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Contemporary Transfusion Science and Challenges

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ABSTRACT

Health care professionals must understand the impact of blood product transfusions and transfusion therapy procedures to ensure high-quality patient care, positive outcomes, and wise use of resources in blood management programs. Understanding transfusions of blood and blood products is also important because of the number of treatments performed, which affects individual patients and health care system resources. This article reviews research findings to acquaint health care professionals with the most successful protocols for blood, blood product, and coagulation factor transfusions. Damage control resuscitation in bleeding trauma patients, protocols for patients without trauma who are undergoing surgical procedures that place them at risk for excessive bleeding, and protocols for patients with sepsis are addressed. Emerging research continues to help guide mass transfusion treatments (restrictive vs liberal, balanced, and goal-directed treatment). Although available study results provide some guidance, questions remain. Additional research by health care professionals is needed.

Key words: blood coagulation factors, blood component transfusion, blood transfusion, resuscitation

Of approximately 30 million patient stays in hospitals in 2013, 2.1 million (7%) included red blood cell (RBC) transfusion in the treatment plan.[1] The cumulative increase in transfusions between 2000 and 2013 was 85.8%, according to the Healthcare Cost and Utilization Project.[1] Positively, the number of patient hospital stays that included RBC transfusions decreased 13.3% from 2011 to 2013.[1] These statistics indicate the importance of establishing evidence-based protocols for transfusions, which was also supported by The Joint Commission and the American Medical Association-Convened Physician Consortium for Performance Improvement in September 2012.[2] The transfusion procedure is performed frequently and in the most critically ill patients, with the potential for dire consequences. As health care professionals, we must get it right.

Health care professionals must provide the most effective transfusion therapy possible to ensure positive patient outcomes. When evidence-based guidelines are followed, patients are best served, blood products and related treatment agents are not wasted, and resources are not allocated unnecessarily so treatment will be accessible to as many patients as

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possible at an affordable cost. Sadana et al[3] made 3 guideline-based recommendations that contribute to high-quality patient treatment and outcomes, preservation of the blood supply, and reduced transfusion costs. First, RBC transfusion is not indicated in hospitalized, hemodynamically stable adult patients with a hemoglobin level of 7.0 g/dL or more. This recommendation is consistent with restrictive guidelines discussed later in this article. Second, RBC transfusion is not indicated in patients undergoing orthopedic or cardiac surgical procedures or in patients with underlying cardiovascular disease with a hemoglobin level of 8.0 g/dL or more. Third, single-unit RBC transfusions followed by reassessment should be the standard of care for patients who are hemodynamically stable and not actively bleeding.[3] This recommendation is consistent with the Choosing Wisely Campaign ("Why give 2 when 1 will do?") and with restrictive and goal-directed treatment.[4] Today, most professionals are aware of the importance of adhering to transfusion guidelines as recommended by Sadana et al.[3] Every health care professional should understand how assessment can play a critical role in selecting the right products and treatments.

Brief History of Transfusion

In 1628 William Harvey made the first known attempt at transfusing blood, and the first human-to-human transfusion occurred in 1795. In 1818 James Blundell successfully transfused 5 of 10 patients, subsequently writing the first guidelines for performing transfusions.[5] In 1840 the first successful whole blood transfusion was performed to treat hemophilia. Trials of blood substitutes, including milk from cows, goats, and humans, were conducted from 1873 to 1880. This practice was halted in 1884 with the creation of saline infusion that resulted in fewer adverse reactions.[5]

The first 3 blood groups were identified in 1900, and in 1907 transfusion achieved a new level of safety with the use of crossmatching.[5] By the early 1900s a number of discoveries facilitated indirect transfusion rather than the direct transfusion method (vein to vein).[5] Among many advances in the 1940s was the separation of plasma into components such as albumin and fibrinogen. The first vacuum bottle was developed and not replaced by the plastic bag until 1950. The Red Cross began collecting and storing blood, and the American Association of Blood Banks (AABB) was established to promote guidelines for blood banks, publishing the first standards in 1958.[5,6] In the early 1960s platelet concentrate was used to control bleeding, and by the end of the decade storage of platelets at room temperature facilitated platelet transfusion therapy. In the decade that followed, the shelf life of other stored blood products increased.[5,6]

By the early 1970s drug companies could remove clotting factor proteins to make plasma-derived factor concentrate, used to treat bleeding disorders by replacing a missing factor protein. By the early 1990s recombinant factor concentrate was produced from animal cells.[7] Factor concentrate is used to control different types of bleeding today. After the identification of AIDS in 1981 and the discovery of HIV as its cause in 1984, screening for HIV and other viruses such as hepatitis virus (1987) and West Nile virus (2002) began. In 2002 the Food and Drug Administration published guidance for the inspection of human cells and tissues, including testing for HIV and hepatitis C virus in donated blood.[6]

Whole Blood

Evidence supports improving access to whole blood in the prehospital and early hospital settings.[8] Limited supplies or access during infrastructure abnormalities have necessitated increased availability.[8] Whole blood was used on the battlefields of World War I, in the Korean and Vietnam Wars, and in the conflicts in Afghanistan and Iraq.[8,9] Despite the frequent use of whole blood by the military, its use in civilian areas has declined since 1970, when apheresis of components became common.[8,9] However, when apheresis is not possible because of natural or manufactured disasters, the use of whole blood may be necessary.[8]

The inability to perform ABO blood typing in the prehospital setting and the rapid need for resuscitation early in the course of hospitalization have limited the use of whole blood in these settings. In 2018 Yazer et al[9] described the principles that the Trauma Hemostasis and Oxygenation Research–AABB working group used to modify AABB guidelines regarding the transfusion of whole blood. In April 2018 the AABB released updated guidelines identifying situations for whole blood use and the crossmatching required.[10] This

change allowed low-titer, group O whole blood to be used without crossmatching in patients with life-threatening hemorrhage regardless of their ABO group. The AABB defined low-titer whole blood as blood with anti-A and anti-B antibody titers of less than 200.[10]

Components

Determining the appropriate product to administer (whole blood or components) is essential. All components may be used to treat patients with coagulopathy or anemia.

Packed RBCs

Packed RBCs (PRBCs) are derived from whole blood. Administration of 1 U of PRBCs should typically increase the hemoglobin level by 1 g and hematocrit level by 3%.[11] Leukocyte reduction (removal or filtration of white blood cells) is often performed before transfusion to reduce the risk of transfusion reactions such as febrile nonhemolytic transfusion reactions.[11] PRBCs are typically transfused to replace blood volume loss in actively bleeding patients, to improve oxygen delivery to tissues, and to treat patients with symptomatic anemia, chronic anemia, or bleeding disorders.[11,12] Packed RBCs can be stored refrigerated up to 42 days.[12] Extended RBC storage can decrease oxygen delivery capacity, decrease nitric oxide metabolism, increase rigidity of the RBC membrane, and increase adherence to endothelial surfaces.[12,13]

Platelets

Platelet transfusion can prevent hemorrhage in patients with thrombocytopenia or platelet function defects.[11] One unit of pooled platelets collected by apheresis requires 4 to 6 donors, equivalent to 4 to 6 U of PRBCs or fresh frozen plasma (FFP) upon transfusion.[14] Indications for platelet transfusion in the absence of active bleeding include a major surgical procedure or invasive procedure in a patient with a platelet count of 50 × 103/μL or less, ocular or neurological surgical procedure in a patient with a platelet count of 100 × 103/μL or less, a patient with an overall platelet count of 10 × 103/μL or less, and a temperature greater than 38°C in a patient with a platelet count of 20 × 103/μL or less.[11,14] Platelets are stored warm and are the most likely cause of contamination from gram-positive and gram-negative bacteria.[15]

Plasma or Fresh Frozen Plasma

Plasma is a derivative of whole blood and is kept in 2 forms: thawed (containing less factor V and VIII) and fresh frozen (containing albumin, fibrinogen, and factors II, VII, IX, X, and XI). Fresh frozen plasma can be stored for up to 28 days, although decreases in factors V and VIII are noted by storage day 5.[11,15] Plasma transfusion should be considered in some massive transfusion situations. For example, an international normalized ratio (INR) of greater than 1.6 in a patient with active bleeding warrants the use of plasma.[11,16] Reversal of a lower INR (eg, < 1.6) requires greater amounts of FFP to correct than would reversal of an INR of 5.2.[17] Emergency reversal of warfarin during major bleeding or intracranial hemorrhage also warrants the use of plasma.[11,16] In addition, plasma may be used to treat acute disseminated intravascular coagulopathy, specifically during the time spent identifying the cause.[11,16] Plasma should be used to treat microvascular bleeding as replacement fluid for apheresis in patients with thrombotic microangiopathies and hereditary angioedema.[11,16]

The Reversal of Trauma-Induced Coagulopathy (RETIC) study compared FFP with fibrinogen concentrate as a first-line treatment of coagulopathy in trauma patients. The results showed an increased risk of multiple organ failure.[18] The RETIC study showed that FFP was not the best choice for limiting blood loss or correcting trauma-induced coagulopathy as compared with fibrinogen concentrate.[18]

Cryoprecipitate

One unit of cryoprecipitate is acquired from 10 U of pooled reduced plasma.[11,15,19] Cryoprecipitate contains von Willebrand factor, factors VIII and XIII, and fibrinogen, all essential components to obtain hemostasis in a bleeding patient.[11,15,19] Each unit contains at least 150 mg of fibrinogen and at least 80 IU of factor VIII.[15] Cryoprecipitate is most appropriately used to treat bleeding associated with fibrinogen deficiency. It should be used only as blood product replacement therapy, not to treat specific factor deficiencies as seen in von Willebrand disease and hemophilia, and only when recombinant or virally inactive preparations are unavailable.[15] This component may be used to treat hemorrhage after cardiac surgical procedures, other surgical bleeding, and massive hemorrhage.[11] Cryoprecipitate is also used as a last line of defense to control uremic bleeding.[15]

Unlike other blood products, compatibility testing and Rh typing are not required.[15]

Albumin

Human serum albumin, a protein produced by the liver, makes up about one-half of the circulating serum proteins and is largely responsible for osmotic regulation.[20] Albumin acts as a carrier protein, transporting molecules such as hormones, enzymes, medications, and toxins.[20] It scavenges for free radicals, has hemostatic effects such as platelet function inhibition and antithrombotic effects, and controls capillary membrane permeability.[20] Albumin is responsible for the colloid pressure in plasma and is often used to augment blood volume.[20]

Specific indications for the use of albumin are hypovolemia, hypoalbuminemia, prevention of central volume depletion after large-volume paracentesis (at a dose of 6-8 g of albumin for every 1000 mL of ascitic fluid removed), ovarian hyperstimulation syndrome, adult respiratory distress syndrome, burns, hemodialysis, and cardiopulmonary bypass.[20] Human serum albumin is limited by the availability of blood donors and donations and has similar risks of viral transmission as the other blood products.[20]

Transfusion Strategies

Restrictive Versus Liberal Transfusion

Restrictive transfusion, now considered standard or usual care, is transfusion intended to maintain a hemoglobin level between 7.0 and 9.0 g/dL. Liberal transfusion is meant to maintain a hemoglobin level of 10.0 g/dL or higher.[21] In 1999 the TRICC (Transfusion Requirements in Critical Care) trial assessed the benefits of using restrictive versus liberal methods of blood transfusion in critically ill patients.[21] Hébert et al[21] found that mortality was 4.6% lower in critically ill patients and 7.4% lower in less acutely ill patients when a restrictive PRBC transfusion strategy (transfusion to treat hemoglobin levels < 7.0 g/dL) was used, compared with patients who were transfused liberally to maintain a hemoglobin level of 10.0 g/dL or greater. The TRISS (Transfusion Thresholds in Septic Shock) trial found similar results in a study of restrictive transfusion, further supporting the standard of care of transfusion to maintain a hemoglobin level of 7.0 g/dL.[22-24] The current transfusion threshold of 7.0 g/dL remains the standard of care for patients who are critically ill, including patients with sepsis but excluding those with acute coronary syndromes or other preexisting cardiovascular diseases (a goal of 8.0 g/dL is recommended for these patients).[12]

Goal-Directed Therapy

Goal-directed therapy focuses on specific targets for treatment outcomes. For example, in sepsis, early goal-directed therapy is defined as transfusion for patients with a hematocrit of 30% and central venous oxygen saturation below 70%.[25] Goal-directed therapy may be guided by laboratory data often obtained from viscoelastic tests. These data help health care professionals identify which components or factors are necessary and at what frequency to achieve a patient outcome of hemostasis.

Laboratory-defined goal-directed therapy is based on the specific component or factor that is low or missing from the bleeding patient; therapy can be tailored to the patient's dynamic needs.[26] A variety of viscoelastic tests may be used and specific treatment agents may be selected on the basis of test results.[27] Quantity and frequency of component or factor administration are based on specific viscoelastic test results.[27] Schöchl et al[26] suggested that goal-directed coagulation therapy can target maintenance or restoration of clot strength. Conventional coagulation assays can be used to guide goal-directed therapy, but they take longer than viscoelastic tests and fail to identify specifics regarding the coagulation cascade addressed by viscoelastic tests.[26,28]

Studies have helped define the goals of treatment for patients with a variety of conditions. Studies expanding on the TRICC trial found either improved or equal mortality when treating patients, including those with sepsis, with the standard protocol.[25] The ProCESS (Protocolized Care for Early Septic Shock) trial[29] and the ARISE (Australasian Resuscitation in Sepsis Evaluation) trial[30] compared early goal-directed therapy with standard practice, which included rapid recognition, early antibiotic treatment, aggressive fluid resuscitation, and transfusion for patients with a hemoglobin level of 7.0 g/dL.[25,29,30] Early goal-directed therapy, initially described by Rivers et al,[31] was defined in the ProCESS and ARISE trials as a continuous central venous oxygen saturation goal of 70% and a transfusion threshold of a hematocrit of 30%.[25,29-31] The results showed no significant difference

in mortality at 90 days between the early goal-directed therapy and standard treatment groups; however, twice as many patients in the early goal-directed therapy group as in the standard practice group received transfusions.[25] According to this information, treatment for critically ill patients, including those with sepsis, should remain standard, with a hemoglobin goal of 7.0 g/dL.[25]

Balanced-Ratio Transfusion

Balanced-ratio transfusion is defined as administering a ratio of 1 U of platelets to 1 U of plasma to 1 U of PRBCs within a 24-hour period.[32] The goal of the balanced-ratio (1:1:1) transfusion is to provide enough of each individual product to achieve the equivalent of transfusing whole blood. Therefore, platelets are not given until 6 U of PRBCs have been administered because 1 U of platelets is equal to 6 U of apheresis-pooled whole blood–derived platelets.[28]

The PROMMTT (Prospective, Observational, Multicenter, Major Trauma Transfusion) study[33] and the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial[34] tested the use of different ratios of blood products on treatment outcomes and survival, focusing on acutely bleeding trauma patients.[32] The PROMMTT trial found that a 1:1:1 ratio of plasma, platelets and RBCs decreased early mortality rates, and patients with transfusion ratios of less than 1:1:1 were 3 to 4 times more likely to die within the first 6 hours.[33] The PROMMTT trial found that increasing the transfusion ratio to 1:1:2 did not improve survival rates at 24 hours or 30 days.[34] PROMMTT showed that early administration of plasma and platelets, even without consistent ratios, improved survival.[33-35]

The 2015 PROPPR trial compared 2 transfusion ratios: a ratio of 1:1:1, in which platelets were administered early in the first round, and a ratio of 1:1:2 (in actuality 1:0:2), in which platelets were not administered until the second round of 6 U of PRBC and plasma was initiated.[28] Results of the PROPPR trial supported the results of the earlier PROMMTT trial, finding no differences in mortality at 24 hours and 30 days between treatment groups of patients with severe trauma and significant hemorrhage.[33-35] The PROPPR and PROMMTT trial results support the use of a 1:1:1 transfusion ratio immediately upon a patient's hospital arrival.[33-35]

Transfusion in patients with uncontrolled hemorrhage should follow a massive transfusion protocol (MTP), employing aggressive resuscitation rather than waiting for the results of laboratory tests such as those typically used in goal-directed therapy.[36] Classic laboratory-defined goal-directed therapy, which has been found to achieve best results for patients with transfusions administered at a 1:1:2 ratio, lags behind balanced-ratio therapy, with plasma and platelet administration approaching a cumulative ratio of 1:1:1, even without guidance of rapid laboratory test results.[34,36] For patients with trauma-associated hemorrhage, the Eastern Association for the Surgery of Trauma recommends using a 1:1:1 ratio (composed of 6 U of plasma, 1 U of apheresis or pooled platelets, and 6 U of PRBCs) for resuscitation.[37] There is little research supporting the use of balanced transfusion during episodes of nontraumatic bleeding, likely because of the lack of standardization for transfusion practices in surgical specialties and subspecialties.[32]

Massive Transfusion Protocols

The purpose of MTPs is to ensure rapid delivery of large amounts of blood products to acutely hemorrhaging patients.[38] Massive transfusion is defined as the transfusion of 10 U or more of PRBCs within a 24-hour period.[33] An analysis of 11 studies demonstrated that MTPs varied widely among institutions, with plasma to platelet to RBC ratios varying from 2:0:5 to 2:1:2. However, all 11 studies showed improved survival and decreased use and waste of blood products once a protocol was initiated.[37]

Identification of bleeding patients who require massive transfusion has long relied on the judgment of surgeons or clinicians, with minimal use of validated tools.[39] Several standardized scoring systems to determine the need for an MTP have been developed and implemented with varying levels of success. The Assessment of Blood Consumption (ABC),[38] which is supported by the Trauma Quality Improvement Program,[40] assigns a numeric value of 0 or 1 to the following criteria: penetrating mechanism, presence of free fluid on focused assessment with sonography in trauma, initial emergency department systolic blood pressure of less than 90 mm Hg, and initial emergency department heart rate of 120 beats/min or more.[38-40] A score of 2 predicts

the need for massive transfusion.[41] The ABC is a valid instrument for predicting the need for massive transfusion early in the care of a patient, with patients correctly classified 84% to 87% of the time.[41]

In a survey by the Trauma Quality Improvement Program, only 11.4% of trauma centers used a prediction score to initiate an MTP.[40] Failure to use the ABC scoring system in particular has been shown to slow physician response time by 35 minutes, compared with using clinician input alone.[39,40] The Trauma Quality Improvement Program also indicated that trauma centers used the judgment of clinicians, particularly trauma surgeons, when deciding to initiate an MTP.[40] The judgment of other physician specialists (such as anesthesiologists and emergency department physicians) and laboratory data from conventional coagulation assays and viscoelastic tests were less often used to initiate an MTP.[40] A review found that a significant downside of the ABC score was the waste of blood products, specifically plasma.[39] Use of the ABC score to activate an MTP resulted in 588 wasted units of FFP, as compared with only 88 wasted units of FFP when the MTP was initiated on the basis of clinician judgment.[39] This study also found no difference in overall mortality or volume of blood product used in a 24-hour period when comparing clinician judgment with the ABC scoring system for initiation of an MTP.[39] Having a system in place to identify the need for MTP activation, coupled with clinical acumen, may be the best approach.

Discussion of goal-directed guidance of MTPs versus ratio-based transfusion suggests that the latter formulaic approach has no significant benefits.[42] In other words, higher plasma and platelet to RBC ratios do not benefit patients or result in good management of resources.[42] A study to determine the amount, timing, and ratios of administered products, with associated morbidity and mortality in patients requiring massive transfusion, found no strong evidence to support different transfusion ratios.[35] However, despite a lack of difference in mortality at 24 hours or at 30 days, the PROPPR trial found that a fixed 1:1:1 ratio for FFP, platelets, and RBCs is associated with improved hemostasis compared with a 1:1:2 ratio.[34] Ultimately, researchers have emphasized the importance of giving the appropriate treatment at the appropriate time.[33,42] An MTP goal directed by thromboelastography may help achieve a more individualized approach.[42]

Damage Control Resuscitation

Although current MTPs are likely appropriate for 90% of patients, these protocols may not be the best course of immediate action when treating the most severely injured patients in shock with coagulopathies.[43] This caution specifically applies to the 1% to 2% of patients presenting with the deadly triad of coagulopathy, acidosis, and hypothermia.[43] For these patients a different resuscitation strategy, damage control resuscitation (DCR), might be superior to MTPs.[43,44] Damage control resuscitation seeks to avoid physiologic exhaustion by administering only treatment that is critical to immediate survival.[44]

Damage control resuscitation can be delivered in almost any situation, including emergency departments, intensive care units, operating rooms during surgical procedures, and interventional radiology suites during emergency embolization procedures.[44] Ball[44] refers to DCR as a mobile intervention that aims to arrest hemorrhage, restore blood volume, and correct coagulopathy, acidosis, and hypothermia. Hypothermia can induce failure of platelet activation, and acidosis can result in coagulation factor dysfunction, specifically impairing the thrombin generation rate that is critical to coagulation function.[43]

In one study, DCR was associated with a 2.5-fold increase in 30-day survival.[45] The study also found an overall decrease in crystalloid and blood product administration and a reduction in the inflammatory consequences of shock.[45] Shrestha et al[46] found that DCR was associated with improved survival (from 73% to 94%) and concluded that the resuscitation technique may improve outcomes after severe liver injury.

The effectiveness of DCR has resulted in the incorporation of some DCR components into MTPs.[40] Components of DCR include rapid recognition of trauma-induced coagulopathy and shock; permissive hypotension; rapid surgical control of bleeding; prevention and treatment of hypothermia, acidosis, and hypocalcemia; avoidance of hemodilution by minimizing the use of crystalloids; transfusion of RBCs, plasma, and platelets in a high unit ratio of greater than 1:1:2 or reconstituted whole blood in a unit ratio of 1:1:1; early

Table 1: Quick Reference Guide to the Coagulation Pathway and Blood Coagulation Factors

Term	Associated Factors	Laboratory Tests
Intrinsic pathway[46]	Factors I, II, IX, X, XI, and XII	Partial thromboplastin time; increasing emphasis on use of viscoelastic tests
Extrinsic pathway[46]	Factors I, II, VII, and X	Prothrombin time; increasing emphasis on use of viscoelastic tests
Common pathway[46]	Factors I, II, V, VIII, and X	
Coagulation factor concentrates	Used to replace factor proteins that are missing or lower than normal in the blood[7]; many types of clotting factors available: factor VII, factor XIII, prothrombin complex concentrate (consisting of factors II, IX, and X or factors II, VII, IX, and X, depending on targeted use[48]), and fibrinogen concentrate	

and appropriate use of coagulation factor concentrates; and use of fresh RBCs and whole blood when available.[40] Damage control resuscitation guidelines also reference the use of viscoelastic tests and viscoelastic monitoring.[40] At this point DCR practices and MTPs begin to merge.

Blood Coagulation Factors

Hemorrhage can be life-threatening whether it results from trauma, surgery, sepsis, or intrinsic or drug-induced coagulopathy. Many products (eg, whole blood, product modifiers, and factors) are available to address the various causes of bleeding. Understanding the coagulation pathway is necessary for comprehending the potential need for blood product transfusion. The intrinsic pathway (consisting of factors I, II, IX, X, XI, and XII) is measured with partial thromboplastin time. The extrinsic pathway (consisting of factors I, II, VII, and X) is measured with prothrombin time, although at present viscoelastic tests are more commonly used.[47] Factors I, II, and X can be activated either intrinsically (by endothelial injury) or extrinsically (with the release of tissue factor by endothelial cells after external damage).[47] Although the intrinsic and extrinsic pathways begin at different places in the coagulation cascade, they ultimately end in a common pathway (involving factors I, II, V, VIII, and X) to stop bleeding.[47] When these pathways lose their ability to control bleeding, interventions using specific clotting factors can aid the coagulation process.

Laboratory abnormalities should not be corrected with blood products unless the patient has clinical bleeding problems or requires a surgical procedure.[48] The use of specific factors should be considered when treating patients with a coagulopathy. These factors, also known as coagulation factor concentrates, include products such as factor VII, factor XIII (eg, recombinant, plasma derived, or von Willebrand factor), prothrombin complex concentrate (composed of factors II, IX, and X or factors II, VII, IX, and X, depending on the targeted use), and fibrinogen concentrate (Table 1).

Identifying the source of coagulopathy is important for choosing the appropriate treatment and is essential when dealing with drug-induced coagulopathies. Testing can reveal whether patients require resuscitation with blood products. Appropriate treatment for an individual patient may include only coagulation factor concentrates or both blood products and coagulation factor concentrates.

Laboratory Testing

Bleeding and coagulopathy are evaluated with multiple laboratory tests. Conventional coagulation assays, including activated partial thromboplastin time, prothrombin time, and INR, assess basic bleeding time and coagulation ability. Testing currently includes viscoelastic tests such as rotational thromboelastometry or thromboelastography, thrombin generation tests, and clot waveform analysis, all of which help identify an abnormality in the clotting cascade.[50] One study found that thromboelastography-guided resuscitation during mass transfusion, as compared with conventional coagulation assay guidance,

improved survival and required fewer plasma and platelet transfusions during the early phase of resuscitation.[42] Although more research is needed to support their use, these viscoelastic tests, referred to as viscoelastic monitoring, can guide correction of coagulopathy with specific blood product components or coagulation factor concentrates.[49] Testing has become important not only at the onset of bleeding but also throughout treatment to determine the right therapy with the right product in the right amount at the right time, as is the case with restrictive and goal-directed therapies.

A randomized trial comparing the effects of an MTP directed by viscoelastic tests (specifically thromboelastography) with a standard MTP directed by conventional coagulation assays found that a thromboelastography-directed MTP resulted in a survival benefit compared with conventional coagulation assay–based guidance. Fewer hemorrhagic deaths at 28 days and fewer early deaths at 6 hours occurred in the thromboelastography group.[42] An MTP with goals directed by thromboelastography also resulted in more ventilator-free days (18 vs 13) and intensive care unit–free days (16 vs 8.5).[42] Guidance based on conventional coagulation assays led to the use of more plasma, platelets, and cryoprecipitate without improvement of coagulation assays. Using more blood product does not necessarily result in a hemostatic advantage.[42]

Alternative and Adjunct Treatment Modalities for Coagulopathy

Alternative modalities, rather than standard blood products, may at times be the best options for treating coagulopathies. Alternative modalities may also be useful as adjuncts to MTP or DCR protocols.

Tranexamic Acid

Hyperfibrinolysis, as seen in trauma-induced coagulopathy, can be treated with tranexamic acid.[50] Tranexamic acid reduces fibrinolysis and stops plasminogen from binding to fibrin, preventing the localization of plasmin that degrades fibrin and prevents clotting.[50] Tranexamic acid use in patients with hemorrhagic shock varies, although its use in massively bleeding trauma patients has become standard and is associated with a reduced risk of mortality, according to the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) and MATTERs (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation) trials.[51,52] These landmark trials found that overall mortality from all causes, including bleeding in traumatically injured patients, improved following administration of tranexamic acid.[38,51] The CRASH-2 trial collaborators suggested that tranexamic acid may be a treatment for other bleeding conditions such as postpartum hemorrhage, although further research is required.[51] Approved originally for the treatment of bleeding from hemophilia, tranexamic acid appears promising for treating traumatically injured and bleeding patients.[26]

A risk of tranexamic acid administration is an increased potential for thrombo-occlusive events, both venous and pulmonary arterial. The frequencies of thrombo-occlusive events were similar in the CRASH-2 and MATTERs trials.[51,52] The rate of thrombo-occlusive events in the tranexamic acid administration group was 2.4% compared with 0.2% in the non–tranexamic acid group.[51] Interpretation of the increased rate of thrombo-occlusive events should take injury severity and survivorship bias into consideration; tranexamic acid reduced mortality by 27% in the overall cohort and 49% in the mass transfusion group.[52] The Eastern Association for the Surgery of Trauma conditionally recommends the use of tranexamic acid as a hemostatic agent in the early phase of treatment (within 3 hours of injury).[37]

Coagulation Factor Concentrates

Over the last 60 years, technological advancements in blood banking have allowed for the separation and purification of clotting factors and, more recently, the creation of recombinant concentrates. These concentrates are useful for treating coagulopathy and reversing anticoagulant medications.[36] The cause of coagulopathy as it relates to the coagulation cascade must be identified. Viscoelastic tests increasingly have been used to prescribe the correct factor concentrate.[53]

Factor VII. Factor VII is used to treat hemophilia A and B in patients with inhibiting antibodies to coagulation factor VIII or IX. Factor VII is also used to treat bleeding during necessary surgical or invasive procedures in patients with congenital and acquired hemophilia, factor VII deficiency, or Glanzmann thrombasthenia.[54] Off-label use of factor VII in bleeding patients increases the rate of

arterial thromboembolic events, specifically coronary and cerebral thromboembolic events.[54] Its use in trauma is not currently supported.[37] The off-label use of factor VII for traumatic and nontraumatic bleeding is not supported by current research, as compared with other coagulation factor concentrates.[54]

Fibrinogen Concentrate and Prothrombin Complex Concentrate. Several trials are currently comparing fibrinogen concentrate with fibrinogen-rich cryoprecipitate and comparing prothrombin complex concentrate with plasma.[38,55] The benefits of fibrinogen concentrate and prothrombin complex concentrate over cryoprecipitate and plasma include ease of use in the field, where blood typing may be difficult; availability for immediate use, as compared with time required for thawing frozen products; greater amounts of available fibrinogen and factors in smaller volumes, resulting in fewer episodes of circulatory overload; and lower risk of infection.[19,38] The cost, which may be a factor in some cases, depends on the product, the volume and frequency of administration needed to address the patient's needs, and associated medical care.

Fibrinogen concentrate and prothrombin complex concentrate have been used to help control bleeding in patients with traumatic injury. These products reduce the amount of plasma, PRBCs, and platelets transfused during the initial resuscitation following a traumatic injury.[55,56] Fibrinogen concentrate and prothrombin complex concentrate can be administered to patients more quickly and in lower volumes than can plasma and cryoprecipitate, reducing the risk of the dilutional effects of blood product administration.[56] Prothrombin complex concentrate may contain 3 factors (usually factors II, IX, and X) or 4 factors (typically factors II, VII, IX, and X) in a single preparation. However, unlike cryoprecipitate, prothrombin complex concentrate lacks von Willebrand factor and factors VIII and XIII, and additional replacement of these specific factors may be necessary.[19]

Coagulopathy

Surgically Induced Coagulopathy

Although massive transfusion is usually equated with resuscitation of trauma patients, it is most frequently used in the treatment of surgical and critically ill patients.[57] Unlike coagulopathies in patients with trauma, coagulopathies induced by surgical procedures and critical illness have diverse causes.[57] An analysis showed no evidence that high ratios of FFP and platelets to PRBCs improved mortality in massively infused patients without trauma (ie, patients with cardiothoracic surgical, gastrointestinal, or hepatopancreatobiliary bleeding).[57] In fact, a potential increase in morbidity was suggested.[57] The researchers acknowledged that the differences among patient conditions included in the study require more investigation into the best resuscitation strategies for patients without trauma.[57] Goal-directed therapy associated with thromboelastography may offer more positive results with nontrauma patients, although further research is needed because optimal ratios are still unknown.[49,58]

Trauma-Induced Coagulopathy

Trauma-induced coagulopathy (TIC) results from severe injury in which tissue hypoperfusion affects multiple coagulation pathways with complex interdependencies, causing a global shutdown of the coagulation system.[59] Conventional coagulation assays, specifically partial thromboplastin time and prothrombin time/INR, have been used to help diagnose TIC. However, point-of-care viscoelastic tests, including thromboelastography and rotational thromboelastometry, have received increasing interest.[59] Subtypes of TIC include coagulation factor deficiency TIC, which is diagnosed by conventional coagulation assays and characterized by increased mortality, and fibrinolytic TIC, which is characterized by activated protein C with resultant increases in end-organ failure, infectious complications, and mortality.[59] The standard treatment for TIC is balanced-ratio transfusion with limited crystalloids along with consideration of adjunct options.[59]

Although balanced-ratio transfusion remains the standard treatment for TIC, goal-directed transfusion may warrant additional attention. Trauma-induced coagulopathy may be associated with activated protein C and the deactivation of factors V and VIII, which inhibit clot formation, suggesting that the use of viscoelastic monitoring (serial viscoelastic tests to assess and guide treatment) in conjunction with adjunct treatment modalities should be further assessed.

Sepsis-Induced Coagulopathy

Sepsis, the systemic inflammatory response of the body as it attacks an infecting organism,

is the leading cause of death worldwide and has a mortality rate of 25%.[60,61] One complication of sepsis is sepsis-induced coagulopathy.[60] Current practice for the assessment and diagnosis of coagulopathy in sepsis includes the use of both conventional coagulation assays and viscoelastic tests.[60]

Coagulopathy presumes simultaneous activation throughout coagulation pathways, resulting in ongoing use and depletion of coagulation factors.[61] Sepsis-induced coagulopathy activates the coagulation cascade; thrombin is generated but not effectively counterbalanced by tissue factor pathway inhibition because of endothelial damage.[61,62] Thrombocytopenia, a common feature of sepsis, is typically seen within the first 4 days of admission to the hospital and is caused by decreased platelet production with increased platelet consumption, obliteration, or splenic sequestration.[61] Transfusion of plasma and platelets should be considered for an actively bleeding patient or a patient at risk of bleeding if a procedure is necessary.[61] Further bleeding risk from alterations in coagulation factors may indicate the use of coagulation factor concentrates (such as prothrombin complex concentrate or fibrinogen concentrate) to avoid the large volume administered with blood products such as plasma or cryoprecipitate.

Cautions and Complications of Transfusion

The complications and risks associated with blood transfusion range from minor to fatal and include transmission of bacteria, viruses, parasites, and prion diseases (such as Creutzfeldt-Jakob disease) and transfusion-associated circulatory overload.[15,63] Transfusion-related acute lung injury is associated with plasma-containing blood products, including whole blood, PRBCs, FFP, and platelets; this risk is reduced when male-donated plasma is used for high-volume transfusions.[11,63] Transfusion-related immunomodulation results from the presence of antigens from the donor blood with a corresponding downregulation of the recipient's immune system.[63]

Some of the most significant adverse effects of massive transfusion are metabolic derangements including hypocalcemia, hypomagnesemia, and hypokalemia due to citrate binding. Citrate is used as an anticoagulant in blood storage bags and converts to bicarbonate in the liver.[64] Frequent evaluation of laboratory test results is necessary to ensure adequate resuscitation with supplemental electrolytes. Citrate intoxication also may present as metabolic alkalosis.[64] Alternatively, elevated carbon dioxide production resulting from nonmassive but frequent blood transfusions can result in intracellular acidosis because of citrate.[64] Hypothermia should be avoided during massive transfusion; refrigerated blood products can rapidly lower a patient's core temperature. Hypothermia can also worsen some coagulopathies, exacerbating hemorrhage. The lethal triad of acidosis, hypothermia, and coagulopathy results in the highest mortality among patients receiving transfusions.[64] Lactated Ringer solution contains calcium and should never be used with blood products or components that contain citrate because the calcium and citrate will bind.[15]

Conclusion

The exploration of blood transfusion began hundreds of years ago. Contemporary science has increased our knowledge of the products and factors that make up whole blood, how they impact the coagulation cascade, and how to treat coagulation abnormalities and deficiencies. The best processes to treat patients have yet to be identified and may include transfusing 1 U of product at a time, performing massive transfusions based on balanced ratios, or using coagulation factor concentrates. Different methods for different transfusion situations are likely to be needed.

The use of a protocol has been shown to improve response time and access to blood products for acutely hemorrhaging patients, resulting in improved survival and decreased use and wastage of blood products.[37] Using a scoring system (specifically the ABC scoring system) rather than clinician input alone to activate an MTP has been shown to improve physician response time, although it did not affect overall mortality and the volume of blood products used.[39,40] Health care professionals should be involved in the development and implementation of evidence-based protocols for their settings.

Medical treatment of patients with hemorrhage, anemia, thrombocytopenia, or coagulopathy has significantly evolved since the first successful human-to-human transfusion in 1795, yet many questions remain. Meeting the precise needs of each patient at

the right time with the appropriate treatment is the key to improving patient outcomes and ensuring the best use of resources in our health care system. Ongoing research should continue to identify best practices for transfusion.

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None reported.

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