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Hemorrhage remains the leading cause of intra-operative deaths and those in the first 24 h. Many cardiovascular and hepatobiliary procedures result in massive hemorrhage and postpartum hemorrhage events in labor and delivery place the patient at a high risk for mortality. Both upper and lower gastrointestinal bleeding (e.g., diverticulosis, esophageal and gastric varices, and peptic ulcer disease) can also result in significant blood loss requiring massive transfusion and resuscitation from hemorrhagic shock. Therefore, safe, timely, and effective transfusion of blood products is critical. The aim of this chapter is to provide clinicians with a discussion of the current literature on the various blood component products, their indications, and unique hemostatic conditions in the surgical patient. While the majority of data concerning optimal management of acquired coagulopathy and hemorrhagic shock resuscitation is based on trauma patients, many of the principles can and should be applied to the surgical patient (or likely any patient) with profound hemorrhage.

The Lethal Triad of Acute Resuscitation

The concept of the lethal triad—hypothermia, acidosis and coagulation—was first promoted in the trauma population in those undergoing emergency surgery. In an effort to prevent its development (or at least attenuate its progression), investigators began advocating for Damage Control Surgery [1–3]. Central to this concept is aggressively and rapidly addressing all three pathologies simultaneously, as each greatly affects the other.

Hypothermia, defined as a core body temperature of 34–36 °C, in the trauma patient primarily results from reflexive peripheral vasoconstriction in the hypovolemic patient.

This phenomenon is further exacerbated by rapid infusion of unwarmed crystalloid fluid during initial resuscitation. This condition impairs coagulation factor activity and platelet function, such as their ability to produce thromboxane, and must be rapidly reversed [4]. Dilutional coagulopathy follows large crystalloid and colloid fluid resuscitation, further promoting ongoing bleeding. Early plasma therapy and platelets have been associated with a reduction in hemorrhage-related mortality [5, 6].

Acidosis has been hypothesized to result from hypoperfusion and excess administration of ionic chloride in normal saline administration. The acidosis disturbs platelet function and morphology, reduces coagulation factor complex activity, and degrades fibrinogen. Approximately 25% of trauma patients present with abnormal coagulation parameters, and these have been associated with poorer outcomes in these patients. The three conditions above contribute to poor clot formation and aggravated coagulopathy [4].

Evidence exists supporting increased survival upon rapid treatment of initial coagulopathy [5, 7]. Pre-emptive strategies have been shown to actually reduce coagulopathy and the number of overall transfusions required to treat the patient [8, 9]. However, challenges to implementation include time limitations of laboratory-guided component therapy since the results of the tests are not immediate. Another difficulty is that once it has been determined that the patient should receive plasma, an additional 30–45 min is required to thaw and deliver the products [5]. As such, hospitals should have in place a thawed plasma program, keeping adequate numbers of “universal” and type-specific thawed plasma available for immediate release. Plasma thawing protocols exist to avoid this issue and will be discussed in later sections. In acutely bleeding patients, massive transfusion protocols should be activated in order to efficaciously restore blood volume and hemostasis and thawed plasma is critical to their success [5, 10]. Blood products can always be sent back should the clinical setting change, but you can’t speed up delivery and preparation of products when you need them.

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Massive Transfusion Protocols

A massive transfusion (MT) is defined as more than ten units of red blood cells (RBC) in 24 h [5]. A massive transfusion protocol (MTP) is the standardization of the delivery and transfusion of RBC, plasma, and platelets in predetermined and predefined ratios as facilitated by a surgical or medical team. In the patient requiring immediate resuscitation, a typical MTP will call for 6–10 units of RBC, with a ratio of RBC to plasma and platelets in 1:1:1–1:1:2 fashion. This protocol and release of products will continue based on ongoing bleeding (Fig. 13.1). These assessments are generally implemented “blind,” with subsequent releases guided by routine coagulation laboratory studies as well as thromboelastography (TEG) [11].

Even before the transfusions take place, MTPs call for the rapid mobilization of blood components by having AB (or low-titer A) plasma and group O RBC [12]. Plasma should be available in either thawed form (5 day shelf-life once thawed) or liquid form (never frozen, absolute shelf-life of 21–26 days). A type and screen should be drawn as soon as possible to allow for the transition from universal products to type-specific ones. The efficacy of an MTP also lies in its early implementation as well as identification of patients who would benefit from such an intervention. Criteria for activation include laboratory values, anatomic injuries, and mechanism

of injury. Although individual laboratory values (hemoglobin, INR, hematocrit, and pH) have been shown to correlate with massive transfusion requirements, MTP activation should never be delayed on the basis of lab results, which can take up to 45 min to return. The urgency in treating severely injured patients requires early and immediate initiation of MTP based on clinical assessment for rapid delivery of blood products to the bedside. Several scoring systems have been developed to facilitate rapid identification of patients requiring MTP activation based on physical and laboratory results (Table 13.1). Several authors have demonstrated that the transfusion of uncross-matched RBCs is an independent predictor of substantial hemorrhage and the transfusion of multiple units of RBC, plasma, and platelets [12, 13]. As such, when one is requesting uncross-matched product for transfusion, the institution’s MTP should be activated.

Prior to the advent of MTPs, resuscitation protocols for severely injured patients began with large volumes of crystalloid followed by RBC transfusions. Later on, plasma, platelets, and cryoprecipitate were administered if the patient had survived the operating theater and then only based on laboratory values and the opinion of anesthesiologists and transfusion specialists. These guidelines recommended transfusions at prothrombin time ratio of >1.5 , platelet counts of $<50 \times 10^9/L$, fibrinogen level $<1.5\text{--}2.0\text{ g/L}$ or after a predetermined volume loss. This approach relied on a reactive

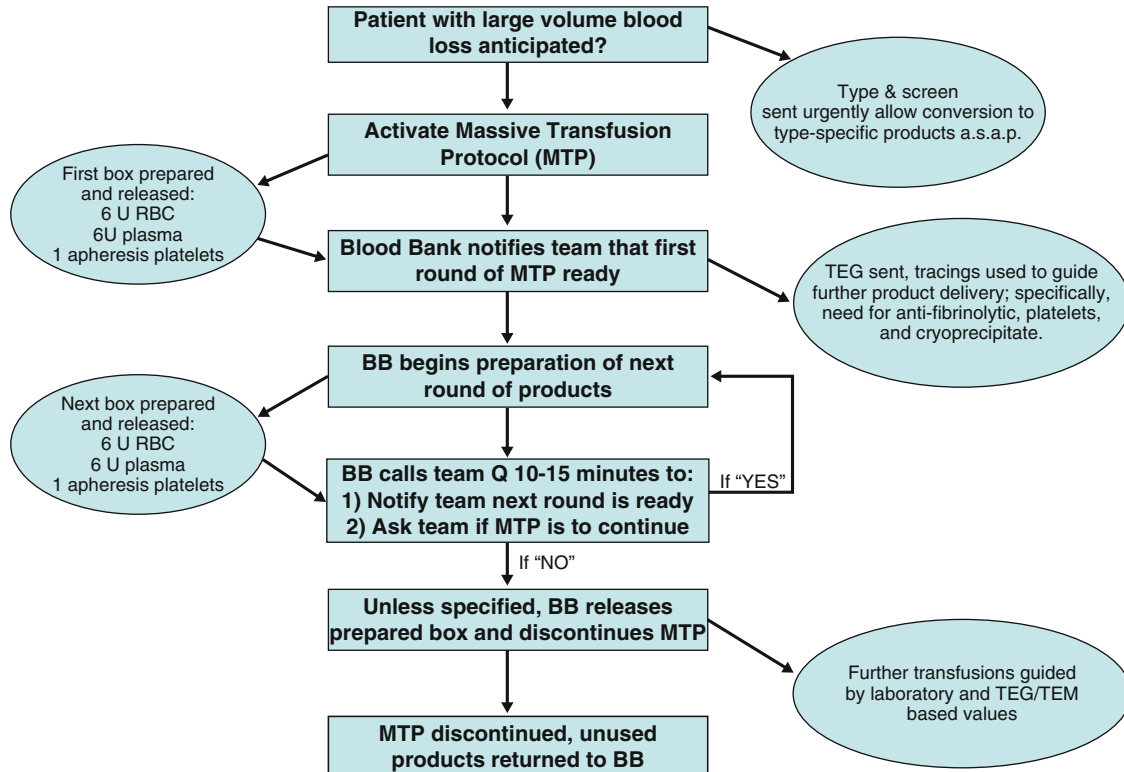


Fig. 13.1 An example of a massive transfusion protocol. (Adapted from Young PP, Cotton BA, Goodnough LT. Massive transfusion protocols for patients with substantial hemorrhage. *Transfus Med Rev* 2011, with permission.)

Table 13.1 Scoring systems and variables used to predict MTP requirements

	ABC	TASH	ETS	McLaughlin
Tachycardia	X	X		
Hypotension	X	X	X	
+FAST	X	X		
Penetrating injury	X			
pH				X
Base deficit		X		
Pelvic fracture		X		
Hemoglobin/hematocrit		X	X	X
Age			X	

ABC Assessment of Blood Consumption Score; Nunez TC, Dutton WD, May AK, Holcomb JB, Young PP, Cotton BA. Emergency department blood transfusion predicts early massive transfusion and early blood component requirement. *Transfusion*. 2010;50:1914–20

TASH Trauma Associated Severe Hemorrhage Score; Yücel N, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, Neugebauer EA, Wappler F, Bouillon B, Rixen D, Polytrauma Study Group of the German Trauma Society. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life-threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60(6):1228–36

ETS Emergency Transfusion Score; Kuhne CA, Zetl RP, Fischbacher M, Lefering R, Ruchholtz S. Emergency Transfusion Score (ETS): a useful instrument for prediction of blood transfusion requirement in severely injured patients. *World J Surg*. 2008;32(6):1183–8

From McLaughlin—McLaughlin DF, Niles SE, Salinas J et al. A predictive model for massive transfusion in combat casualty patients. *J Trauma*. 2008;64 Suppl 2:S57–63, with permission

strategy where the clinician was constantly “catching up” with values representing an earlier hemodynamic state of the patient [14].

While this standard resuscitation method is adequate for patients who are not in shock or not bleeding, studies have demonstrated that it does not suffice for the subset of patients who have sustained serious injuries, are coagulopathic or in shock [5]. One reason is that the coagulopathy is addressed after a time lapse since the original laboratory values were obtained. Other reasons for the suboptimal results of this method are due to the ratios of each blood component product infused. Specifically, evidence exists that demonstrates that large volume of crystalloid fluids is associated with increased hemorrhage and lower survival rates [15]. It has been hypothesized that this effect is due to insufficient replenishing of hemostasis factors, and the complex coagulopathy of dilution, consumption of factors, and fibrinolysis is not adequately addressed. MTPs also offer the advantage of reducing intraoperative crystalloid use and hence, reducing opportunities for hemodilution.

Damage control resuscitation (DCR) expands on the MTP process and calls for low-volume resuscitation, sparing the patient of resuscitation with fluids such as crystalloids and colloids that are low in hemostasis factors [15]. Instead, DCR adheres to transfusion of blood products in a ratio of plasma and platelets to red blood cells consistent with that

which is being lost to hemorrhage. It also involves more permissive hypertension, and acting preemptively on the hypovolemic, hemorrhaging patient. DCR is also supported by findings from the military, which demonstrated improvement in outcomes in severely bleeding patients who were transfused in ratios of products similar to whole blood. A large amount of retrospective civilian trauma data has demonstrated that an RBC to plasma ratio between 3:2 and 1:1 is associated with increased survival [5]. Fox et al. found that patients undergoing vascular surgery with DCR had improved revascularization and graft patency. Their results demonstrated that recombinant VIIa, whole blood, FFP, platelets, cryoprecipitate and minimal crystalloid prevented early graft failures [16].

A recent randomized, multicenter trial further supports higher ratios in bleeding patients [6]. Investigators at 12 centers in North America randomized 680 trauma patients to receive a ratio of either 1:1:1 or 1:1:2. The trial showed a significant reduction in hemorrhage-related 30-day mortality (15% vs. 9%, $p=0.03$), all-cause 3-h mortality (11% vs. 5.8%, $p=0.02$), and a strong trend towards reduction in 24-h all-cause mortality (17% vs. 12.7%, $p=0.12$) when a 1:1:1 plasma: platelets: RBC ratio was used, compared to 1:1:2. The study did not show a difference in non-hemorrhage deaths or overall mortality.

While there is a wealth of data in the trauma population, less data is available regarding coagulopathy in the severely bleeding patient in other surgical specialties. It is, however, important to consider the underlying pathology responsible for exsanguination, such as in obstetric patients, as well as related comorbidities, such as uremia, pharmacologic anticoagulation, in assessing for need of blood products [5]. For instance, Kılıç et al.’s review of resuscitation in patients with gastrointestinal bleeding found that 1:1:1 ratios of RBCs, FFPs, and platelets reduced dilutional coagulopathy, similarly to trauma patients. Patients undergoing open thoracoabdominal aortic aneurysm repair are also vulnerable to coagulopathy due to systemic heparinization, hypothermia, and left-heart bypass with a centrifugal pump [17]. As well, several authors have noted its benefit in the vascular population [16, 18, 19]. Mell evaluated 168 patients with ruptured abdominal aortic aneurysm who had massive hemorrhage in the perioperative period. Their findings showed reduced 30-day mortality in patients who were transfused 1:1 RBC to plasma ratios. These patients also experienced lower rates of colonic ischemia. The value of this study is that the average age of patients was 73 years, much older than the average trauma patient, demonstrating applicability of MTPs in different patient age populations [19].

Lastly, evidence on MTPs has focused on the acutely bleeding surgical patient, and less is known about patients in other surgical settings. Due to the less emergent nature of such settings, it is likely that MTPs are activated more reactively, and it

may have a different effect on patient outcome [5]. However, some groups have shown that those patients receiving less than massive transfusion levels may still benefit from higher plasma to red blood cell ratios [20]. Wafaisade and colleagues demonstrated decreased mortality rates in such patients. To date, unfortunately, no randomized studies exist in the bleeding, non-trauma patient.

Blood Component Products

Red Blood Cells

Red blood cells are the component of choice used to restore hemoglobin levels in resuscitation. Over 30% of ICU patients receive RBC transfusions and over 40% are transfused during hospitalization [21]. The Cardiovascular Health Study found that anemia is associated with increased mortality in elderly patients, emphasizing the importance of

treatment [22]. However, correction of anemia in the non-bleeding surgical patient has not been well studied, and its benefits remain controversial.

While most would agree that actively bleeding patients should be maintained at a hemoglobin between 8 and 10 g/dL, agreement is lacking as to what degree of anemia exceeds benefit:harm ratio in the non-bleeding population (Fig. 13.2). The majority of literature currently supports more conservative trigger points in the non-bleeding population, between 7 and 8 g/dL. Englesbe and colleagues reviewed the literature in surgical patients and found that survival was not improved when postoperative patients were transfused to correct a hematocrit of 25% [23]. The authors recommended making the decision to transfuse using a host of physiological measures and evaluation of the patient's compensatory ability, not only the hemoglobin or hematocrit. They have used a hematocrit of 16% for initiating transfusion in cases where the patient has excellent compensatory ability, and 21% when they lacked such capabilities. The 21% trigger should

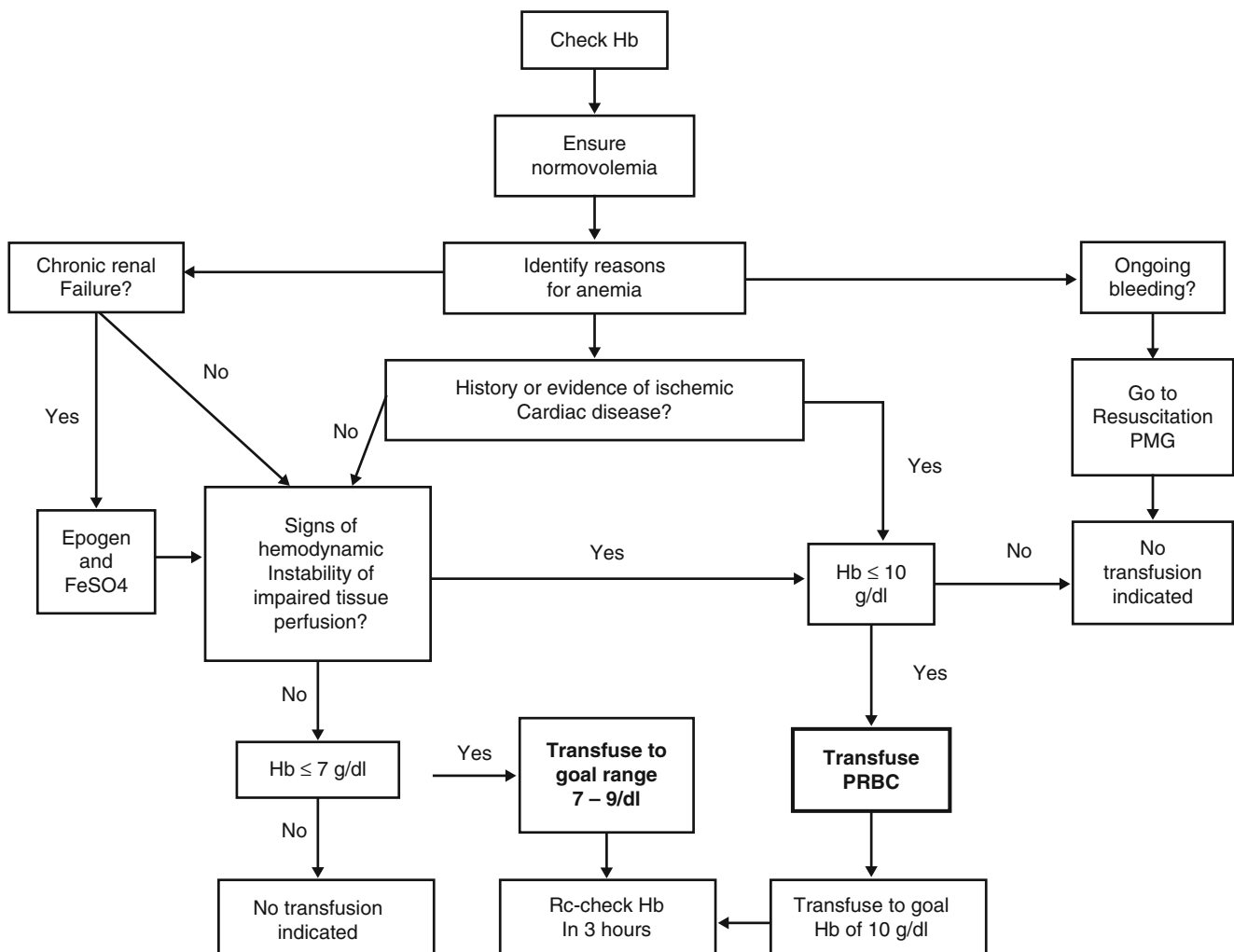


Fig. 13.2 Example of a practice management guideline for managing anemia in the ICU patient

also be employed in stable elderly patients without hypotension, tachycardia, or hypoxia. Investigations have not yet shown benefits in stratification of surgical patients by specialty or procedures [24].

Among critically ill patients, high quality evidence supports conservative triggers for RBC transfusion in critically ill patients [25]. A multicenter randomized, controlled, clinical trial of 838 critically ill patients compared the outcomes of patients who were transfused at hemoglobin levels of less than 7.0 g/dL and those who were transfused at hemoglobin levels below 10.0 g/dL [25]. Their study ultimately found that the more restrictive trigger of 7.0 g/dL was superior to the liberal one and patients experienced improved 30-day survival rates. Of note, of the various patient populations studied, this improvement was not found to be significant in patients with acute myocardial infarction and unstable angina. Based on this, many would argue that in patients with acute cardiac events, data does not robustly support either strategy over the other.

It is important to be mindful of false triggers for transfusion, such as anemia due to hemodilution, commonly seen in patients receiving fluids during prolonged hospital stays. A peripheral hematocrit is not enough to determine the patient's red blood cell levels, and calculations of total blood volume, red blood cell volumes, and normalized hematocrit are necessary [26]. Van et al. report that relying on peripheral hematocrit alone resulted in over-diagnosis of anemia in 23.8% of analyses, and this finding can lead to unnecessary transfusions. Blood Volume Analyzers are one option that has been shown to separate anemia due to hemodilution compared to other sources such as surgical bleeding [26].

In patients with prolonged hospital stays and critically ill patients, it is important to keep in mind anemia due to phlebotomy for various laboratory testing and other needs [21]. Between 40 and 240 mL of blood per day is collected from ICU patients, with surgical patients generally on the higher end. Hence, the conservation of blood and reducing unnecessary blood draws is key to preventing a need for RBC transfusions. So one must weigh the use of "serial hematocrits" in following patients with solid organ injury or gastrointestinal bleeding against the associated "serial phlebotomies."

Erythropoietin

A randomized, double-blind, placebo-controlled trial investigated the role of epoetin alfa, a recombinant erythropoietin, in reducing the RBC transfusion requirement of long-term acute care patients, thereby reducing risks associated with transfusions [27]. Investigators found that treatment with epoetin alfa significantly increased hemoglobin concentration and reduced the likelihood of receiving an RBC transfusion by greater than 70%. Another randomized, double-blind,

placebo-controlled study demonstrated that a once weekly dose of epoetin alfa augmented the erythropoietin response [28]. As for its effects on mortality, Corwin et al. conducted a prospective, randomized, placebo-controlled trial of 1460 medical, surgical, or trauma patients [29]. Weekly injections of epoetin alfa were shown to decrease mortality at day 29 and day 140, especially in trauma patients compared to placebo. However, epoetin alfa was associated with an increase in thrombotic events, and did not affect the number of patients who received a transfusion of RBCs.

Iron Supplementation

Iron sucrose has also been investigated as a possible adjunct to RBC transfusions in order to reduce transfusion requirements. To answer this question in colorectal cancer surgery patients, Edwards et al. conducted a randomized prospective blinded placebo-controlled trial of 60 patients [30]. Patient outcomes, which were assessed using change in hemoglobin levels, serum iron markers, transfusion rate, length of hospital stay and perioperative events, were unaffected by the addition of 600 mg of iron sucrose.

Plasma

Plasma is an acellular blood product consisting of clotting factors involved in coagulation and fibrinolysis, as well as proteins involved in immune reactions and maintenance of the oncotic balance of blood. Plasma can be obtained from separation of whole blood or unique plasma donations from a donor using plasmapheresis. Common indications for plasma are reversal of warfarin-induced anticoagulation, massive transfusion in trauma and surgery, procedures with limited bleeding or risk thereof, liver disease with coagulation factor deficiencies, single coagulation factor deficiency, and thrombotic thrombocytopenic purpura (TTP) [31].

Historically, plasma transfusions have been associated with various side effects including transfusion-related acute lung injury (TRALI) [32]. However, these complications have been dramatically reduced with blood donation centers transitioning to male only and or nulliparous female donors [33]. Recent estimates place the risk of TRALI at 4.2 cases per 1,000,000 units transfused [34]. These current low risks need to be weighed against its numerous benefits. Each unit contains >400 mg of fibrinogen, helping to address the losses during hemorrhage. Plasma also acts as a tremendous buffer (due to high citrate content) in shock patients with severe acidosis. In fact, plasma has a buffering capacity 50 times that of standard crystalloid products [35]. In hypovolemic patients, plasma is as an excellent volume expander with high oncotic pressures. Compared to other resuscitation fluids, plasma is more effective in maintaining vascular endothelium integrity and clot stability [36].

Norda et al. studied two types of plasma—thawed plasma and liquid plasma (never frozen). Liquid plasma is an AABB approved product and may be stored at 2–6 °C for up to 26 days. Both of these types of plasma have been considered clinically equivalent. As for their individual components, liquid plasma has been shown to contain levels of Factor V and von Willebrand factor at levels 70% or greater [37]. Murad et al.'s meta-analysis of 37 studies on adults transfused with plasma (compared with non-transfused controls) demonstrated that in the setting of massive transfusions in trauma patients, transfusion was associated with increased survival and a decrease in multiorgan failure [31]. However, the meta-analysis also demonstrated increased risk of mortality in patients who received plasma not part of a massive transfusion protocol. Their findings highlight the need of assessing each individual patient's indication for plasma transfusions. Of note, none of these studies involved the use of plasma in patients with hemorrhagic shock. In this population of patients, the incidence of multiorgan failure has been shown to be lower than comparison cohorts (most likely as a result of less overall transfusions in the higher plasma group) [10, 15].

Alternative Plasma Protocols

Because of the nature of frozen plasma, transfusion delays of 45 min occur as units are thawed and prepared. Young and colleagues surveyed members of the University Health System Consortium, consisting of 107 academic medical centers and 232 affiliated hospitals and found that only 60% of participating hospitals had thawed plasma sufficient for the first cycle of their MTP [5]. This problem delays the critical availability of plasma in the initial phase of resuscitation. Reviews of plasma, cryoprecipitate, and platelet transfusions alongside massive blood transfusion protocols have demonstrated that earlier use of plasma and platelets in trauma patients have decreased the incidence of coagulopathy [38]. Unfortunately, by the time one or more blood volumes have been lost, plasma may still be unavailable in the absence for a thawed or liquid plasma program. Hence, protocols have been established to reduce wastage of products and use them for patients in an efficacious manner [39].

Thawed plasma is prepared by thawing FFP or FP24, after which it may be used for an additional 96 h beyond the standard 24-h post-thaw shelf life. Extending the lifespan of plasma allows transfusion of units that would otherwise expire untransfused, postponing the need to dispense more FFP. Implementation of a thawed plasma protocol, under which a blood bank technologist identifies and re-labels eligible FFP and FP24 as “thawed plasma” at the start of each shift, was shown to reduce the number of units wasted by 80%. [39].

Thawed plasma may be used in all cases where FFP is indicated, with two exceptions: neonates and certain patients requiring the higher levels of factor V and VIII present in FFP. Radwan and colleagues demonstrated that the implementation of a protocol with thawed plasma readily available in the emergency department, rather than stored in the blood bank, results in a significant reduction in time-to-transfusion of plasma [40]. This study also found that this earlier administration of plasma was associated with markedly reduced blood product use within the first 24 h of hospitalization and a 60% odds reduction in 30-day mortality.

Maintaining a consistent and rapidly available inventory of thawed plasma requires attentive management and rotation of product that are near expiration to avoid wastage of expired units. A study by Novak et al. that evaluated plasma usage by the 12 institutions in the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial found that keeping an inventory of thawed plasma for immediate use resulted in an increase in the number of units discarded at the end of the 5 day shelf life at several medical centers [41]. The institutions that reported no appreciable increase in waste were those that consistently recycled untransfused, unexpired units back into the general blood product inventory to be made available for use in other departments. Development of such protocols may mitigate the number of discarded units while maintaining adequate supply in for early use in the ED.

As previously noted, however, thawed plasma only has a five shelf-life and, more importantly, only 4–5% of the population are blood type AB. Therefore, it is not surprising that many blood banks are unable to provide adequate stores of thawed AB plasma. As such, many centers have begun using liquid plasma and or low-titer A plasma as an alternative. Liquid plasma is never frozen and is kept refrigerated, with storage life of 21–26 days. Recent data suggests that liquid plasma may maintain superior coagulation profiles during storage (compared to thawed plasma) [42, 43]. Approximately 40% of the US population is blood type A, offering a tremendous increase in plasma donor pool. Low-titer A plasma has the potential to serve as an alternative to AB plasma in these universal donor settings. Similar to that with liquid plasma, several centers (including ours) have recently adopted low-titer A plasma for emergency use [44].

Platelets

The purpose of platelet transfusions is to avoid spontaneous hemorrhage, which can occur at very low platelet levels, especially in patients who are already hemorrhaging or have various platelet deficiencies and abnormalities of function. Along with plasma and fibrinogen, platelets are key in

achieving hemostasis in the obstetric patient with postpartum hemorrhage [45]. Approximately 50,000 cells/L of platelets are necessary in order to achieve adequate hemostasis. In addition to the total number of platelets, their quality is also important to overall hemostatic function. A patient's platelets must be efficacious, that is, remaining in circulation and completing its physiological role in clot formation [46]. This efficacy can be assessed by various modalities, from the traditional laboratory coagulation studies to viscoelastic testing such as thromboelastography (TEG).

Cryoprecipitate

Cryoprecipitate consists of von Willebrand factor/VIII complex, factor XIII and fibrinogen. It is used to supplement plasma transfusions with fibrinogen, especially in patients with fibrinogen levels of less than 100 mg/dL, the level at which hypofibrinogenemia results in bleeding [5]. It is named cryoprecipitate because single units of plasma are rapidly frozen to -30°C and are slowly thawed overnight to 4°C , causing many clotting factors such as fibrinogen to precipitate out of the solution [32]. Indications for cryoprecipitate include factor VII deficiency, congenital or acquired hypofibrinogenemia, disseminated intravascular coagulation, and massive transfusion.

Unlike plasma, virus-inactivated cryoprecipitate is not yet available, and studies on the efficacy of SD FFP and MB FFP have not shown a benefit [32]. The complications of cryoprecipitate are similar to those of plasma, with a slightly lower occurrence of complications associated with higher volumes of plasma, such as TRALI and hemolysis [32].

Whole Blood

The practice of using whole blood is largely uncommon due to the separation of blood components for targeting specific deficiencies currently supported by evidence-based medicine. Decision-making for each transfusion requires laboratory testing, and each product must carefully be stored and transported to the site of need. When this is not possible, such as in acute settings with limited resources, whole blood transfusions can adequately resuscitate certain patients. Grosso et al. recount a case of collecting whole blood from hospital personnel donors in a US field surgical hospital in Kosovo. This whole blood was used to treat exsanguinating coagulopathy in an acutely bleeding patient. The advantage of whole blood is its ability to increase hemoglobin levels, similarly to red blood cells, and its ability to restore blood volumes, similarly to crystalloids [47]. Because of its physiological ratios of each blood component, it may hold an advantage over individual blood component transfusions, but more work is necessary to substantiate this idea.

Recombinant Activated Factor VII

Recombinant activated factor VII (rFVIIa), originally developed for use in hemophilia A and B patients, has recently been explored in various off-label uses, such as stemming acute bleeding alongside standard replacement therapy. Mayo et al. demonstrate the use of a coagulopathy score that they found to be statistically correlated to rFVIIa response and survival in thirteen trauma patients in Israel [48]. This finding was turning point in the understanding of rFVIIa indications due to its previous contraindication in coagulopathy. Other uses for rFVIIa are factor VII deficiency, thrombocytopenia, functional platelet disorders, von Willebrand disease, intracranial bleeding, and reversal of warfarin overdose, liver disease, and transplantation. However, little evidence is currently available to support these uses [48].

Transfusion-Related Complications

Before entering the discussion on complications related to transfusions, the difficulty of study design to answer such questions must be appreciated. There are ethical obstacles to randomizing patients to transfusion and non-transfusion arms. Hence, many trials show patients who received more blood component transfusions fared worse than patients who did not, but this may be entirely because of the condition of the patients that necessitated the transfusions [23]. Khorana et al.'s retrospective cohort study of 504,208 patients hospitalized with cancer demonstrated that RBC and platelet transfusions were associated with increased mortality, as well as venous and arterial thrombotic events. However, it is unclear if this is a causal relationship [49].

As with large-scale introduction of exogenous elements to the body, immune reactions can develop sequelae that are well known with blood product transfusions. The most feared of these immune reactions are hemolytic reactions. To prevent these events, it is critical to crossmatch patients and donor blood whenever possible. The most common cause of hemolytic reactions due to transfusion of an incorrect match is clerical error. Hemolytic reactions in blood transfusions occur because each individual carries antibodies against the blood group (A or B) that it does not express endogenously. Hence, when products containing anti-A or anti-B antibodies in plasma, such as plasma, are transfused to patients of A, B or both blood groups, the donor antibodies stage an attack on the patient's red blood cells. Allergic reactions are another common immune-mediated complication of transfusions. Severely anaphylactic reactions are more common after plasma compared to RBC transfusion [32]. Patients present with wheeze, hypotension, tachycardia, laryngeal edema, and urticarial rash.

TRALI is defined as acute lung injury occurring within 6 h of transfusion with a blood product, with most commonly reported cases occurring due to FFP [50]. TRALI is the most

common cause of death due to transfusion [32]. TRALI is characterized by respiratory insufficiency, not limited to but including tachypnea, cyanosis, dyspnea, and acute hypoxemia [50]. In patients with gastrointestinal bleeding, TRALI is further exacerbated by the presence of end-stage liver disease. Proposed mechanisms for this phenomenon have included antibody-mediated reactions, but these findings are not definitive and many are subject to selection bias due to no screening in the asymptomatic population [50]. Autopsies and animal models have suggested hyperactive PMN involvement, since mass infiltration was noted [50]. A two-event model has also been proposed, with the first event dictated by the clinical health of the patient and the second event by the quality (affected by storage, donor immunologic components) of the blood product [50]. The treatment of TRALI is aggressive respiratory support and ventilation in more severe cases, such as in critically ill patients [50]. Practices to reduce the risk of TRALI include prestorage leukoreduction as well as avoiding the use of old blood products, defined as older than 14 days for RBCs and older than 2 days for platelet concentrates. Another prevention strategy is using only male donors or donors who have never been pregnant due to look back studies showing fewer TRALI events in blood donations from those populations [51]. Eder et al. demonstrated that preferential distribution of plasma from male donors reduced the reported number of TRALI cases. However lethal these rare events are, it is critical to understand the risk–benefit ratio in such cases. As noted earlier, current rates of TRALI are estimated at just over 4 cases per 1,000,000 units transfused [52].

Transfusion-associated immunomodulation refers to the immunosuppression resulting from the introduction of foreign antigens via blood products to the host [23]. The exact mechanism of this effect has not yet been elucidated, but plasma components, WBCs, metabolic products from storage processes are thought to play a role. This effect may be responsible for the immunosuppressive effects of transfusions on severely ill patients. Transfusions can cause sensitization to HLA antigens, creating a unique problem in potential kidney transplant patients. Studies have demonstrated increased sensitization of patients on a kidney transplant waiting list after transfusion, rendering them unsuitable candidates for living donation. Their only remaining alternative once this has occurred is to wait for a cadaveric graft, which takes up to 4 times longer, and may never receive a transplant. Hence, non-life-sustaining transfusions should be avoided in potential kidney transplant recipients [23].

Red blood cell transfusion is also an independent predictor of SIRS, ICU admission, mortality, length of hospital stay, and the development of multiple organ failure (MOF) [53]. In particular, the age of the blood plays an important role, with increased age of RBCs resulting in increased instances of MOF. RBCs are not alone in this adverse event. A multicenter prospective cohort study demonstrated that

plasma was independently associated with increased risk of MOF and ARDS of 2.1 % and 2.5 % [54]. The same study found, however, decreased risk of MOF per unit of cryoprecipitate, and platelets were not found to be associated with MOF or ARDS [54].

In addition to MOF, blood transfusions are associated with transmission of infectious diseases. In their review of the current literature, Englesbe et al. found that patients who received transfusions experienced a significant increase in nosocomial infection rates compared to those who did not receive transfusions, and that the occurrence of nosocomial infections increased with each additional unit of RBCs transfused [23]. *Staphylococcus aureus* is the most commonly transmitted bacterial pathogen [51]. Bacterial pathogens in blood products arise mainly from donor skin, and platelets are especially prone to these contaminants [32]. However, bacterial infections are less common than viral infections in blood transfusions.

Despite increased screening and testing, each RBC transfusion is associated with a risk for viral infections such as hepatitis [27]. Virus risks in the UK in plasma have been estimated at 1 in 8 million for HIV, 1 in 30 million for HCV, and 1 in 900,000 for HBV [32]. Since up to 50 % of adult donors are CMV carriers, there is a risk of transmission of this virus to patients, especially the immunosuppressed, transplant patients and neonates [32]. Compared to viral causes, bacterial, endotoxin and prion contamination rates are more rare [32]. In order to avoid this deleterious complication, virus-inactivated preparations of plasma exist, such as methylene blue and solvent-detergent treated products. While these options may offer increased viral protection, they have been associated with loss of clotting factors [32]. The most stringent testing protocols and sensitive tests may not ever eradicate the risk of infectious agent transmission as new pathogens of unknown methods of spread are constantly emerging and may not actively be screened for in its early emergence. In addition, long incubation period of pathogens before seroconversion of blood make it even harder to prevent [27]. Prion diseases transmitted by transfusion has been a concern in the UK, following the BSE epidemic. Unfortunately, no screening test for this condition has been established, and the occurrence of prion diseases in blood products in the UK is largely unknown. In order to avoid transfusions with prion disease, plasma has been imported from the USA since 2002 for pediatric transfusions [32].

Another concerning complication is the loss of efficacy in stored blood, and the adverse effects it causes. These consequences of the storage process are known as a storage lesion. With current technology, the shelf life of red blood cells cannot be extended further than its physiological shelf life of 120 days, and 35 and 42 days is the limit of viability in whole blood and adenine-saline preservation, respectively [27]. Even this length of shelf-life results in counterproductive

transfusions. Specifically, RBC products older than 2 weeks have been shown to not improve oxygen uptake in septic patients. In fact, RBCs of that age have been associated with higher mortality, increased adverse events, extended hospital stay, and electrolyte imbalances. This reduction in efficacy may be due to decreased ability of the older RBCs to unload oxygen [27]. Another proposed mechanism is that since stored RBCs have depleted nitric oxide, this may have a vasoconstrictive effect, leading to thrombosis and the observed increases in venous and arterial thrombotic events in patients with increased RBC and platelet transfusions [49]. The question is how realistic it is to maintain strict storage age in a finite and scarce resource such as blood. A double-blind, prospective randomized pilot study demonstrated that controlling the storage age of RBCs in transfusion compared to the current standard of care is feasible and results in decreased exposure to older blood [55]. More evidence is needed to determine precisely the cut-off age of RBCs in their efficacy and availability. In stored platelets, it has been estimated that the recovery rate of 5-day-old platelets is about 50%, with many nonviable platelets being sequestered into the spleen [38]. For these reasons, there is some concern that platelet counts performed immediately after transfusion do not provide an accurate picture of platelet function [38].

Given the complications listed above, a discussion of known preventative measures is warranted. Transfusion with RBCs that have not been leukoreduced has been associated with increased risk of multiple organ failure and degenerating leukocytes may cause RBC toxicity. Furthermore, nationwide leukoreduction protocols in Canada were shown to lower mortality rates [27]. Currently, in the USA, leukoreduction is not a standard practice despite evidence of benefit, and additional work is required to determine effects on outcome in various patient populations, such as ICU patients [27].

Hospitalized patients receiving transfusions are already in a vulnerable state of health, and when transfusion-related adverse events occur, it is most regrettable. With institutional triage protocols and transfusion guidelines, such unnecessary harm can be avoided, and cost reduction of a limited and precious resource can be achieved [56]. Protocols and scoring systems, such as the Emergency Transfusion Score (ETS), have been successfully shown to triage patients in need of transfusions and those for whom it would be unnecessary [57].

Special Populations

The Anticoagulated Patient and the Patient Receiving Platelet Inhibitors

There are many considerations to address in the management of an anticoagulated surgical patient, such as reversing anticoagulation fully before operation, in order to avoid bleeding

complications. In the non-elective setting, such as life-threatening hemorrhage or emergent surgical indications, this process must be sped up, using prothrombin complex concentrate (PCC) [58]. Available in 4 factor (II, VII, IX, X) and 3 factor (lacking VII) forms, PCC can be used to improve hemostasis and reverse anticoagulation quicker in patients taking warfarin [56]. In addition, patients on warfarin should receive vitamin K (10 mg) along with concurrent PCC administration.

Major disadvantages of these newer oral factor Xa and thrombin inhibitors are the lack of a specific antidote to rapidly reverse anticoagulation in the case of life-threatening hemorrhage and an inability to follow their “efficacy.” There are currently no tests available to follow their degree of anticoagulation in a clinical setting. Four-factor PCCs have been used off-label (with some success) with the newer oral anticoagulants such as rivaroxaban and apixaban. However, PCCs are ineffective at reversing the anticoagulant effect of dabigatran. Administration of the anti-dabigatran antibody (idarucizumab) or removal of the drug via hemodialysis may be warranted [59, 60]. Additionally, oral activated charcoal is effective at reducing the absorption of oral anticoagulants if given within 3 h of ingestion.

Unlike plasma, PCC can be administered without the need for crossmatching or thawing, has more predictable concentrations of clotting factors, and has been shown to reverse warfarin-related coagulopathy. The clotting factors are also in high concentrations, approximately 25 times that of plasma, decreasing the volume of PCC needed. In addition, the INR is rapidly corrected, taking about 15 min [58]. Four-factor PCC is administered as a single dose of 35 units per kg, or 50 units per kg if the patient is on warfarin with an $\text{INR} \geq 6$. Repeat doses have been associated with increased risk for thromboembolic events and have not been shown to improve efficacy.

Anticoagulated patients and patients using antiplatelet agents are especially vulnerable to coagulopathies, which may develop during resuscitation. Kılıç et al.’s findings recommend using individualized treatment, providing the deficient blood component as per laboratory value deficiency. In addition, patients who are overly anticoagulated with warfarin may also be treated with PCC containing vitamin K dependent factors [51].

In the surgical patient, it is important to discontinue aspirin and reversible platelet inhibitors such as clopidogrel 10 and 7 days, respectively, before an operation to avoid bleeding complications [58]. However, risks of thrombotic events in discontinuation of these agents in cardiovascular surgeries have been noted [58]. Because of these risks with anticoagulated patients and patients receiving antiplatelet agents, it is important to weigh the benefits of the surgery against these risks, among others.

Obstetrical and Gynecological Patients

Obstetric patients are one subpopulation of actively bleeding surgical patients that can easily confuse the provider. Their generally young age may lead one to dismiss some vital sign changes or lab values, while alterations of their physiology in response to pregnancy often result in the misinterpretation of critical findings. During pregnancy, blood becomes less viscous in order to increase oxygen carrying capacity while minimizing increased cardiac load as much as possible. Intravascular volume, and more specifically, plasma volume increases proportionately more than red cell volume, creating a “physiologic anemia of pregnancy” [61]. Fibrinogen, von Willebrand factor, and factors VII, VIII, IX, X, XII are synthesized more frequently while levels of factors XI and XIII and platelets decrease [45]. Levels of factor II decrease, yet interestingly, prothrombin time (PT), and partial thromboplastin time (PTT) remain unaffected [61]. Mechanical obstruction of the uterus on the inferior vena cava and other vessels encourages stasis and the formation of thrombi. The summation of these effects results in a net hypercoagulable state [61].

The utero-placental circulation has increased activity of both coagulation and fibrinolysis, contributing to increased levels of fibrin degradation products such as D-dimer, especially in the third trimester [45]. This effect may contribute to the hemostatic challenges in obstetric patients. Antifibrinolytics such as tranexamic acid and aminocaproic acid can be used to treat hyperfibrinolysis. In fact, tranexamic acid has been shown to reduce blood loss after elective cesarean section and vaginal delivery [45]. Plasma and cryoprecipitate contain fibrinogen and may be used to replenish fibrinogen in states of hypofibrinogenemia (<180 mg/dL).

Postpartum hemorrhage (PPH) is a major cause of obstetric mortality that may require peripartum hysterectomy and is the most common cause of maternal mortality worldwide. PPH, in general, is not associated with underlying coagulation disorders but rather acute events related to placenta abnormalities, trauma from large births or instrumentation, or uterine atony [45]. In addition to rapid surgical intervention, hematologic management of PPH includes rapid volume replacement and blood transfusions. These patients are likely to benefit from management strategies similar to that for acutely injured patients who are in shock from hemorrhage.

In obstetrical patients, rFVIIa has also been found to control and decrease hemorrhage. Segal et al.’s observation of three patients with PPH, hypovolemic shock, and DIC who received massive transfusions suggests that rFVIIa may be beneficial adjunctive therapy after the completion of hysterectomy. The therapeutic effect of rFVIIa may be due to its binding of tissue factor at the site of vessel injury and forming a complex, activating platelets and facilitating fibrin clot formation [62]. However, these findings have not been consistent in

the current literature, and especially because of the expense of rFVIIa, the decision to administer this to the patient must involve a thorough consideration of the benefits, if any [45].

The Non-Hemorrhaging Surgical Patient

Intensive care unit (ICU) patients are another patient population that frequently receives blood transfusions in order to correct their anemia, which has been shown by a large body of work to indicate worse prognosis [27]. These patients are anemic due to sepsis, occult blood loss, hemorrhage, decreased production, and functional iron deficiency. ICU patients with low hemoglobin levels are more likely to suffer from complications such as sepsis, and they are more likely to experience delayed weaning from ventilator support. The decision to transfuse such patients should weigh the benefits and the risks of blood transfusions, especially given the patients’ increased susceptibility to infections, iatrogenic events, and increased metabolic demands [28]. Vincent et al.’s multicenter prospective observational study of 1136 patients demonstrated that ICU patients frequently received transfusions, with a transfusion rate of 37 % during their stay. The patients who received transfusions also experienced a higher mortality rate, prolonged hospital stay, and decreased organ function [28]. There is also evidence suggestive of increased transfusions in patients with hemoglobin levels higher than the generally accepted trigger value of 8 g/dL. Specifically, Vincent et al. [28] found that under 30 % of cases, patients with hemoglobin levels greater than 9 g/dL received blood transfusions. Hence, future work is needed to recommend strict hemoglobin cutoffs for transfusion.

TEG and TEG-Guided Therapy

In the acute trauma setting, conventional coagulation testing (CCT), which consists of prothrombin time, international normalized ratio (INR), partial thromboplastin time, and platelet count, is used to assess coagulation status. This approach, however, is limited by slow results, incomplete characterization of the coagulation abnormality, and poor prediction of patient outcome. Furthermore, CCTs, which are riddled with delays from time to arrival in the laboratory and duration of testing, end up reflecting the coagulation state of the patient after 30–45 min of interventions and resuscitation [63]. Since CCT only examines plasma factors, the integral role of platelets and their function is ignored. In addition, the CCT assesses only the extrinsic pathway, intrinsic pathway, and platelet count, painting an incomplete picture of the pathologies of clotting in the severely exsanguinating patient. These deficiencies are addressed by thrombelastography (TEG), a test that creates a dynamic,

graphical representation of the coagulation characteristics of a blood sample from initial clot formation to fibrinolysis. Since specific coagulation components have specific disturbances on TEG, this test reveals diagnostic as well as therapeutic information [64].

The procedure involves obtaining an uncitrated whole blood sample, activation of the specimen with kaolin, and spinning the sample in a thromboelastograph machine within 4–5 min in order to avoid clotting [64]. If this timeframe cannot be achieved, a “reversal” method can be used, where citrate is used to avoid clotting until the sample has arrived at the laboratory, at which point, the citrate will be “reversed” using calcium chloride as per manufacturer instructions. While this method has been shown to affect TEG results, it has not been shown to be inferior to the standard method and may be used in centers where 4–5 min from sample collection to running the TEG is not realistic [64].

Rapid TEG differs from conventional TEG in its addition of tissue factor to the blood sample and kaolin, accelerating activation of the clotting cascade. This modification makes it well suited for the trauma setting since its results are available much earlier, namely under 20 min, compared to kaolin TEG and CCTs, which can take over 30 min, without sacrificing accuracy [64].

Interpreting the results involves analyzing each of the sequential measurements (Fig. 13.3). Reaction time, or R-time, in TEG is the time until initial clot formation. It is also known as activated clotting time (ACT) in r-TEG in order to denote intentional anticoagulant agents in the sample. Factor deficiency or severe hemodilution can prolong reaction time or ACT. Next, *k*-time represents the time needed to reach 20-mm clot strength, and has a normal range of 1–2 min. The α -angle, normally between 66 and 82°, represents the rate of clot formation. In platelet deficiency or hypofibrinogenemia, where one of the two key components of clots is missing, the *k*-time is increased and the α -angle is

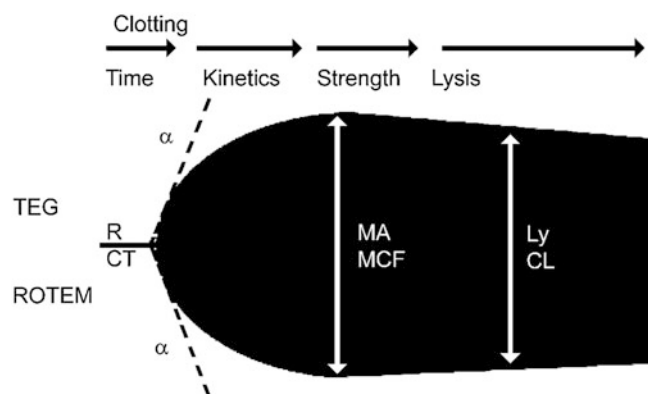


Fig. 13.3 The various sequential measurements of TEG. (Adapted from Johnsson PI, Ostrowski SR, Secher NH. Management of major blood loss. *Acta Anaesthesiol Scand*. 2010;54:1039–49, with permission.)

decreased. Oshita et al.’s linear regression analysis of 36 samples from healthy individuals reported that MA and *k*-time were linearly related to platelet count [65]. The maximal amplitude (MA) of the tracing represents platelet contribution to clot strength (normal range 54–72 mm). It is decreased in states of platelet dysfunction and hypofibrinogenemia. The *G*-value represents overall clot strength, including platelet function as well as enzymatic, and is decreased in hypocoagulable states (normal 5.3–12 K dynes/cm²). The LY30 is the percent of amplitude reduction at 30 min after the MA, and is elevated in hyperfibrinolytic states (normal range 0.0–7.5%) [64].

The use of r-TEG is further facilitated by advanced software that displays the r-TEG tracing as the test is being performed, providing physicians with “real time” results. Cotton et al. report that early r-TEG parameter tracings (ACT, *k*-time and *r*-value) appeared within 5 min while later values (α -angle, MA) were seen within 15 min, compared to CCT panels, which were not available until 48 min [64]. Installation of graphical software in the trauma bay, operating room, and shock-trauma intensive care unit computers can further facilitate the rapid access to TEG results [64].

TEG data results compare well to the previous standard, CCTs. Cotton et al. [64] conducted a pilot study of 272 patients to investigate the role of rapid thromboelastography (r-TEG) in (1) assessing speed of results (2) correlation with CCT findings, and (3) predictability of early transfusions of pRBCs, plasma, and platelets. Their findings demonstrated that graphical r-TEG is available within minutes, an improvement compared to CCTs. They also demonstrated that ACT, *r*-value, and *k*-time strongly correlated with PT, INR, and PTT. MA and α -angle strongly correlated with platelet count, and ACT, *r*-value, α -angle and MA were predictive of pRBC, plasma, and platelet transfusions within the first 2 h of arrival. In fact, an ACT > 128 predicted massive transfusion in the first 6 h and an ACT < 105 predicted patients that did not receive transfusions in the first 24 h [64]. In addition, comparison of TEG and CCT in cardiopulmonary bypass patients found that TEG measures were useful surrogates for CCT values [66]. Because of the speed of their availability and predictive ability, integrating TEG results in MTPs can strengthen decision-making and management of patients and improve patient outcomes (Tables 13.2 and 13.3).

A wide array of evidence exists in surgical patients in support of TEG’s ability to predict prognosis, and in some instances, guide therapy that improves it. Table 13.1 is an example of TEG-guided protocol with such an aim. Platelet dysfunction in cardiopulmonary bypass patients has been attributed to microvascular bleeding, and TEG has been used in the setting of cardiac surgery as a predictor of worsening patient outcomes due to this mechanism [17]. Solomon et al. demonstrated that fibrinogen clot elasticity assessed by TEG correlated to fibrinogen concentration in cardiopulmonary

Table 13.2 Thrombelastography treatment algorithm for actively bleeding patients implemented at Rigshospitalet, University of Copenhagen, Denmark

TEG parameter	Treatment
<i>R</i> (11–14 min)	2×FFP or 10 mL/kg
<i>R</i> >14 min	4×FFP or 20 mL/kg
<i>MA</i> (46–50 mm)	1 PC or 10 mL/kg
<i>MA</i> <46 mm	2 PC or 20 mL/kg
Angle <52°	2×FFP or fibrinogen
Ly30>8%	Tranexamic acid

R reaction time, *alpha angle* clot dynamics, *MA* maximal amplitude, *Ly30* lysis in percent 30 min after *MA* is reached, *FFP* fresh frozen plasma, *PC* platelet concentrate

From Johansson PI, Ostrowski SR, Secher NH. Management of major blood loss: an update. *Acta Anaesthesiol Scand.* 2010;54:1039–49, with permission

Table 13.3 Rapid thrombelastography (r-TEG) transfusion and treatment guidelines

rTEG value	Treatment
ACT ≥ 128 s	Transfuse plasma
<i>r</i> -value ≥ 1.1 min	Transfuse plasma
<i>k</i> -time ≥ 2.5 min	Transfuse plasma, add cryoprecipitate/fibrinogen source if angle also abnormal
<i>α</i> -angle ≤ 60°	Transfuse cryoprecipitate/fibrinogen source, add platelets if <i>MA</i> also abnormal
<i>MA</i> ≤ 55 mm	Transfuse platelets, add cryoprecipitate/fibrinogen source if angle also abnormal
LY-30 ≥ 3%	Administer tranexamic acid

ACT activated clotting time; time from start of assay to initiation of clot, *r*-value reaction time value; time between beginning of assay and initial clot formation, *k*-time clot kinetics; time needed to reach 20 mm of clot strength, *α*-angle alpha angle; rate or acceleration of clot formation, *MA* maximal amplitude; contribution of functional platelets to clot formation, assessment of platelet–fibrin interactions, *LY-30* % lysis at 30 min; amplitude reduction of clot 30 min after achieving *MA* (degree of fibrinolysis)

bypass patients [67]. TEG has been found to predict the risk of postoperative bleeding, and has been used to direct desmopressin therapy and FFP transfusion requirement in cardiopulmonary bypass patients [17].

TEG has been shown to be useful in liver surgery, especially in transplantation. Unlike other surgeries, liver surgery poses the additional problem of increased risk of coagulation factor deficiencies due to hepatic dysfunction and lack of synthesis. TEG-guided transfusion algorithms in this area have been shown to reduce the transfusion requirements in such patients [17]. However, Ogawa et al.'s prospective observational study of 26 patients undergoing cardiac surgery did not find a significant correlation between TEG measures and volume of intraoperative and total transfusions [66]. Despite these findings, Ronald et al.'s literature search and appraisal of 170 studies on the topic found otherwise [68]. They investigated thromboelastography in cardiac

surgery patients and found fourteen studies that provided the best evidence. Their synthesis concluded that TEG can guide transfusion therapy algorithms and result in decreased blood component requirements. In orthopedic surgery patients, TEG was used in a prospective study to identify disturbed fibrin polymerization as a pathological mechanism in dilutional coagulopathy, and to rescue this state with fibrinogen administration [69].

To further support the use of viscoelastic testing in the bleeding patient, a recently completed randomized trial from Denver demonstrated that TEG-directed resuscitation and transfusion resulted in significantly lower mortality (20% vs 36%, $p=0.02$) than those resuscitated and transfused according to conventional lab tests (INR, platelet count, fibrinogen). In addition, these outcomes were achieved with transfusion of less plasma ($p=0.022$) and less platelets ($p=0.041$) [70].

However, TEG has been found to be less sensitive for certain categories of platelet inhibition. In addition, hemostasis point of care tests such as PFA-100 and TEG are affected by nonopioid analgesic drugs. Scharbert et al.'s crossover, double-blinded, placebo-controlled study demonstrated that in low back pain patients scheduled for invasive pain therapy, cytochalasin D-modified thromboelastometry had a low sensitivity for detecting platelet inhibition by diclofenac [71].

Conclusions

There are hemostatic states unique to the surgical patient as a result of medications such as warfarin, perioperative bleeding especially in high bleeding risk surgeries, and emergent surgical indications such as trauma. Various mechanisms affect coagulation cascades in these patients, and techniques from the standard coagulation tests to TEG are currently available. These have shown mostly success in predicting the course of the patient and guiding therapy. The therapeutic options include various blood product components, ranging from whole blood to concentrations of individual factors. Using physiological ratios of RBCs, plasma, and platelets have improved patient survival in the massively hemorrhaging patient. However, like all powerful therapy, they are associated with adverse effects. Preventative options such as decreasing storage lengths and screening for infectious agents have drastically reduced these risks. Lastly, administering these products in a rapid and directed fashion would not be feasible without in-house triage and massive transfusion protocols. These algorithms include steps that must be taken to smooth out logistics of urgent transfusions, such as anticipating adequate thawing times of fresh frozen plasma and collaborating with blood banks to crosscheck appropriateness of each order.

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