associated with plasma transfusion, the use of plasma for volume expansion is no longer an accepted practice [61]. More contemporaneously, plasma has been used in a number of clinical settings, including treatment of active hemorrhage, as a replacement solution for specific populations receiving pharesis therapies, and for the prevention of bleeding in patients with abnormal coagulation parameters [61–63]. Frequently, however, plasma transfusions have been administered in the absence of evidence-based indications [64, 65]. In terms of utilization, the United States has historically observed a consistent increase in plasma component administration. However, this trend notably reversed in the most recent National Blood Collection and Utilization Survey [14].

As with all blood products, transfusion of plasma is not without risk. As such, clinical decisions relating to plasma transfusion should carefully weigh the risk-to-benefit ratio. In 2011, the National Blood Collection and Utilization Survey reported that almost four million units of plasma were transfused in the United States alone [14]. While guidelines exist for the use of plasma in specific care scenarios, indications are limited and equipoise remains in many clinical contexts [28, 61, 62, 64]. Worryingly, despite a lack of evidence, approximately 30 % of transfusions are believed to be administered outside of published guidelines [66, 67]. Nationally, there are inconsistencies in plasma transfusion practice, with the most commonly cited rationale being efforts to correct abnormal pre-procedural international normalized ratios (INR) in non-bleeding patients [13]. This rationale is based on the assumption that an elevated INR correlates with increased bleeding, and that plasma transfusion will normalize the INR and prevent bleeding complications. Importantly, however, this indication is generally not supported by current evidence and is not endorsed as an indication for plasma transfusion by most society guidelines [61, 68]. When considering the available evidence suggesting a poor correlation between mild-to-moderate INR abnormalities and peri-procedural bleeding complications [69], attempts to correct INR through plasma transfusion appear to be ineffective and unnecessarily expose patients to the risks associated with plasma administration.

In the setting of active bleeding, it is perhaps equally worrisome that plasma transfusion is often delayed and/or inadequately dosed, thus propagating coagulopathy, bleeding, and the need for further massive transfusion [70]. In the absence of massive hemorrhage, current guidelines suggest a typical dose of plasma around 10–15 mL/kg predicted body weight [63]. This dose is expected to raise clotting factor levels by 25–30 % [62]. Thus the average 70 kg patient would require approximately 1 L of plasma to reverse coagulopathy, assuming ongoing factor losses had ceased. Recent efforts suggest that these dosing regimens may be inadequate, noting suboptimal correction of actual in vivo coagulation factor content [71]. In an investigation specifically addressing this issue, upwards of 30 mL/kg of plasma were needed to reliably increase coagulation factor content to desired levels [71]. The issue of under-dosing plasma replacement has come to the forefront in the setting of massive transfusion where far more liberal plasma transfusion practices (e.g. 1 unit of plasma for every unit of RBC administered) are now frequently endorsed.

Indications

Presently, a number of clinical practice guidelines for plasma transfusion exist [28, 61, 62, 64]. When collating all available data, current recommendations include:

1. Replacement of inherited single coagulation factor deficiencies for which no virus-safe fractionated product exists [61]
2. Replacement of specific protein deficiencies [72]
3. Replacement of multiple coagulation factor deficiencies with associated severe bleeding, massive transfusion, and/or disseminated intravascular coagulation [61, 70]
4. As a component of plasma exchange in patients with thrombotic thrombocytopenic purpura [61]
5. Urgent reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrates are not available [61]

The use of plasma for the prevention of bleeding in patients with liver disease, deranged coagulation parameters and planned invasive procedures remain a matter of debate. While its utility in this setting was originally endorsed to prevent bleeding, more recently numerous studies have documented that INR poorly predicts bleeding risk in these patients and that response to plasma is both unpredictable and short-lived [73]. Opponents of this indication cite concerns regarding both the level of true underlying coagulopathy (as inferred by an elevated INR) and plasma's efficacy in this population [74]. This stems from our knowledge regarding the inherent differences in clotting factor levels and anticoagulant proteins as compared to patients without liver disease. As such, this practice is not strongly supported (Grade C recommendation, Level IV evidence) [61]. This topic is discussed below—efficacy. The most frequent indications for plasma administration encountered in the surgical ICU are for the replacement of multiple coagulation factor deficiencies with associated severe bleeding and for patients with disseminated intravascular coagulation [61].

Importantly, specific contraindications to plasma transfusion include the presence of an isolated coagulation factor deficit when factor concentrates can be used, reversal of oral anticoagulation therapy in the absence of bleeding, and treatment of hypovolemia. In the setting of oral vitamin K antagonist therapy, if there is no active bleeding or requirement for emergent high-risk surgery, vitamin K should be a first-line therapy. When active bleeding co-exists, therapy should include use of prothrombin complex concentrates (PCCs). These agents are felt to carry a lower risk of transfusion-associated pulmonary and infectious complications, while also providing more rapid and predictable replacement of the Vitamin K-dependent coagulation factors.

Efficacy

As with the transfusion of RBCs, early and liberal plasma administration appears warranted in patients with massive hemorrhage [70, 75]. While there is some discrepancy in the literature regarding the optimal ratio of plasma to RBCs [76], a systematic review by Roback and colleagues in 2010 found that overall, use of a plasma:RBC ratio greater than 1:3 was associated with a reduction in mortality and multiorgan failure [64]. However, a concern with the majority of the observational studies that have suggested benefit with liberal plasma transfusion is the issue of survival bias [76, 77]. Moreover, a growing body of evidence has linked liberal plasma transfusion to adverse outcomes in those who do not ultimately experience massive hemorrhage [76–80]. In light of these concerns, we endorse the need for more definitive clinical trials to determine the optimal strategy for coagulation factor replacement in this setting. The recently published PROPPR trial noted improved hemostasis with more liberal plasma administration (1 unit of plasma for every unit of RBC), but the primary outcomes of mortality at 24 h and 90 days did not improve with these more liberal approaches to plasma administration).

Data relating to the efficacy of plasma transfusion in non-bleeding patients have been gaining attention in recent years. Indeed, a number of reports have concluded that modest abnormalities in coagulation tests, such as INR, do not correlate well with surgical blood loss or the need for subsequent RBC transfusions [81, 82]. Furthermore, the impact of plasma transfusion on outcomes is uncertain in the absence of bleeding. In part, these findings can be explained by the nonlinear relationship between INR and plasma coagulation factor levels [13, 83]. Since thrombus formation is directly proportionate to in vivo coagulation factor concentrations and not the INR, it is unsurprising that bleeding and hemostasis are therefore not well correlated with the latter. Indeed, though plasma transfusion will often correct a markedly elevated INR, the associated change in actual coagulation factor concentrations is frequently insufficient for adequate hemostasis [84]. In contrast, evidence suggests that it is often not possible to correct more modest elevations in the INR (e.g. INR 1.1–1.85), since the INR for a unit of plasma itself often falls above the normal range [66, 69].

It is generally accepted that most patients can continue to generate thrombus so long as coagulation factor activity levels exceed ~30 % [62]. Therefore, at an INR level of ≤1.6—corresponding to a factor level of at least 30 % in most patients [82, 85]—it is unlikely that transfusion of additional plasma will significantly alter a patient's ability to form thrombus. An important exception to this relates to patients with liver disease. In this setting, it has previously been demonstrated that INR values do not represent the same degree of clotting factor deficiency as is seen with patients on Warfarin for any given INR. In fact, patients with liver disease will typically have lower levels of factor VII [86]. In addition, these patients are also typically deficient in the anticoagulant protein "Protein C" [74], therefore INR values and associated bleeding risk must be interpreted with caution in this context. Of note, a landmark study by Spector and colleagues demonstrated that transfusion of additional plasma in attempt to correct these patients' INRs typically only resulted in a temporary correction [87]. For this reason, and in view of the potential risks, the use of FFP in patients with liver disease remains controversial.

While a number of observational studies have raised concern regarding the efficacy of plasma transfusion, no randomized trials have evaluated liberal versus conservative plasma transfusion strategies as has been seen with RBCs. This will be an important future step in refining current transfusion practice. Meanwhile, others have purported the use of thromboelastography (TEG) and thromboelastometry

(ROTEM) as tools to better evaluate individual thrombus forming ability in a timely point-of-care manner [88]. Although application of these relatively new technologies is not yet widespread, several investigators have concluded that their use provides a more timely and specific assessment of coagulation status with reduced subsequent blood product exposure [89–91]. Furthermore, a retrospective before-and-after study by Görlinger et al. noted that coagulation assessment in cardiac surgical patients with ROTEM resulted in increased use of specific factor concentrates and an overall reduction in blood product transfusions without any associated increase in morbidity or mortality [89].

Platelet Transfusion

Platelets are obtained either from whole blood donation or via direct apheresis and can be safely stored at room temperature for up to 5 days from collection [92]. In the clinical setting, they are transfused when platelet count is reduced or function is abnormal in order to facilitate hemostasis (therapeutic) or to prevent hemorrhage (prophylactic). Here, we discuss the temporal trends in clinical practice, indications, and efficacy for platelet transfusion.

Past and Current Practice

Thrombocytopenia is common in the critically ill, with ~40 % of critically ill patients having platelet counts below 150×10^9/L [5]. The etiology of thrombocytopenia is most often multifactorial, but in the surgical ICU most cases relate to hemodilution or sepsis [5, 93]. In addition, factors such as bone marrow suppression, liver disease, medication side-effects, bleeding, and consumptive disorders such as disseminated intravascular coagulation (DIC) are frequently encountered in these populations [5]. Although platelet transfusion itself is not without risk, previous observational studies have demonstrated thrombocytopenia to be associated with major bleeding events, increased hospital and ICU lengths of stay, and mortality [94]. Unfortunately, few randomized trials have investigated platelet transfusion thresholds and their association with patient-important outcomes. At present, prophylactic platelet transfusions for specific platelet count thresholds (e.g. $<10 \times 10^9$/L) in critically ill patients continue to be supported in the literature [95–97]. However, the literature also suggests that platelets continue to be given outside of these recommendations [98]. In 2007, Cameron and colleagues noted that non-cardiac surgical patients at their institution were typically transfused platelets outside of existing guidelines, with a mean platelet count of 85×10^9/L [99]. Perhaps more concerning is the increased awareness of the risks associated with platelet transfusion in the critically ill [5, 100].

Indications

In the presence of thrombocytopenia or abnormal platelet function with clinically significant active bleeding, platelet transfusion should be considered with a target platelet count of $\geq 50 \times 10^9$/L [101–103]. Prior to undergoing invasive procedures, platelet transfusion may also be considered for patients with a platelet count $< 50 \times 10^9$/L ($<100 \times 10^9$/L in neurosurgical/ophthalmologic procedures) [104]. Evidence suggests that bleeding due to thrombocytopenia is minimal above this threshold, provided platelets are functional [105]. In the situation whereby platelet count is normal but suspicion for platelet dysfunction exists (e.g. antiplatelet therapies or congenital disorders), platelet transfusion may also be appropriate when significant bleeding is present. An anticipated platelet response in a 70 kg adult would be an increase of $5–10 \times 10^9$/L per unit transfused, thus guiding appropriate dosing [106].

In the absence of clinical bleeding, evidence-based guidelines suggest the administration of platelet components for platelet counts $< 10 \times 10^9$/L to prevent spontaneous hemorrhage (20×10^9/L when fever, sepsis, heparin therapy, DIC, or other conditions leading to increased platelet consumption coexist). These indications are mostly supported by a number of studies evaluating transfusion strategies in patients with leukemia and bone marrow failure [55–57].

Efficacy

In most patients, platelet transfusion will produce a predictable rise in platelet count. Serial transfusions may produce a state of platelet refractoriness, however this is most commonly seen in patients with hematologic malignancies [106, 107]. With regard to achieving the desired end effect of hemostasis or hemorrhage prevention, the majority of evidence to date focuses on platelet transfusion in the setting of hematologic malignancies. In these patients, prophylactic platelet transfusion has been shown to be beneficial at a threshold of $< 10 \times 10^9$/L [107] with reduced rates of non-fatal severe hemorrhage [95, 96]. However, the generalizability of these findings to the surgical ICU patient population remains unclear. Indeed, there is remarkably scant data to guide platelet administration in this setting. Nonetheless, in the absence of massive hemorrhage, it is generally accepted that transfusing platelets when counts are $>50 \times 10^9$/L is not supported by current evidence. The exception to this is in the setting of massive transfusion, when application of the 1:1:1 ratio of RBCs, plasma, and platelets has been purported primarily following investigations in military populations which have noted improved survival [108–110]. The advantages and disadvantages of this approach are discussed in more detail below under the section "Massive Transfusion."

In summary, while evidence for prophylactic and therapeutic platelet transfusion is strong in the setting of hematologic malignancies and bone marrow failure, clinical equipoise remains with regard to the optimal transfusion trigger in critically ill surgical patients. Much of the current data are based upon expert opinion. As such it is anticipated that ongoing clinical trials, the platelet dose (PLADO), and prospective randomized optimal platelet and plasma ratios (PROPPR) trials will serve to better define optimal platelet transfusion practice.

Cryoprecipitate Transfusion

Cryoprecipitate is fractionated from plasma donation and contains fibrinogen, von Willebrand factor, factors VIII and XIII, and fibronectin [111]. Each bag of cryoprecipitate contains approximately 350 mg of fibrinogen, with approximately 2100 mg per pool (six donor units). Each pool of cryoprecipitate results in approximately a 45 mg/dL increase in serum fibrinogen levels [111]. Cryoprecipitate is stored frozen and must be transfused within 6 h of thawing. In the clinical setting, cryoprecipitate is primarily used for acquired hypofibrinogenemia. Here, we discuss the temporal trends in clinical practice, indications, and efficacy for platelet transfusion.

Indications

Historically, cryoprecipitate has been used to treat hypofibrinogenemia, along with other conditions such as von Willebrand's disease, hemophilia, and factor XIII deficiency [111]. However, with the widespread availability of specific factor concentrates, desmopressin and other such targeted therapies, use of cryoprecipitate for these unique conditions is now rarely seen. Current literature endorses the use of cryoprecipitate for bleeding associated with either congenital or acquired hypofibrinogenemia or dysfibrinogenemia [111].

Without detailed evidence-based recommendations for cryoprecipitate use, many physicians continue to transfuse outside of these guidelines [112]. As with other blood products, concern remains that this practice is exposing patients to unnecessary potential harms without the equivalent reciprocal benefit.

Efficacy

The transfusion of cryoprecipitate has a clear theoretical benefit in treating patients with hypofibrinogenemia. While some inconsistencies exist [113, 114], a large number of early human and animal studies demonstrated multiple benefits including decreased hemorrhage and increased survival [115, 116]. More recently, Idris and colleagues have demonstrated that cryoprecipitate transfusion results in the expected rise in serum fibrinogen levels, with this benefit appearing to be more pronounced in patients with acute versus chronic deficiencies [117]. Although this study did not directly evaluate the impact of cryoprecipitate transfusion on bleeding events, Lee and colleagues went on to study the impact on fibrin-based clot formation in cardiac surgical patients [118]. This study demonstrated cryoprecipitate transfusion both increased serum fibrinogen and the quality of fibrin-based clot formation assessed using thromboelastometry. In the same year, a large multicenter prospective observational study evaluated cryoprecipitate use in trauma patients [119]. These authors concluded that transfusion practice was highly variable between institutions, but that cryoprecipitate transfusion was not associated with in-hospital mortality. Furthermore, cryoprecipitate was recently demonstrated to independently add to survival benefit in war casualties with hemorrhagic shock [120]. Despite this stepwise generation of promising data relating to cryoprecipitate use in recent years, recent literature puts a greater focus on the role of fibrinogen and prothrombin complex concentrates in these scenarios [121–123]. This evolving topic is discussed in greater detail below under the heading massive transfusion. Importantly, randomized trials are necessary to better determine the clinical efficacy and optimal dose for cryoprecipitate transfusion.

Risks of Transfusion

As with all medical therapies, blood transfusion is not without risk. Indeed, it was the risk of transfusion-transmitted infections that prompted some of the earliest investigations into blood product safety, efficacy, and management [19]. Subsequently, due to advances in our understanding of adverse infectious events, numerous changes in donor screening, product testing, and transfusion practice have taken place [124]. Collectively, these efforts have dramatically reduced the risk of traditionally recognized complications such as the vertical transmission of infectious disease [12]. However, as scrutiny over the potential adverse effects of blood product administration rose, additional complications with substantial impact on patient-important outcomes have come to light. Here we discuss the risks of blood product transfusion, focusing on the acute events commonly encountered in the surgical intensive care unit.

Transfusion-Related Acute Lung Injury

Though the syndrome of Transfusion-Related Acute Lung Injury (TRALI) had been recognized since the mid-1980s [125], formal definitions for this serious complication remained absent for decades. In 2004, content experts from around the world convened and proposed what are now the

Table 35.1 Transfusion-Related Acute Lung Injury (TRALI) and possible TRALI definitions from the 2004 Canadian Consensus Statement

1. TRALI	
(a) ALI	
• Acute onset • Hypoxemia (PaO_2:$FiO_2 \leq 300$ mmHg or $SpO_2 < 90$ % on room air [or other clinical evidence of hypoxemia]) • Bilateral infiltrates on frontal chest radiograph • No evidence of left atrial hypertension (i.e. circulatory overload) as the sole explanation for the critical findings	
(b) No preexisting ALI before transfusion	
(c) Onset during or within 6 h of transfusion	
(d) No temporal relationship to an alternative risk factor for ALI	
2. Possible TRALI	
(a) ALI	
(b) No preexisting ALI before transfusion	
(c) During or within 6 h of transfusion	
(d) A clear temporal relationship with an alternative risk factor for ALI	

ALI acute lung injury, *FiO2* fraction of inspired oxygen, *PaO2* partial pressure of arterial oxygen, *SpO2* oxygen saturation
Adapted with permission from John Wiley and Sons: Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion. 2004;44(12):1774–89 [126]

most widely accepted criteria for TRALI [126]. These criteria define TRALI as the new onset of acute lung injury (ALI) within 6 h of blood product transfusion in the absence of additional, temporally related ALI risk factors (Table 35.1) [126]. In the presence of alternate ALI risk factors, patients are classified as having "possible TRALI." TRALI's true incidence has been a matter of debate over recent years with estimates ranging from less than 1 % in the broad population of all hospitalized patients, up to 8.2 % in certain high-risk surgical populations and the critically ill [125, 127–131]. In truth, the incidence of "clean" TRALI cases (no additional risk factors for ALI) is likely at the lower end of this spectrum, while the composite of TRALI/possible TRALI is likely best represented by the upper ranges. Regardless, a growing body of evidence suggests we frequently underestimate the rate of TRALI due to a number of flaws in case identification and reporting [132–135]. Notably, TRALI is consistently noted to be the leading cause of transfusion-related death reported to the FDA [12].

Although all blood components carry the potential for precipitating a TRALI reaction, high plasma volume components such as plasma (e.g. FFP, FP24, thawed plasma) and apheresis platelets carry the greatest risk per component transfused [136, 137], occurring with five to six times the frequency when compared with isolated RBC transfusion [138]. Despite this observation, red blood cells account for the largest number of TRALI cases due to the greater overall number of RBC units transfused. Of note, recent changes in the procurement of transfusable plasma components (e.g. male-only donor policies, HLA antibody testing) have greatly reduced the rate of plasma-associated TRALI [139–143]. The notable exception to this trend is group AB plasma which is still occasionally obtained from multiparous female donors [144].

In terms of the mechanism(s) underlying TRALI, a leading theory remains the "two-hit hypothesis" in which a susceptible host (susceptibility factors may include infection, shock, surgical insult, or critical illness) is primed for a TRALI reaction. Thereafter, the passive delivery of donor antibodies in the blood component interact with cognate recipient leukocyte antigens—the "second hit"—activating sensitized recipient neutrophils, producing an inflammatory reaction within the lung, and leading to inflammatory lung edema (acute respiratory distress syndrome). As multiparous female donors are at risk of developing anti-leukocyte antibodies [145]; numerous countries (including the US) have removed these individuals from the transfusable plasma donor pool. As noted above, these practices have been associated with significant reductions in the rate of plasma-associated TRALI. Of note, a significant number of TRALI cases have occurred in the absence of detectable donor antibody or cognate recipient antigen [146, 147]. Such cases have led to the proposition of an alternative "second hit" that is thought most likely to be the result of infusing alternate soluble biologic modifiers (e.g. neutral lipids, cell-free hemoglobin) that are also capable of activating sensitized neutrophils. For more detailed discussion on TRALI mechanisms, we note a number of excellent recent reviews [148–150]. Unfortunately, there are currently no effective therapies for the treatment of TRALI and therefore management remains primarily supportive with oxygen supplementation and ventilator support when needed [151]. As with lung injury that occurs in the setting of alternative major risk factors for ARDS, low-tidal volume ventilation is recommended for patients with TRALI who require invasive ventilatory support.

Transfusion-Associated Circulatory Overload

Though first described over 70 years ago [152], consensus definitions for transfusion-associated circulatory overload (TACO) have only recently been described. At present, the criteria outlined by the Centers for Disease Control National Healthcare Safety Network (CDC-NHSN) are the most broadly endorsed for defining TACO [153]. Specifically, the CDC-NHSN criteria require the new onset or exacerbation of 3 or more of the following within 6 h of transfusion end [153]:

- Acute Respiratory Distress (cough, dyspnea, orthopnea)
- Elevated Brain Natriuretic Peptide (BNP)
- Elevated Central Venous Pressure (CVP)
- Evidence of Left Heart Failure
- Evidence of Positive Fluid Balance
- Radiographic Evidence of Pulmonary Edema

Unfortunately, many of the elements outlined above are subjective and non-specific, thereby limiting their utility when attempting to make a diagnosis of TACO. Characteristically, TACO manifests with acute onset respiratory distress, tachycardia, and hypertension following blood product administration [154]. However, the criteria outlined above do not formally require respiratory distress in order to achieve the diagnosis, perhaps another significant limitation of the present definition.

The reported incidence of TACO varies quite substantially ranging from less than 1 % to upwards of 11 % [155–157]. The historical absence of a consensus definition for TACO, challenges with case adjudication, differing case screening methodologies (active versus passive), and our incomplete understanding of its pathophysiology all contribute to these highly variable incidence rates and likely underestimate the true burden of TACO. Importantly, data from prior reports do suggest that TACO is more prevalent in the critically ill. Frequently described as a less severe transfusion-related complication, it should be noted that Transfusion-Associated Circulatory Overload (TACO) is the second leading cause of transfusion-related death, accounting for 34 % of the transfusion-related fatalities reported to the FDA in 2013 [12] and with a case fatality estimated to range between 5 % and 15 % [12, 158].

Although TACO has been documented to occur with all blood product components, observational data suggest potentially greater risk with plasma transfusion [155]. While unproven, this association may relate to the large volume of plasma that is often transfused when attempting to reverse the effects of anticoagulant therapies. Mechanistically, TACO is believed primarily the result of fluid overload with resultant hydrostatic pulmonary edema [159]. Supporting data include identified associations between volume of blood product transfused, rate of transfusion, overall volume status, and the presence of cardiovascular or renal disease [155, 160–162]. Additional reported risk factors include extremes of age, severe chronic anemia, and transfusion in a setting of hemorrhagic shock [155, 161–163]. Notably, a number of studies have identified cases of TACO occurring after low-volume or even single unit transfusion [164]. This, in concert with the typical hypertensive response associated with TACO [165], has led to the proposition of additional alternate mechanisms of TACO, including microcirculatory nitric oxide trapping [166] as well as leukocyte and platelet-derived inflammatory mediators [167].

In terms of TACO prevention, suggested measures include the avoidance of unnecessary transfusions, reduced rates of necessary transfusions, and consideration of prophylactic diuretic administration [159]. For established TACO, treatment is generally supportive with oxygen supplementation and ventilatory support as needed. In light of the frequent co-existence of cardiovascular disease, non-invasive ventilatory strategies should be considered early in the course of syndrome onset with the hopes of avoiding the need for invasive mechanical ventilation. Should the hemodynamic status allow, diuretic therapy can be considered with the hopes of mitigating excess intravascular volume and attenuating the patient's pulmonary edema [159]. Of note, though assisted diuresis may have theoretical benefit, this intervention has never been rigorously tested to confirm a beneficial effect.

Acute and Delayed Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions (AHTR) typically occur as a result of clerical error at some point in the process beginning with collection from the donor and ending with administration of the implicated blood product to the transfusion recipient [168]. The resulting administration of an ABO incompatible RBC unit results in the strong binding of complement, intravascular hemolysis and activation of the coagulation cascade [168, 169]. Collectively this results in disseminated intravascular coagulation, bleeding, hypotension, and organ failure. Fortunately, improvements in the systems and processes within our hospitals as well as the policies surrounding blood product administration have significantly reduced the frequency of AHTRs. However, when they do occur, consequences for patients can be devastating with 16 % of transfusion-related fatalities reported to the FDA in 2013 being attributed to AHTRs [12]. Adverse reactions can be seen with non-ABO donor RBC antigens as well. Often, these interactions result in delayed hemolytic transfusion reactions. The presence of anti-Kidd antibodies in the transfusion recipient provides an example. Similar reactions have also been noted with the Kell, Duffy, and Rh RBC antigen families [168, 170]. Although AHTR are most frequently observed with RBC transfusion, similar reactions can be seen with out-of-group platelet transfusion if the transfusate contains a sufficient amount of incompatible plasma.

Allergic and Anaphylactic Reactions

Although allergic reactions can occur with all blood product types, they are more frequent with high-plasma volume components. The frequency of allergic reactions varies by product ranging from as low as 0.03 % with RBCs to as high as 6 % with platelets [171]. Anaphylaxis is extremely rare; occurring at a rate of between 1 in 20,000 to 1 in 47,000 per product transfused [171], accounting for 5 % of transfusion-related fatalities between 2009 and 2013 [12]. Reactions can range from mild to life-threatening, presenting with signs/symptoms ranging from pruritis, erythema and urticarial skin rashes to angioedema, wheezing, airway obstruction, and

shock. In patients with IgA deficiency or anti-IgA, risk of anaphylaxis is increased to around 1 in 1200 transfusions [171]. For this reason, such patients are generally provided washed RBC and platelet units as well as plasma procured from IgA-deficient donors. The management of allergic reactions includes cessation of the transfusion and administration of antihistamines. In severe reactions, epinephrine, glucocorticoids, and other supportive measures including oxygen supplementation, endotracheal intubation with mechanical ventilation, fluid resuscitation, and vasoactive support may be required [171].

Febrile

Febrile transfusion reactions are the most common acute transfusion reaction, occurring in approximately 1 % of all transfusions and accounting for between half and three-quarters of all reported adverse transfusion events [172]. The clinical presentation is that of a rise in temperature exceeding 1 °C in the absence of hemolysis and other more likely causes of fever. Febrile reactions typically present within 4 h of transfusion and manifestations are generally mild in nature. Occasionally, patients may experience more marked symptoms with rigors and chills. Indeed this may be the only presenting complaint in a patient treated with pre-transfusion antipyretics, although evidence for this intervention remains a matter of debate [173]. Febrile reactions can be seen with any WBC-containing blood product, but are most commonly observed with RBC and platelet transfusions. The etiology of febrile transfusion reactions is believed related to cytokines released from WBCs during apoptosis. Notably, the introduction of leukoreduction strategies has led to a significant reduction in the frequency of febrile reactions [172, 174]. The cornerstones of managing a febrile transfusion reaction include discontinuation of the transfusion episode and administration of antipyretics.

Transfusion-Related Immune Modulation

Though incompletely understood, the potential impact of transfusion on recipient immune function has been long recognized. Indeed, prior to the routine use of immunosuppressant medications, this side effect of transfusion was used to the advantage of patients undergoing solid organ and hematopoietic stem cell transplantation [175, 176]. While the specific mechanisms underlying this potential effect remain incompletely defined, available literature supports a variety of transfusion-related immunomodulatory effects including suppression of cytotoxic cell and monocyte activity, release of immunosuppressive prostaglandins, inhibition of interleukin-2 (IL-2) production, and increased suppressor T-cell activity [177]. Concerning for surgical and critically ill patients, multiple lines of evidence have associated transfusion episodes with increased risk of nosocomial infections [8, 37]. Furthermore, others have expressed concern relating to cancer recurrence [177]. Notably, the introduction of universal leukoreduction for RBC units appears to have attenuated, although not completely eliminated, the association between RBC transfusion and numerous adverse outcomes including infectious complications [178]. Ongoing research efforts will continue to refine our understanding of the mechanisms and clinical impact of TRIM.

Additional Risk Factors Associated with Transfusion

Hypotensive transfusion reactions are infrequent and the incidence is poorly characterized [179]. Their manifestations—characteristically a rapid decrease in systolic blood pressure of 30–80 mmHg within 15 min of transfusion—are often mild and readily remedied with transfusion cessation and simple supportive measures. Patients undergoing concomitant hemodialysis, bedside leukoreduction, and those using angiotensin-converting enzyme inhibitors [180] are believed to be at increased risk of hypotensive reactions.

Transfusion-transmitted infections (TTI) have been a recognized risk of transfusion for decades. Modern blood management ensures all products undergo extensive and mandatory pathogen screening [124]. These measures have substantially reduced, though not completely eliminated, the risk of TTIs—which are a particular concern for products stored at room temperature, such as platelets. Indeed, septic transfusions with bacterially contaminated platelets are thought to occur in 10.6 per million transfusions [181]. Presentation typically consists of fever, rigors, tachycardia, hypotension, and other features of bacteremia. Management of suspected TTI includes transfusion cessation, collection of recipient blood cultures, and initiation of broad spectrum antibiotics. The residual product should be retained for further testing by the transfusion laboratory and to enable quarantining of additional products collected from the implicated donor [182].

Transfusion-associated graft versus host disease (TA-GVHD) is an uncommon but universally fatal transfusion risk that occurs upon the introduction of viable donor lymphocytes into a susceptible recipient. TA-GVHD may be caused by whole blood, RBCs, platelets, granulocytes, and fresh (but not frozen) plasma with immunosuppressed patients being most at risk. In rare circumstances, inadvertent human leukocyte antigen matching of the donor and recipient may also trigger this reaction. Presenting features include fever, erythematous rash, gastrointestinal upset, liver dysfunction, and ultimately a profound pancytopenia. Death in these patients is typically secondary to sepsis and multiorgan failure [183]. In the surgical critically ill, a milder variant of

TA-GVHD known as "postoperative erythroderma" may present as a transient widespread erythema without the subsequent development of fully established TA-GVHD [184]. Efforts to reduce the risk of TA-GVHD in high-risk populations include the use of blood product irradiation and other pathogen inactivation technologies [185].

Massive Transfusion

Hemorrhagic shock remains a leading cause of trauma-related death, second only to devastating neurologic injury [186]. Appropriate and timely hematologic management of victims of major trauma has been identified as paramount for preventing the lethal triad of coagulopathy, acidosis, and hypothermia [187]. Indeed, failure to adequately prevent or manage coagulopathy has been associated with adverse patient outcomes, including increased mortality [188]. These findings have stimulated interest in more aggressive transfusion therapies in those experiencing trauma-associated massive hemorrhage.

Although the term "massive transfusion" has been variably defined, it generally encompasses the rapid transfusion of a large volume of blood products for the treatment of uncontrolled hemorrhage. The most broadly endorsed definitions of massive transfusion in adults include:

1. Transfusion of ≥10 units RBCs (approximately total adult blood volume) within 24 h [189]
2. Transfusion of four units RBCs within 1 h and anticipated need for ongoing blood product support [190]
3. Replacement of 50 % of the estimated total blood volume with blood products within 3 h [191]

In recent years, our understanding of the pathophysiology of massive hemorrhage has improved substantially and identification of the acute coagulopathy associated with trauma—known as Trauma-Induced Coagulopathy (TIC)—has resulted in several changes in clinical practice. TIC is common (25–40 % of major trauma cases) and frequently presents very early following the trauma event, often prior to the initiation of significant resuscitation [188, 192]. TIC appears to occur when thrombin generation resulting from tissue injury co-occurs with shock. This combination leads to activation of the protein C system with a resultant hypocoaguable state, thus contributing to persistent bleeding [192–194]. Additionally, dilution of both coagulation factor content and platelets resulting from large-volume resuscitation that is devoid of these blood constituents is believed to play a role in the development and propagation of TIC as well.

Cognizant of the frequent occurrence of TIC as well as its association with adverse patient outcomes, enthusiasm for more aggressive and early plasma and platelet transfusion has increased dramatically [108, 109, 195]. Due to the historic absence of rapid and reliable clinical tests that might guide specific platelet and coagulation factor replacement strategies, identification of optimal ratios of RBCs to plasma and platelets has been the focus of investigation. To this end, early military data first purported the use of a 1:1:1 ratio (RBC:plasma:platelet transfusion) theorizing that its composition more closely resembled whole blood and may prevent the occurrence of TIC [110]. Multiple subsequent studies, primarily in military populations, have noted improved survival with these massive transfusion protocols (MTPs) [108, 109, 196]. Importantly, however, concerns related to issues such as survival bias [76, 77, 197, 198], increased rates of adverse outcomes in those who do not ultimately require massive transfusion [199–201], as well as the unclear generalizability of such findings to civilian trauma populations as well as non-trauma massive hemorrhage scenarios attenuate enthusiasm for the broad implementation of these MTPs without further study. Of note, the prospective randomized optimal platelet and plasma ratio (PROPPR) trial is currently underway to further evaluate the optimal ratio to be used in civilian hospitals.

More recently, emerging data have highlighted the importance of fibrinogen replacement in massive bleeding [122]. This follows the observation that hypofibrinogenemia was independently associated with the occurrence and severity of hemorrhage in several surgical populations including obstetric [202] and cardiac surgical patients [203]. Subsequently, a number of case reports and randomized trials have corroborated these results in various surgical populations. Specifically, fibrinogen transfusion was noted to produce rapid correction of laboratory parameters of coagulation [204], cessation of hemorrhage [204], improved clot firmness [205], and reduced perioperative allogeneic transfusion requirements [123, 206] when compared to standard care. Moreover, these studies suggest fibrinogen concentrates have a good safety profile. Indeed, no thromboembolic events were directly attributed to the use of fibrinogen, and these products likely offer a reduced incidence of viral and prion transmission when compared to cryoprecipitate [207].

Recently, there has been increased interest in the use of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) as tools to provide a more accurate, and specific, near real-time point-of-care assessment of coagulation status. Aside from the relative speed of these tests when compared to traditional laboratory measurements, proposed advantages include the fact that whole blood is tested as opposed to centrifuged blood with whole cells removed. Importantly this ensures that the overall assessment of coagulation accounts for clotting factors, platelets, erythrocytes, and other tissue factor bearing cells. It is felt that this may provide a more accurate in vitro assessment of the in vivo coagulation environment [91]. Emerging literature has described successful TEG/ROTEM-targeted administration of PCCs and fibrinogen in bleeding surgical critically ill patients [89, 90, 208].

Indeed, these tests may support optimal coagulation factor resuscitation by providing a more accurate assessment of specific coagulation defect(s) present, and by avoiding delays associated with traditional laboratory testing such as prothrombin time and activated partial thromboplastin time. However, although promising, additional studies are still needed to better understand the value and impact of their use in heterogeneous clinical contexts.

Blood Product Alternatives

Correction of deranged coagulation resulting from nutritional deficiencies or specific Vitamin K antagonist therapies (e.g. Warfarin) may be aided by the administration of Vitamin K. Indeed, Vitamin K replacement is recommended, in concert with additional therapies such as plasma transfusion or PCC, in all patients with major acute bleeding in the setting of Vitamin K antagonist therapy unless specific contraindications are present [209]. It should be noted that time to onset will be delayed several hours after administration and will vary depending upon the route of delivery. For urgent or emergent reversal, intravenous Vitamin K is recommended and the clinician should be aware of the potential for rare, but severe anaphylactic reactions with intravenous Vitamin K therapy [61, 210].

Prothrombin complex concentrates (PCCs) contain variable amounts of the vitamin K-dependent clotting factors II, VII, IX, and X. Those with limited quantities of factor VII are termed three-factor PCCs and those with more substantial quantities are termed four-factor PCCs [211]. In addition, variable amounts of Proteins C, S, Z as well as Antithrombin III and heparin may be present (Table 35.2) [212]. These products are derived from human plasma but have clotting factor concentrations 25 times that of normal plasma [213]. Prior to storage, these concentrates undergo extensive viral and leukoreduction processing. While the risk of transfusion-transmitted viral infections as well as both TRALI and TACO are essentially absent, appropriate restrictions must be applied in patients with a history of heparin-induced thrombocytopenia (HIT) [211].

The primary indication for PCCs has historically been hemophilia with associated coagulation factor inhibitors [214]. However, there is extensive and growing experience with the use of these products as alternatives to plasma transfusion for both oral anticoagulant reversal in patients with acute major bleeding as well as in the setting of massive transfusion [122, 215, 216]. Kcentra (CLS Behring), a four-factor PCC, recently received approval for use in the former circumstance by the United States Food and Drug Administration and PCCs in general have been endorsed by the American College of Chest Physicians for use in the management of bleeding associated with Vitamin K antagonist therapy for some time [209]. Early data suggest that PCCs may have a role in correcting the anticoagulant effects associated with direct thrombin and factor Xa inhibitors as well [216–218], but additional study is needed to better understand their role in this setting.

Data relating to the pharmacokinetics to PCCs are limited and the half-lives of individual factors are variable; as such, dosing strategies have proven challenging. A number of studies have compared FFP and PCCs at a dose of 25–50 IU/kg and found that PCCs produce a more rapid and complete correction of the INR [219–221]. To date, a single prospective randomized controlled trial has been undertaken to evaluate PCCs comparative safety and efficacy [222]. In this study, Sarode et al. report non-inferiority of four-factor PCCs compared to FFP for the urgent reversal of vitamin K antagonists in non-surgical patients [222]. Additional favorable features of PCCs include the low volume infusion required to adequately replace coagulation factor content, thereby avoiding the risk of volume overload often encountered with FFP [222]. PCCs are also typically more readily available as their storage at room temperature negates the need for thawing and warming and they can be safely infused at a faster rate [223].

Table 35.2 Constituents of commercial prothrombin complex concentrates

	Factor II (U/mL)	Factor VII (U/mL)	Factor IX (U/mL)	Factor X (U/mL)	Protein C (U/mL)	Protein S (U/mL)	Protein Z (U/mL)	AT III (U/mL)	Heparin (U/mL)
Beriplex (CSL Behring)	20–48	25-Oct	20–31	22–60	15–45	13–26	*	0.2–1.5	0.4–2.0
Octaplex (Octapharma)	Nov-38	24-Sep	25	18–30	31-Jul	Jul-32	*	*	*
Profilnine (Grifols)	Present	Present	Present	Present	*	*	*	*	0
Bebulin (Baxter)	Present	Present (low)	Present	Present	*	*	*	*	0.15 U/U factor IX
FIEBA (Baxter)	Present non-activated	Present activated	500, 1000 or 2500 U/vial non-activated	Present non-activated	*	*	*	*	0

AT III antithrombin III, * not disclosed on packaging label

Modified with permission from Wolters Kluwer Health: Levy JH, Tanaka KA, Dietrich W. Preoperative hemostatic management of patients treated with vitamin K antagonists. Anesthesiology. 2008;109(5):918–26 [212]

PCC administration is of course not without risk and reported adverse events include allergic reactions, HIT, and thromboembolic events [211, 215]. Indeed, the latter is the primary concern precluding the widespread use of PCCs for urgent reversal of oral anticoagulation therapy. However, uncertainty remains with regard to whether the few documented thromboembolic events noted in prior studies truly related to PCC use versus patients underlying risk factors. While this potential risk remains under investigation, available data suggest that PCCs have a relatively good safety profile [224–226].

Similarly, numerous investigators have begun exploring alternate potential applications for recombinant factor VIIa (rFVIIa). Originally developed for the treatment of serious bleeding in hemophilia, rVIIa is commercially available as a lyophilized powder that is stored at 2–25 °C and reconstituted at the time of use with L-histidine in water to achieve an end volume of 7 mL [227]. Novel applications have been in the setting of bleeding in major surgery [228–230] and trauma [231] as well as liver disease [232], obstetric [233], and intracranial [234] hemorrhage. While these observational studies and single-center clinical trials were encouraging, subsequent multicenter clinical trials have failed to reproduce analogous results in all clinical scenarios. Although Gill and colleagues reported a reduced incidence of reoperation for bleeding and RBC transfusion in patients treated with rFVIIa following cardiac surgery [235], Boffard et al. noted that it was only efficacious in the setting of blunt versus penetrating trauma [236]. Similarly, other investigators have described a lack of efficacy in variceal bleeding [237], hepatectomy [238], intracranial hemorrhage [239], and congenital cardiac surgery [240]. In the setting of anticoagulant reversal, results have been equally inconsistent. Importantly, despite the correction in laboratory coagulation parameters seen with rFVIIa, its ability to achieve hemostasis does not necessarily appear to correlate [241, 242]. Perhaps more concerning is their questionable safety profile. Indeed a recent large systematic review concluded that rFVIIa was associated with an increased risk of arterial thromboembolic disease, particularly ACS [243]. Meanwhile others have noted an increase in venous thromboembolic disease [244], and in cardiac surgical patients, incidence of stroke appeared to be increased [245].

Another appealing alternative to plasma in the setting of major hemorrhage is fibrinogen concentrates. These products have been approved in Europe since the 1960s [246], however they have only recently been approved by the United States Food and Drug Administration for congenital afibrinogenemia and hypofibrinogenemia. Data surrounding their use are limited, but suggest they provide efficacious improvements in coagulation parameters and may be life saving in massive hemorrhage, particularly when refractory to other therapies. Indeed fibrinogen concentrates have been shown to reduce surgical bleeding in obstetric [202] and cardiac surgical patients [203] without increasing adverse effects such as thromboembolic complications [207].

Anti-fibrinolytic therapies such as tranexamic acid or aminocaproic acid have shown promise in reducing the need for allogeneic blood products and improving patient-important outcomes in major trauma [247, 248]. Most recently the CRASH-2 trial found that early tranexamic acid administration in trauma patients resulted in both reduced all-cause mortality and reduced mortality due to bleeding, although transfusion requirements were similar in the treatment and placebo groups. Importantly, these investigators did not find any increase in vascular occlusive events in the treatment arm. Furthermore, a number of additional surgical populations have replicated similar results including orthopedics, cardiovascular, liver transplantation, urologic, gynecologic, and obstetric surgery [249]. However, persistent concern over the potential for exaggerated thrombosis has precluded more robust adoption of these strategies. Clearly, this is an area where additional research is needed. Additional specific factor concentrates (e.g. vWF, Factor IX, VIII) and alternative therapeutics (e.g. Desmopressin/Estrogen) also have roles in specific clinical conditions. However, detailed discussion of these various therapeutic options are beyond the scope of this chapter.

Summary

Blood product administration is common in the perioperative setting, particularly in the surgical ICU. A large proportion of these transfusion events occur outside of current evidence-based guidelines and are of unclear clinical benefit. Transfusion-related complications can be life-threatening and are poorly recognized and inconsistently reported. In general, restrictive transfusion practices should be employed in the absence of major acute bleeding. In contrast, the transfusion community has increasingly endorsed the early and liberal use of blood products in the setting of trauma-related hemorrhagic shock. The role for novel therapeutics such as PCCs and fibrinogen concentrates as alternatives to traditional transfusion therapies appears to be expanding, although additional evidence is needed before such strategies are more broadly implemented.

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