Hemorrhage and Transfusions in the Surgical Patient

12

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Introduction

Hemorrhage is the leading cause of intraoperative deaths. 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. Gastrointestinal bleeding from diverticulosis, varices, and ulcer disease can result in significant blood loss requiring massive transfusion and resuscitation from hemorrhagic shock. Timely and effective transfusion of blood products is of critical in these scenarios. The frequency in which blood component products are transfused in surgical patients begs for a greater understanding of them. 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 combat its development (or at least attenuate its effects), several authors began advocating for Damage Control Surgery [1, 2]. However, the principles of Damage Control have spread through the trauma centers and into the operating theaters and intensive care units [3]. Central to this concept is aggressively and rapidly addressing all three components simultaneously, as each greatly affects the other.

Hypothermia, 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]. Crystalloid and colloid fluids also contribute to hemodilution of clotting factors, further promoting ongoing bleeding. Hence, in this situation, early plasma therapy and platelets have been shown to improve outcomes [5].

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 previously mentioned contribute to poor clot formation and aggravated coagulopathy [4].

Evidence exists supporting increased survival upon rapid treatment of initial coagulopathy [5, 6]. Preemptive strategies have been shown to actually reduce coagulopathy and the number of overall transfusions required to treat the patient [7, 8]. 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, it may take another 30–45 min 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 are discussed in later sections. In acutely bleeding patients, massive transfusion protocols are often activated in order to efficaciously restore blood volume and hemostasis and thawed plasma is critical to their success [5, 6].

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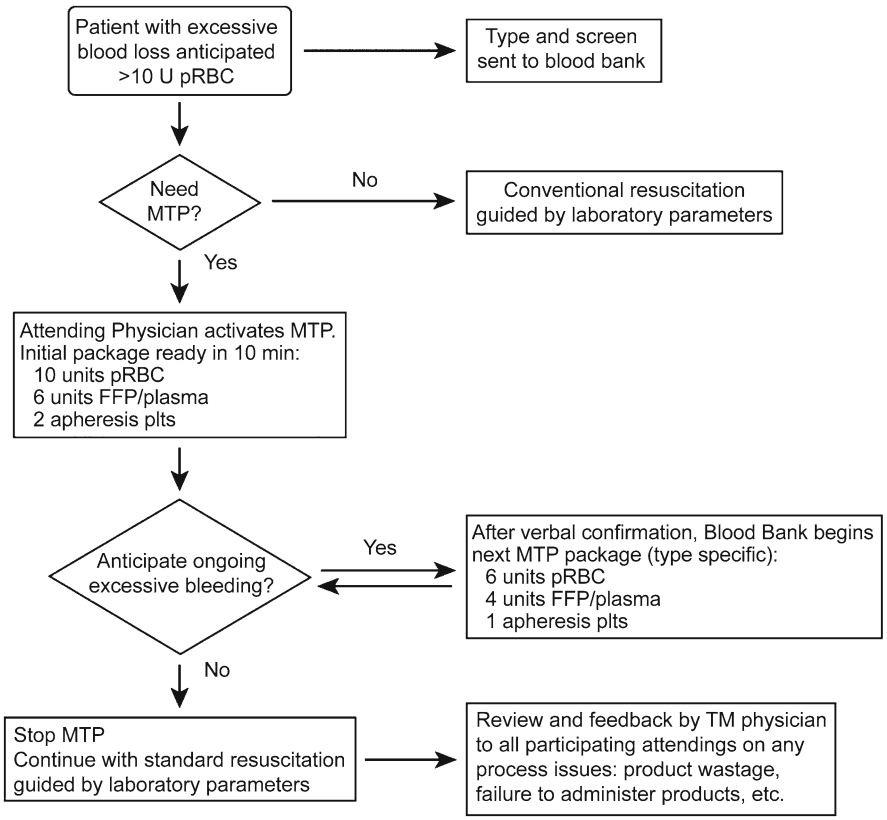

Fig. 12.1 An example of a massive transfusion protocol. Adapted from reference [5]

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 six to ten units of RBC, with a ratio of RBC to plasma and platelets in 1:1:1 to 1:1:2 fashion. This protocol and release of products will continue based on ongoing bleeding (Fig. 12.1). These assessments are generally implemented "blind," with subsequent releases guided by routine coagulation laboratory studies as well as thromboelastography (TEG) [9].

Even before the transfusions take place, MTPs call for the rapid mobilization of blood components by having AB thawed plasma and group O RBC [10]. 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. 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 [10, 11]. 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 <1.5–2.0 g/L or after a predetermined volume loss. This approach relied on a reactive strategy where the clinician was constantly "catching up" with values representing an earlier hemodynamic state of the patient [12].

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 [13]. 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 [14]. 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 US Army's Institute of Surgical Research, which demonstrated improvement in outcomes in severely bleeding patients who were transfused in ratios of products similar to whole blood. Civilian trauma data has also shown that RBC to plasma ratio between 3:2 and 1:1 lead to reduced 30-day mortality and increased odds of 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, fresh frozen plasma (FFP), platelets, cryoprecipitate and minimal crystalloid prevented early graft failures [15].

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 pRBCs, FFPs, and platelets reduced dilutional coagulopathy, similarly to trauma patients [16]. 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 [15, 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.

Thawed 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. 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 [21]. Unfortunately, by the time one or more blood volumes have been lost, plasma may still be unavailable in the absence of 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 [22].

Blood Component Products: Red Blood Cells

Red blood cells are the component of choice used to restore hemoglobin levels in resuscitation. More than 30% of intensive care unit (ICU) patients receive RBC transfusions and more than 40% are transfused during hospitalization [23]. The Cardiovascular Health Study found that anemia is associated with increased mortality in elderly patients, emphasizing the importance of treatment [24]. However, correction of anemia in surgical patients has not been readily studied, and its benefits remain controversial.

In their review, Englesbe et al. note that there is not yet a consensus of in what degree of anemia can RBC transfusions offer a benefit [25]. They discuss the current findings by various studies, which have found that survival was not increased when postoperative patients were transfused to correct a hematocrit of 25%, and similarly, while studies favor transfusion in cardiac patients with a hematocrit of 33% or less, a true benefit remains to be seen. Hence, they recommend making the decision to transfuse using a host of physiological

measures and evaluation of the patient's compensatory ability, not only the hematocrit. They have used a trigger of a hematocrit of 16% for initiating transfusion when the patient has excellent compensatory ability, and 21% when this is not the case [25]. The 21% trigger should also be employed in stable elderly patients without tachycardia or hypoxia. Otherwise, their investigations have not yet shown benefits in stratification of surgical patients by specialty or procedures. One surgical population that has been studied with regards to transfusion is patients undergoing infrarenal abdominal aortic aneurysm surgery. A meta-analysis of randomized controlled trials demonstrated that intraoperative autotransfusion in these patients decreased the allogeneic blood transfusion requirement [26].

High quality evidence, notably Hébert et al.'s, exists to support conservative triggers for RBC transfusion in critically ill patients [27]. This 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. 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 [27].

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 [28]. Van et al. report that relying on peripheral hematocrit alone resulted in overdiagnosis 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 [28].

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 [23]. 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 pRBC transfusions.

Erythropoetin

Because RBC transfusions are associated with certain risks that are discussed in a later section, it is important to also consider possible alternatives or treatments that reduce transfusion requirements, such as epoetin alfa. Silver et al.'s 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[29]. Their findings showed that treatment with epoetin alfa significantly increased hemoglobin concentration and the odds ratio for receiving an RBC transfusion compared to patients on the placebo arm was 0.28 [29]. Additionally, Vincent et al.'s randomized, double-blind, placebo-controlled study demonstrated that a once weekly dose of epoetin alfa augmented the erythropoietin response [30]. Knight et al.'s review found that patients with cancers of various organs who did not have anemia, most due to correction with epoetin alfa, required less transfusions and experienced more quality of life [31]. However, epoetin alfa is limited by its delayed onset at 5–7 days. As for its effects on mortality, Corwin et al. conducted a prospective, randomized, placebo-controlled trial of 1,460 medical, surgical, or trauma patients [32]. 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 [32].

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 [33]. Patient outcomes, which were assessed using change in hemoglobin levels, serum iron markers, transfusion rate, length of hospital stay and perioperative events, were found to be unchanged by the addition of 600 mg of iron sucrose [33].

Blood Component Products: 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 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) [34].

Historically, plasma transfusions have been associated with various side effects including transfusion related acute lung injury (TRALI) [35]. However, these complications have been dramatically reduced with blood donation centers transitioning to male only and/or nulliparous female donors [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. However, studies have noted that C1 esterase inhibitor (C1INH) was consumed by day 14 in 22% of plasma products due to cold-induced contact activation [37]. In order to avoid this effect that places patients at risk for inadequate perfusion, some institutions have introduced a maximum storage time of 7 days for nonfrozen plasma [37].

Murad et al.'s meta-analysis of 37 studies on adults transfused with plasma compared with nontransfused controls demonstrated that in the setting of massive transfusions in trauma patients, transfusion may be associated with increased survival and decreased multiorgan failure. However, they also noted increased mortality in patients who received plasma not part of a massive transfusion protocol. This finding may be due to the unbalanced ratio of transfusion of products, unlike in mass transfusion protocols, which call for 1:1 transfusion of RBCs and plasma. In addition, plasma transfusion was associated with increased risk of developing TRALI, and by itself did not reduce transfusion requirements [34]. Their findings, in the first comprehensive meta-analysis and systematic review of plasma transfusion outcomes, highlight the need of assessing each patient's indications for plasma. The maturation of this field will be needed to strengthen the findings, which the authors did note were subject to survivor biases in some studies. However, none of these studies involved the use of plasma in patients with hemorrhagic shock. In this population of patients, the incidence of multi-organ failure has been shown to be lower than comparison cohorts (most likely as a result of less overall transfusions in the higher plasma group) [13, 14].

Blood Component Products: 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 post-partum hemorrhage [38]. 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 [39]. This efficacy can be assessed by various modalities, from the traditional laboratory coagulation studies to the more recent thrombelastograms (TEG), also known as thromboelastography, and this topic is covered in the last section.

Blood Component Products: 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 [35]. 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 [35]. 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 [35].

Blood Component Products: 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 [40]. 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 [40]. 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.

Blood Component Products: 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 13 trauma patients in Israel [41]. This finding was a 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 [41].

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 [25]. 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 [42]. However, it is unclear if this is a causal relationship.

As with large-scale introduction of exogenous elements to the body, immune reactions can develop, a sequela that is notorious in blood products. This complication is particularly devastating in severely ill patients. The most notorious of these immune reactions are hemolytic reactions. In order to prevent this event, it is important to cross-match patient 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 [35]. 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 [43]. TRALI is the most common cause of death due to transfusion [35]. TRALI is characterized by respiratory insufficiency, not limited to but including tachypnea, cyanosis, dyspnea, and acute hypoxemia [43]. Unfortunately, the occurrence of TRALI in critically ill patients who received a blood transfusion is estimated to be around 25% and increases with each subsequent transfusion, has a mortality rate of approximately 40%, and it is the most common transfusion-related complication [16]. Eighty-five percent of patients with bleeding varices receive blood transfusions, and the trigger for transfusions is much debated. 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 [43]. Autopsies and animal models have suggested hyperactive PMN involvement, since mass infiltration was noted [43]. 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 [43]. The treatment of TRALI is aggressive respiratory support and ventilation in more severe cases, such as in critically ill patients [43]. 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 [16]. Eder et al. demonstrated that preferential distribution of plasma from male donors reduced the reported number of TRALI cases [44].

Transfusion-associated immunomodulation refers to the immunosuppression resulting from the introduction of foreign antigens via blood products to the host [25]. The exact mechanism of this effect has not yet been elucidated, but plasma components, white blood cells (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 four times longer, and may never receive a transplant.

Hence, non-life-sustaining transfusions should be avoided in potential kidney transplant recipients [25].

Red blood cell transfusion is an independent predictor of systemic inflammatory response syndrome (SIRS), ICU admission, mortality, and length of hospital stay, and the development of multiple organ failure (MOF) [45]. 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 FFP was independently associated with increased risk of MOF and acute respiratory distress syndrome (ARDS) of 2.1% and 2.5% [46]. 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 [46].

In addition to MOF, blood transfusions are notorious in lay media for their association with infectious agents. In their review of the current literature, Englesbe et al. found that patients who received transfusions compared to those who did not experienced significant increase nosocomial infection rates, and each additional pRBC transfused correlated to increased infection risk [25]. *Staphylococcus aureus* is the most commonly transmitted bacterial pathogen [16]. Bacterial pathogen in blood products arise mainly from donor skin, and platelets are especially prone to these contaminants [35]. 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 [29]. Virus risks in the UK in FFP have been estimated at 1 in 8 million for HIV, 1 in 30 million for HCV and 1 in 900,000 for HBV [35]. Since up to 50% of adult donors are cytomegalovirus (CMV) carriers, there is a risk of transmission of this virus to patients, especially the immunosuppressed, transplant patients and neonates [35]. Compared to viral causes, bacterial, endotoxin and prion contamination rates are more rare [35]. 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 [35]. The most stringent testing protocols and sensitive tests may not ever eradicate the risk of infectious agent transmission due to several reasons. First, new pathogens of unknown methods of spread are constantly emerging and may not actively be screened for in its early emergence, such as human immunodeficiency virus (HIV) and West Nile virus. Another obstacle in prevention is the incubation period of pathogens before seroconversion of blood [29].

Prion diseases transmitted by transfusion has been a concern in the UK, following the bovine spongiform encephalopathy (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 [35].

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 [29]. 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 [29]. 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 pRBC and platelet transfusions [42]. 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 [47]. 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 [21]. For these reasons, there is some concern that platelet counts performed immediately after transfusion do not provide an accurate picture of platelet function [21].

Given the complications listed previously, 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 [29]. 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 [29].

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 [48]. 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 [49].

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 nonelective setting, such as life-threatening hemorrhage or emergent surgical indications, this process must be sped up, using prothrombin complex concentrate (PCC) [50]. Unlike FFP, PCC can be administered without the need for cross-matching 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 [50].

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 [16]. In addition, patients who are overly anticoagulated with warfarin may also be treated with PCC containing vitamin K dependent factors [16].

Due to the teratogenocity of warfarin, pregnant patients requiring anticoagulation receive heparin as the preferred drug for preventing pulmonary embolism or in thromboprophylaxis in atrial fibrillation [51]. Insertion of a venal caval filter is another option.

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 [50]. However, risks of thrombotic events in discontinuation of these agents in cardiovascular surgeries have been noted [50]. 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 results 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" [51]. 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 [38]. Levels of factor II decrease, yet interestingly, prothrombin time (PT) and partial thromboplastin time (PTT) remain unaffected [51]. Mechanical obstruction of the uterus on the inferior vena cava and other vessels encourage stasis and the formation of thrombi. The summation of these effects result in a net hypercoagulable state [51].

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 [38]. 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 caesarean section and vaginal delivery [38]. Plasma and cryoprecipitate contain fibrinogen and may be used to replenish fibrinogen in states of hypofibrinogenemia (<180 mg/dL).

Post-partum 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 [38]. 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 [52]. 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 [52]. 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 [38].

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 [29]. 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 [53]. Vincent et al.'s multicenter prospective observational study of 1,136 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 [53]. 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. found that in under 30% of cases, patients with hemoglobin levels greater than 9 g/dL received blood transfusions [53]. Hence, future work is needed to recommend strict hemoglobin cut offs for transfusion.

Thrombelastography 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 [54]. 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 [55].

The procedure involves obtaining an uncitrated whole blood sample, activation of the specimen with kaolin and spinning the sample in a thrombelastograph machine within 4–5 min in order to avoid clotting [55]. 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

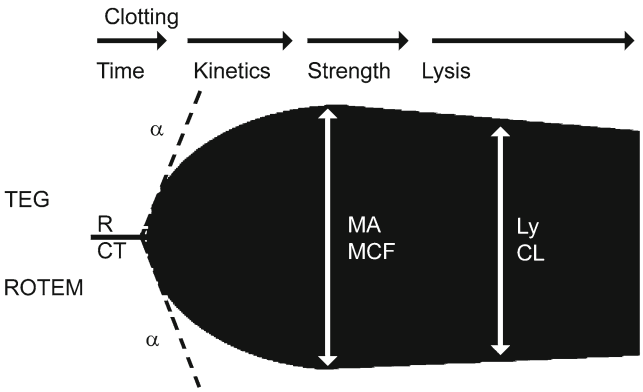

Fig. 12.2 The various sequential and parallel measurements of TEG and ROTEM [4]

method and may be used in centers where 4–5 min from sample collection to running the TEG is not realistic [55].

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 [55].

Interpreting the results involves analyzing each of the sequential measurements (Fig. 12.2). 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 -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 are missing, the *k*-time is increased and the -angle is 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 [56]. 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/cm^2). 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%) [55] (Figs. 12.3 and 12.4).

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 (-angle, MA) were seen within 15 min, compared to CCT panels,

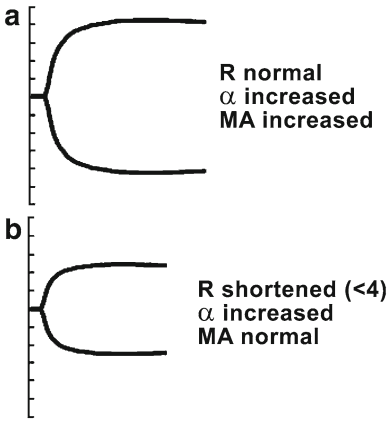

Fig. 12.3 TEG tracings in hypercoagulation abnormalities. **(a)** Platelet hypercoagulability. **(b)** Cascade hypercoagulability. Adapted from reference [62]

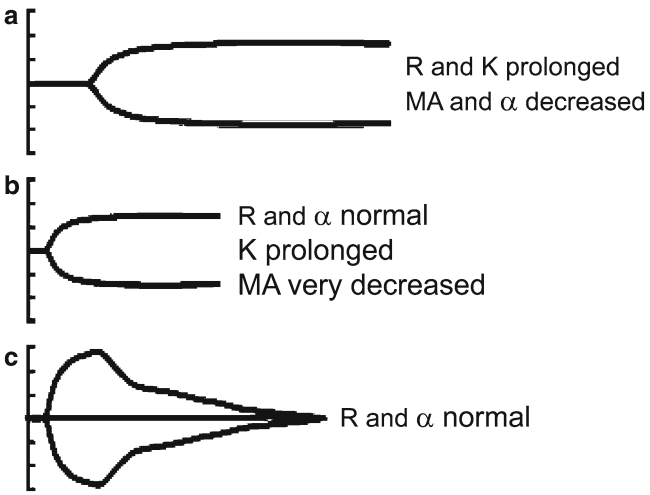

Fig. 12.4 TEG tracings in hypocoagulation abnormalities. **(a)** Decreased coagulation factors or heparin **(b)**. Thrombocytopenia or decreased platelets **(c)**. Fibrinolysis. Adapted from reference [62]

which were not available until 48 min [55]. 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 [55].

TEG data results compare well to the previous standard, CCTs. In 2011, Cotton et al. conducted a pilot study of 272 patients to investigate the role of rapid thrombelastography (r-TEG) in (1) assessing speed of results, (2) correlation with CCT findings, and (3) predictability of early transfusions of pRBCs, plasma, and platelets [55]. 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 -angle strongly correlated with platelet count, and ACT, *r*-value, -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 [55]. In addition, comparison of TEG and CCT in cardiopulmonary bypass patients found that TEG measures were useful surrogates for CCT values [57]. 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.

Table 12.1 Thrombelastography treatment algorithm for actively bleeding patients implemented at Rigshospitalet, University of Copenhagen, Denmark [4]

TEG parameter	Treatment
R (11–14 min)	2× plasma or 10 ml/kg
R > 14 min	4× plasma or 20 ml/kg
MA (46–50 mm)	1 PC or 10 ml/kg
MA < 46 mm	2 PC or 20 ml/kg
Angle < 52°	2× plasma 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, *plasma* fresh frozen plasma, *PC* platelet concentrate

Treatment algorithm based on r-TEG values implemented at the Texas Trauma Institute, University of Texas Health Science Center-Houston [63]

ACT >128 sec	Plasma and RBCs
k-time >2.5 min	Cryoprecipitate (or fibrinogen) and plasma
α-angle <60 deg	Cryoprecipitate (or fibrinogen) and plasma
mA <55 mm	Platelets and cryoprecipitate (or fibrinogen)
LY30 >3%	Tranexamic acid (or aminocaproic acid)

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 12.1 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 bypass patients [58]. 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. Despite these findings,

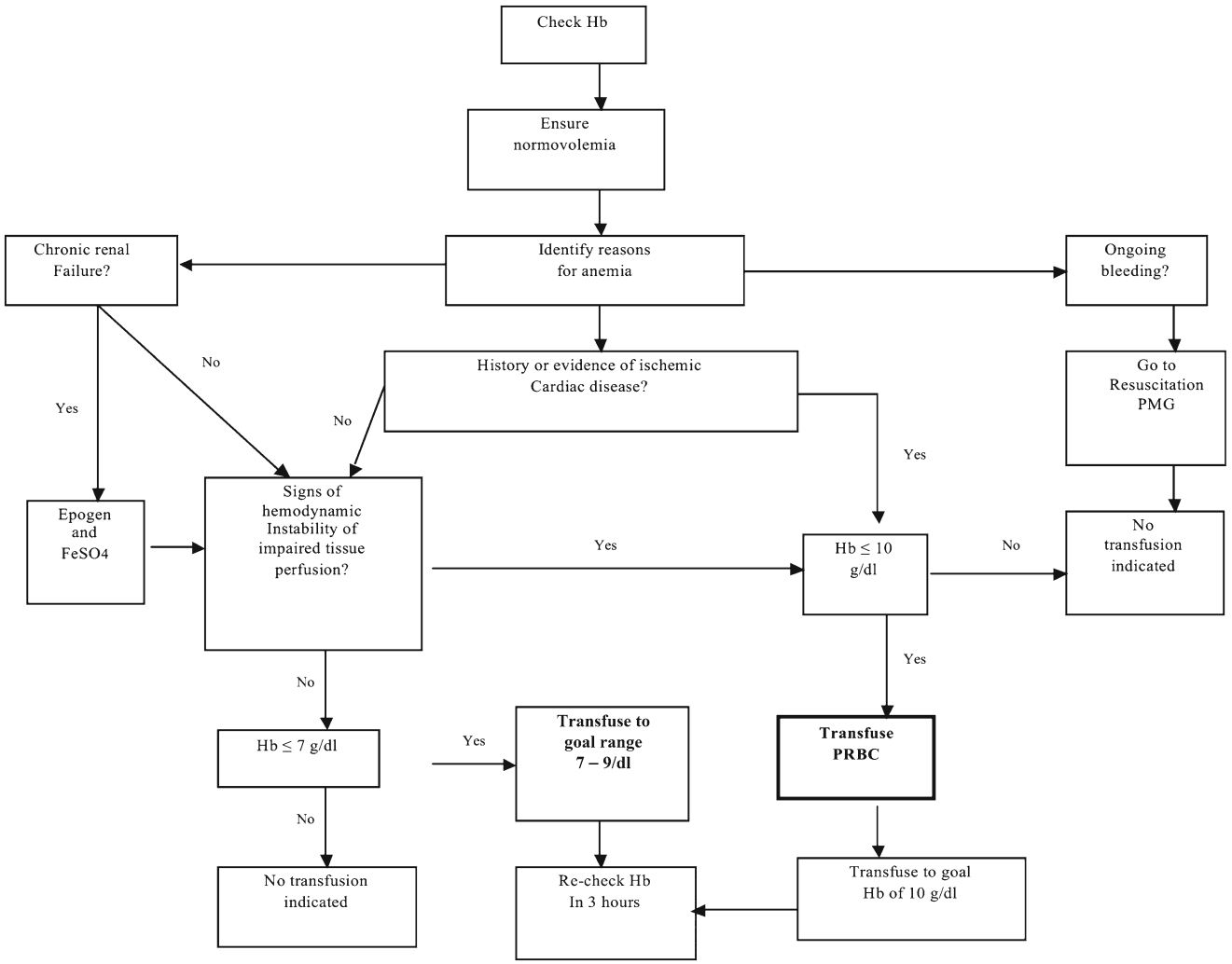

Fig. 12.5 Example of a practice management guideline for managing anemia in the ICU patient

Ronald et al.'s literature search and appraisal of 170 studies on the topic found otherwise [59]. They investigated thromboelastography in cardiac surgery patients and found 14 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 [60].

However, TEG has been found to be less sensitive for certain categories of platelet inhibition. In addition, hemostatis point of care tests such as PFA-100 and TEG are affected by nonopiod 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 [61].

Conclusion

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 pRBCs, FFP, 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 FFPs and collaborating with blood banks to cross-check appropriateness of each order (Fig. 12.5).

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