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Transfusion Management of Obstetric Hemorrhage

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INTRODUCTION

The importance of transfusion medicine in the management of postpartum hemorrhage (PPH) cannot be overstated and is reflected in the historical record with the first series of successful human-to-human transfusions being performed by James Blundell in 1818, a London obstetrician treating patients with PPH[1]. Blundell wrote the following[2]:

> '. . . if you have under care a patient in whom the flooding has been copious, in whom, further, the womb has been emptied, and the haemorrhages been stopped; should this woman, as I have myself on several occasions seen, be sinking gradually into the grave, so that even to those who have seen much of floodings the case appears to be without hope: under such circumstances, I affirm that it is highly proper to have recourse to the operation of transfusion, provided we are competent to perform it.'

Such prescriptions remain valid today. Without the timely availability of blood products to treat life-threatening anemia and correct the resulting coagulopathy, the morbidity and mortality from obstetric hemorrhage would surely be higher than the current estimates of 100,000–140,000 annually[3,4]. Indeed, the countries with the worst mortality rates from obstetric hemorrhage have significant disadvantages with respect to available medical care[5], including the presence of an adequate and safe blood supply[6,7].

Even in developed countries with sophisticated systems of providing medical care, delayed or improperly executed transfusion contributes to morbidity and mortality associated with obstetric hemorrhage[8]. Compared to other medical disciplines such as emergency medicine and cardiothoracic surgery, hemorrhage requiring transfusion is a relatively rare event in daily obstetric practice. Estimates for PPH incidence vary in the literature but range from 3 to 5%, with less than 1% of obstetric patients being transfused, often in the direst of emergency situations[9,10]. This circumstance results in a lack of familiarity among obstetricians regarding the indications for the use of specific blood components, requesting appropriate laboratory assessment of coagulopathies, and, of equal importance, the mechanisms for ordering blood products emergently. The recently observed increases in PPH incidence in the US and other high resource countries underscore the importance of increasing knowledge of transfusion practice among obstetricians[10,11]. The goal of this chapter is to provide a concise review of blood products and their use in obstetric hemorrhage, with emphasis on transfusion management of massive obstetric hemorrhage. *[Editor's note: This chapter comprises two major sections: a thorough discussion of the various components of blood transfusion products and an exceptional section on management of major obstetric hemorrhage. Readers have the option to continue as their specific interests direct them. L.G.K.]*

BLOOD TRANSFUSION PRODUCTS

Red blood cells

Product description and selection for transfusion

Erythrocytes are the primary delivery system of oxygen to tissues, and play a secondary role for transport of carbon dioxide and nitric oxide as well as in the minor regulation of vascular tone[12]. Erythrocytes are most commonly transfused as packed red blood cells (pRBC), a source of concentrated erythrocytes obtained from either citrated whole blood by centrifugation or the sedimentation of red cells; apheresis (the extracorporeal separation of blood components by centrifugation) is an alternative method of preparation. pRBC units are stored with citrate anticoagulant and a preservative solution to allow extension of storage up to 42 days. Volumes of pRBC units after addition of preservative solution normally range between 300 and 400 ml[13]. These pRBC products are hemoconcentrated relative to circulating blood, with typical pRBC unit hematocrits ranging from 55 to 65%[14], although flow properties remain similar to whole blood. Storage of pRBC units is maintained at 1–6°C, and units must be transfused within 4 hours after issue from the blood bank if not kept under refrigeration.

Because hemolytic transfusion reactions are a significant risk of red cell transfusion, prevention of this potentially fatal occurrence is of primary importance in the selection of pRBC units for transfusion. A

pre-transfusion type and screen test achieves this in two manners: first, identifying the patient's ABO group and RhD type and, second, screening the patient's serum for clinically significant red cell alloantibodies to other non-ABO blood group antigens. Identification of non-ABO alloimmunization is of particular importance in obstetric transfusion, as fetomaternal hemorrhage with maternal exposure to foreign RBC antigens occurs in virtually all pregnancies[15]. Red cell units selected for transfusion must not only be ABO compatible with the recipient's plasma (see Table 1), but also antigen negative for any RBC alloantibody specificity. Compatibility between donor and recipient must be determined prior to transfusion by either serologic or computer crossmatching[16]. Provision of ABO-group specific blood is typically possible within 10–15 minutes once type and screen is complete; on the other hand, identification of additional RBC alloantibodies requires serologic crossmatching which can take 45 minutes or longer, depending on compatible pRBC unit availability. When the delay in issuing type-specific or antigen-negative blood would potentially be life threatening, emergency uncrossmatched (most often group O) blood may be administered prior to completion of compatibility testing. Whenever possible, however, emergency uncrossmatched blood provided to women of childbearing age should be RhD negative to avoid the risk of RhD alloimmunization[16].

The need for large volumes of pRBC units during a massive transfusion may necessitate giving antigen-positive units to antigen-negative or previously sensitized patients. For patients who are not previously sensitized (i.e. giving RhD positive units to an RhD negative patient), this may increase the likelihood of alloimmunization, putting future pregnancies at increased risk for hemolytic disease of the fetus and newborn (HDFN). Estimations for RhD alloimmunization after transfusion range from 30 to 80%[17], with lower alloimmunization rates noted for other clinically significant RBC antigens. If under such circumstances the patient receives one RhD-positive pRBC unit, dosing of anti-RhD immunoglobulin depends on the total volume of RhD-positive red cells administered[18]. Should the patient receive two or more RhD-positive units, exchange transfusion can reduce the total circulating RhD antigen burden as well as reduce the amount of anti-RhD immunoglobulin needed for prophylaxis[19]. Regardless of the amount transfused, consultation with a transfusion medicine physician is recommended for advice regarding management.

Increased vigilance for RBC alloantibody detection should be in place for pregnancies occurring after massive transfusion. For women receiving anti-RhD immunoglobulin as prophylaxis after receiving RhD-positive RBC units, serologic testing for anti-RhD formation may not be conclusive for several months after dosing[19]. Clinicians transfusing uncrossmatched blood in the context of obstetric hemorrhage also should be aware of the increased risk of hemolytic transfusion reactions due to the risk of an undetected clinically significant recipient antibody directed against the recipient's red cells (see section on Acute hemolytic transfusion reactions below). In a patient with life-threatening hemorrhage, not uncommon in the course of PPH, the risk of hemolysis in antigen-positive transfusions to alloimmunized patients must be balanced against the risk of exsanguination.

Indications and contraindications

The only widely accepted criterion for pRBC transfusion is for treatment of symptomatic anemia. Signs and symptoms of blood loss such as diaphoresis, dizziness and tachycardia correlate with blood volume loss up to 15% of a patient's total blood volume, a volume typically lost during a normal vaginal or uncomplicated cesarean delivery[20]. These early clinical signs of hemorrhagic shock may be somewhat masked, however, by the parturient's presentation at delivery. Progression of hypovolemic shock with blood loss greater than 25–30% total blood volume will present with hypotension, agitation, tachypnea, oliguria progressing to anuria and, finally, collapse and cardiac arrest. The time duration between the early and later signs of shock is not rigid, and therefore careful attention to the patient's blood loss at time of delivery (including occult blood loss under drapes or intra-abdominally), vital signs and symptoms is critical in preventing the progression of irreversible shock by providing timely RBC transfusion[21].

Transfusion guidelines for red cells often reference specific levels as triggers in patients without active hemorrhage. For example, the American Society of Anesthesiology Task Force on Blood Product Replacement states that pRBC transfusion is rarely indicated with a hemoglobin level of more than

Table 1 ABO compatibility of blood products for adult transfusion

Recipient blood group	*Recipient alloantibodies*	*ABO Compatible blood products*			
		Packed red blood cells	*Plasma*	*Platelets**	*Cryoprecipitate*
O	Anti-A, anti-B	O	A, B, AB, O	A, B, AB, O	A, B, AB, O
A	Anti-B	A or O	A, AB	A, B, AB, O	A, B, AB, O
B	Anti-A	B or O	B, AB	A, B, AB, O	A, B, AB, O
AB	None	A, B, AB, O	AB	A, B, AB, O	A, B, AB, O

*ABO-incompatible platelet transfusions should be avoided if possible to prevent recipient hemolysis from high-titer donor ABO isoagglutinins as well as decreased platelet survival

10 g/dl and virtually always indicated with a hemoglobin less than 6 g/dl[22]. The American Association of Blood Banks (AABB) has recommended that, in stable hospitalized patients without cardiovascular disease, a restrictive RBC transfusion trigger of a hemoglobin level 7–8 g/dl be employed[23]. However, in patients with brisk hemorrhage, target hemoglobin levels (such as 8 g/dl) are often cited, but no consensus on this point exists[24].

A growing number of observational studies suggest that erythrocytes undergo significant alterations during prolonged storage that result in several adverse patient outcomes, including infection, prolonged hospital admission and a higher risk of morbidity and mortality[25]. Considering the widely recognized risks of allogeneic transfusion (infectious disease exposure, transfusion reactions and alloimmunization to RBC antigens, among others) and potential risks from RBC storage, a conservative approach to red cell transfusions may be prudent in the patient who is not experiencing acute and/or massive blood loss. Transfusion decisions between those thresholds should be driven by alterations in the physical exam and vital signs, co-morbidities and the potential for continued blood loss[26]. Stated another way, red cell transfusion should not be administered as a panacea to correct anemias when circumstances permit correction with pharmacologic or nutritional therapies, such as erythropoietin or iron supplementation.

Dose and therapeutic effects

In a 70 kg adult with normal blood volume, a single pRBC unit can be expected to increase the recipient's hemoglobin by 1 g/dl or the hematocrit by 3%. In obstetric patients, however, whose blood volume at term can be as high as 50% above baseline, the expected hemoglobin increase post-transfusion could potentially be substantially less. The accurate assessment of transfusion responses is particularly difficult in patients with active hemorrhage, so replacement of red blood cell mass may be in part driven by clinical judgment and the use of massive transfusion protocols (see below).

Plasma

Product description and selection for transfusion

Plasma is the acellular fraction of blood, separated from the cellular blood components by either centrifugation of citrated whole blood or donor apheresis, with typical units averaging just under 300 ml volume. Currently, multiple forms of plasma are in use worldwide for replacement of all coagulation factors, including the labile factors FV and FVIII. The most widely recognized form is fresh frozen plasma (FFP), so named because of the regulatory requirement for freezing at −18°C or below within 8 hours of collection[13]. Plasma frozen within 24 hours after phlebotomy (FP24) is a product with growing usage; it is similar to FFP in its preparation from whole blood except that it is frozen at or below −18°C within 24 hours after collection[13]. The preparation of plasma products for transfusion requires thawing at 30–37°C and typically requires approximately 30 minutes. If the prepared plasma is not transfused within the initial 24-hour post-thaw period, it can be relabeled as 'thawed plasma' for use within 5 days after the initial thaw[27]. The use of thawed plasma not only extends the available plasma inventory, but also provides rapidly available plasma products for management of massive hemorrhage, particularly emergency uncrossmatched AB plasma for use when the patient's blood type is unknown[28]. Solvent/detergent-treated plasma (SD-P) is an additional pooled plasma product which undergoes a pathogen inactivation treatment, most frequently with 1% tri-(n-butyl)phosphate and 1% Triton-X 100. This treatment significantly inactivates lipid-enveloped viruses such as HIV[29], but is ineffective against non-lipid enveloped viruses such as hepatitis A. Although SD-P retains clotting factor levels close to those in other licensed plasma products, some reductions in protein C, protein S and antitrypsin activity have been noted[30,31]. Currently this product is not approved for use in the US, but is available in Europe and other jurisdictions.

Plasma contains ABO isoagglutinins, the naturally occurring antibodies directed against ABO antigens, and therefore must be ABO-compatible with the recipient's red cells (see Table 1). Group AB plasma, which lacks the isoagglutinins directed against A and B antigens, is compatible with all blood types and is used as emergency release plasma when there is insufficient time for determining the recipient's blood type. RhD compatibility between donor and recipient is not required for plasma transfusion.

Indications

Notable variation exists in published guidelines for plasma transfusion[32], although agreement is present on its indication for replacement of coagulation factors in bleeding or surgical patients, particularly those suffering from disseminated intravascular coagulation (DIC) or undergoing massive transfusion. Consensus on laboratory values for transfusion 'triggers' is lacking, but many guidelines recommend use of the international normalized ratio (INR) at or greater than 1.5 as a range which would indicate the need for plasma transfusion[33]. For massive hemorrhage, empiric transfusion of plasma in set ratios to RBC units is widely practiced (as discussed in the section on massive transfusion), although definitive data for accepting this practice as standard of care are lacking[34].

Plasma is indicated for coagulation factor replacement in patients with congenital factor deficiencies (such as factors II, V, X and XI), but should not be used for factor replacement in congenital factor deficiencies if a specific factor concentrate is available (e.g. FVIII in hemophilia A patients). Additional indications include rapid reversal of warfarin in an actively bleeding patient, but considering the contraindication

for use of warfarin in pregnancy, such use should virtually never be seen in routine obstetric practice. Contraindications for plasma include its use as a colloid blood volume expander, a nutritional supplement, or as a source of immunoglobulin.

Dose and therapeutic effect

A volume of 1 ml of plasma in a non-pregnant individual contains approximately 1 unit of coagulation factor activity; plasma products contain slightly less than 1 U/ml clotting factors due to the approximately 10% dilution from the anticoagulant solution[35] and the biological variability in factor levels between individual donors[36]. Administration of a 10–20 ml/kg dose of plasma typically increases circulating coagulation factor levels by 20–30%[37]. This dosage would be appropriate for FFP and FP24, as well as for thawed plasma; these three products are considered essentially equivalent for almost all clotting factors except for FV and FVIII, despite slight variations between clotting factors existing between these products[38–40]. Higher plasma doses present increasing risks for volume overload in the recipient unless given in the context of ongoing blood loss or therapeutic plasmapheresis.

Cryoprecipitate and plasma, cryoprecipitate reduced

Product description and selection for transfusion

Cryoprecipitate, also known as cryoprecipitated antihemophilic factor or 'cryo', is a blood fraction derived from frozen plasma by thawing at 1–6°C and collection of the cold-precipitated proteins, typically yielding 10–15 ml per plasma unit derived from whole blood. This fraction contains enriched amounts of factor VIII, von Willebrand factor (vWF), fibrinogen, fibronectin and factor XIII[13]. Cryoprecipitate is stored frozen at −18°C or below, and preparation time for this product also takes 30 minutes or more for thawing and pooling individual units into one dose. Unlike plasma, cryoprecipitate cannot be stored in a thawed form, and it is the blood product which routinely takes the longest time to prepare when used in massive transfusion. After thawing, cryoprecipitate must be kept at room temperature prior to transfusion. Cryoprecipitate administration in adults does not need to be ABO compatible, although the use of large volumes of ABO-incompatible cryoprecipitate may result in positive direct antiglobulin test results in recipients and, rarely, mild hemolysis[41]. Rh compatibility does not need to be considered for pre-transfusion product selection.

The remaining plasma supernatant after the preparation of cryoprecipitate is termed plasma, cryoprecipitate-reduced, also known as 'cryo-poor plasma' or cryosupernatant. This blood fraction is depleted in vWF, FVIII, FXIII and fibrinogen as compared to other plasma products. However, many other remaining clotting factors are found at levels similar to those in FFP or FP24, including factors II, V, VII, IX, X and XI[13,35].

Indications, dosage and therapeutic effect

Cryoprecipitate was originally used as a source of FVIII in patients with hemophilia A; however, the availability of safer and more concentrated FVIII sources has largely superseded its use in these patients. The primary indication for cryoprecipitate in modern transfusion practice is as a fibrinogen concentrate[41]. Cryoprecipitate remains the only widely available fibrinogen concentrate in the US, whereas purified pharmacologic fibrinogen concentrates are available in Europe[42]. Each unit of cryoprecipitate is expected (according to FDA requirement) to contain at least more than 80 IU FVIII and more than 150 mg fibrinogen, with typical adult doses ranging from 6 to 10 pooled units. The 2009 Circular of Information jointly issued by the FDA, the Red Cross, the AABB and other responsible organizations recommends the following formula for calculating cryoprecipitate dosage: body weight (in kg) × 0.02 = number of cryoprecipitate units to raise fibrinogen by 50–100 mg/dl[13]. Recovery of transfused fibrinogen from cryoprecipitate can be impacted by thrombosis or fibrinolysis. A recent retrospective review of plasma fibrinogen increments following cryoprecipitate transfusion in the setting of trauma found a mean increase of 55 mg/dl after an average of 8.7 units (±1.7) transfused[43].

The depletion of FVIII, fibrinogen, vWF and FXIII in cryosupernatant limits its utility for use as a plasma product, and it is not an equivalent substitute for FFP, FP24, or thawed plasma. The primary use for cryosupernatant is as a replacement fluid during therapeutic apheresis for treatment of thrombotic thrombocytopenic purpura[13]. However, it has potential utility for treating acquired coagulation factor deficiency in Jehovah's Witness patients. Whereas many Jehovah's Witness patients refuse transfusion, the Jehovah's Witness community leadership has allowed for individuals to consider accepting processed fractions of blood products[44]. Cryoprecipitate, as a fraction of plasma, has been accepted by some Jehovah's Witness patients in treating coagulopathy associated with cardiopulmonary bypass[45]. Similarly, some Jehovah's Witness patients may accept cryosupernatant (after informed consent) for treating other sources of acquired clotting factor deficiencies[46], such as obstetric hemorrhage (see Chapter 72 for a full discussion of PPH in Jehovah's Witness patients).

Platelets

Product description

Platelets are small (2–3 μm in diameter) anucleate cell fragments which not only bind to injury sites, providing a phospholipid scaffold upon which coagulation enzymes assemble for thrombin generation, but also contribute key protein and molecular elements for fibrin clot formation[47]. Platelets for transfusion are obtained from preparation of platelet concentrates, whole blood or donor platelet apheresis. Platelet

concentrates contain greater than 5.5×10^{10} platelets per unit derived from a single 450–500 ml whole blood collection, with a typical adult dose formed by pooling four to six concentrates[13]. Apheresis platelets contain greater than 3×10^{11} platelets per unit, and have the advantage over platelet concentrates in that they represent only a single donor exposure per transfusion, reducing the risk of transfusion-transmitted infections[48]. Some *in vitro* differences have been observed between platelets derived from the different collection methods[49], although differences regarding their *in vivo* properties remain uncertain. Most blood banks and transfusion services use these products interchangeably, driven in part by cost and individual product availability[50].

Platelet concentrates have several properties which make them unique among the blood products discussed in this chapter. First, platelets are cold intolerant. Exposure of platelet concentrates to refrigeration temperatures of 4°C results in platelet shape changes, functional defects and increased circulatory clearance rates[51–53]. Second, platelets have the shortest shelf life of any transfused product: the time from the point of collection to expiration is a mere 5 days. This is due in part to the relatively short functional life of platelets (7–10 days in the circulation), but also to the risks of storing platelets at room temperature which allows for ongoing bacterial proliferation of potentially contaminated units[54]. Platelets, whether in the form of platelet concentrate or apheresis platelets, are a plasma-rich product. In ideal circumstances, this product should be ABO compatible with the recipient to avoid the infusion of ABO isoagglutinins. However, inventory shortages may prompt the use of ABO-incompatible platelets at times. Whereas the vast majority of ABO-incompatible platelet transfusion recipients suffer no ill effects, hemolytic transfusion reactions have been reported in rare instances after such transfusions[55,56]. The ABO-incompatible platelet transfusions at highest risk are those from group O single donor products administered to group A or B recipients, due to the tendency of group O individuals to form high titer anti-A and anti-B[57]. Finally, although platelets do not bear RhD antigens, trace red blood cell content in platelet products support the practice of transfusing RhD-negative donor platelets to RhD-negative recipients to avoid alloimmunization. Should inventory shortages necessitate transfusion of RhD-positive platelets to RhD-negative recipients, treatment with an anti-RhD immunoglobulin product can be considered to avoid RhD alloimmunization[56]. The British Committee for Standards in Haematology recommend 250 IU anti-RhD immunoglobulin for prophylaxis of up to five adult-sized doses of RhD-positive platelets given in a 6 week period[19].

Indication, dose and therapeutic effect

Platelet transfusion serves two purposes: (1) as prophylaxis against hemorrhage in severely thrombocytopenic patients (most widely defined as less than 10,000/μl platelets); and (2) for treatment of bleeding in patients with thrombocytopenia or platelet dysfunction[13,48,58]. Circumstances necessitating prophylactic platelet transfusion are rarely encountered in parturients, and the less than 10,000/μl platelet transfusion trigger was established primarily in patients with hematologic malignancy and/or stem cell transplant recipients with hypoproliferative thrombocytopenia[48]. For obstetric patients, on the other hand, a higher prophylactic transfusion threshold may be considered in light of the large vascular uteroplacental interface, but to date no studies specifically address this clinical question. Therapeutic platelet transfusion in the context of massive transfusions or DIC should be administered with the aim of keeping the recipient's platelet count at more than 50×10^9/l[59].

MASSIVE TRANSFUSION IN POSTPARTUM HEMORRHAGE

Timely recognition of excessive blood loss of PPH is critical for successful transfusion management. Such recognition is challenging, not only because of difficulties in assessing volume of blood loss at the time of delivery, but also because of variability in the definitions of massive hemorrhage. Although the definition of excessive hemorrhage in obstetric patients at time of delivery has been widely accepted as blood loss of greater than 500 ml for vaginal deliveries and 1000 ml for cesarean deliveries, as discussed in other chapters of the text, obstetricians' estimations of blood loss at time of delivery generally are erroneous and skewed towards underestimations of these volumes[60] (see Chapters 9 and 41). Moreover, the reported literature uses a variety of definitions when clinicians are assessing hemorrhage.

Hemoglobin levels showing a 10 g/dl decrease or greater from antepartum levels have been suggested as a measure of severe PPH, but this construct has very limited practical utility during acute management[61]. Definitions of what constitutes massive hemorrhage in non-obstetric patients (primarily civilian trauma or military casualties) have shown even greater variability, and have been cited as transfusion of more than 10 pRBC units within 24 hours, a loss of more than one entire blood volume within 24 hours, or a loss of more than 50% of the total blood volume within 3 hours[35,62]. Meta-analysis of retrospective massive transfusion studies suggests that these massive hemorrhage definitions under count patients who suffer mortality due to hemorrhage and who may benefit from management with massive transfusion protocols[63]. Clinicians, in general, and obstetricians, in particular, are therefore left to balance multiple considerations at the bedside when determining whether a parturient has crossed the threshold into the zone of what will retrospectively be regarded as excessive blood loss.

Massive transfusion in trauma

Equally daunting to obstetricians is determining the appropriate transfusion management in massive PPH,

particularly as no published studies at the time of this writing describe results and outcomes from this specific population on which to base decisions[64]. Rather, the vast majority of data regarding massive transfusion is derived from military and trauma settings and/or databases. Uncontrolled hemorrhage in trauma patients is often complicated by coagulopathy arising from tissue damage, hypothermia, under perfusion and acidosis. Further complicating this self-perpetuating 'bloody vicious cycle'[65] was the adoption of resuscitation protocols first derived from casualty management in the Korean and the Vietnam Wars. These protocols promoted aggressive crystalloid infusion first to support blood pressure and cardiac output, followed by red cell transfusion to replace oxygen-carrying capacity; and only then were plasma and platelet transfusions recommended to correct coagulopathy observed in laboratory testing, a factor which required time and expertise, and clearly delays treatment in obstetric patients[66]. Although worldwide expert opinion embraced these protocols in the 1980s and early 1990s[67–69], they were never subject to randomized controlled trials. Eventually it became apparent that high volume crystalloid resuscitation not only increased coagulopathy in patients with hemorrhagic shock, but also increased adverse outcomes such as acute respiratory distress syndrome and cardiac dysfunction[70].

A retrospective review of Iraq military casualties drew attention to the potential for the preemptive use of plasma, showing a striking difference between mortality rates in patients receiving low and high ratio plasma : RBC concentrations (1 : 8 plasma : RBC, 69% mortality versus 1 : 1.4 plasma : RBC ratio, 19% mortality)[71]. Similar findings have been found in controlled observational studies of trauma patients requiring massive transfusion, with improved survival noted in patients who received higher plasma : RBC transfusion ratios[66,72,73]. Pooled analysis of 10 observational studies where the plasma : RBC ratios ranged from 1 : 2.5 to 1 : 1 showed an association with significantly reduced mortality (odds ratio 0.38, 95% confidence interval 0.24–0.60)[74].

Platelet transfusion in trauma-related coagulopathy has similarly been examined, with both military[75] and civilian data[76,77] showing improved survival with higher platelet : RBC transfusion ratios. Based on the data emerging from recent military experiences, the Surgeon General of the United States Army issued guidelines for use of massive transfusion in combat as follows: plasma : RBC : platelet transfusions in a 1 : 1 : 1 ratio, with a single platelet unit equaling a platelet concentrate derived from whole blood collection[78].

Fibrinogen

The early coagulopathy seen in trauma not only results in coagulation factor and platelet consumption, but also hypofibrinogenemia. Observational studies performed during the early 21st century suggest that early transfusion of cryoprecipitate may convey a survival advantage in trauma patients. A retrospective review of 252 massively transfused military casualties showed a high fibrinogen : RBC ratio, defined as 0.2 g fibrinogen or more (totaled from all transfused blood products) per RBC unit, was significantly associated with improved survival (24% mortality in high fibrinogen : RBC versus 52% mortality in low fibrinogen : RBC ratios, $p < 0.001$) and decreased deaths due to hemorrhage (44% incidence in high fibrinogen : RBC group versus 85% incidence in low fibrinogen : RBC group, $p < 0.001$)[79]. Civilian trauma data comparing a prospective cohort ($n = 132$) to historic controls ($n = 84$) showed a similar association, with those receiving more than 1 : 1 cryoprecipitate : RBC units having a significantly higher 24-hour and 30-day survival as compared to those receiving less than 1 : 2 cryoprecipitate : RBC (84% versus 57% and 66% versus 41% survivals, respectively; $p < 0.01$ for both)[76].

These findings regarding the role of fibrinogen in massive transfusion may be of particular importance for obstetric hemorrhage management, as pregnant women between 35 and 42 weeks' gestation show a marked elevation in fibrinogen levels, with reference ranges reported from 350 to 650 mg/dl as compared to 197–401 mg/dl in non-pregnant individuals[80]. Clinical observation by obstetricians suggests that the fibrinogen level decreases more rapidly in the obstetric patient undergoing massive hemorrhage compared to individuals with war-induced or civilian trauma, but this possibility has not been subject to verification (personal communication from Cynthia Wong to Louis Keith February 22, 2012). Charbit and colleagues examined 128 women suffering from PPH, defined as either severe or non-severe, to determine whether routine coagulation laboratory testing abnormalities were predictive of PPH severity[81]. In multivariate analysis, fibrinogen levels less than 2 g/dl were the only marker associated with PPH severity, with a positive predictive value of 100%. *[Editor's note: This study is seminal and has not yet been replicated in the published literature. However, a personal discussion with Dr Anne-Sophie Ducloy-Bouthors in London on February 25, 2012 confirmed that this was her experience as well, when asked specifically about the Charbit reference. L.G.K.]*

There is biologic plausibility in considering that, similar to massive transfusion in trauma, patients with obstetric hemorrhage may benefit from more aggressive fibrinogen replacement. Indeed, fibrinogen concentrates such as Haemocomplettan® or RiaSTAP® (both CSL Behring, Marberg, Germany), have been used in obstetric hemorrhage management in Europe, with salutary patient outcomes presented as correction of hypofibrinogenemia or reduced blood product transfusion[82–84]. A randomized controlled trial in Denmark is currently enrolling subjects, comparing 2 g of fibrinogen concentrate versus saline early in the course of PPH with the primary outcome examining the incidence of allogeneic blood product transfusion[85]. This study should provide insight into the utility of fibrinogen concentrates in PPH management.

Massive transfusion protocols for postpartum hemorrhage

The potential for applying these emerging massive transfusion data from trauma and military cohorts to patients with PPH is slowly becoming more appreciated by the obstetric community[86]. However, not all institutions have specific protocols for obstetric massive transfusion[87], and fewer still have published these protocols. In 2007, Burtelow and colleagues from Stanford University Medical Center described applying a trauma massive transfusion protocol to obstetric patients suffering PPH[88]. In this protocol, an emergency release package of six pRBC, four thawed plasma and one apheresis platelet are rapidly prepared and delivered in less than 15 minutes. The protocol also describes reflexive laboratory assessment of coagulopathy, with initial values for PT/aPTT, fibrinogen, D-dimer and a complete blood count drawn at the time of protocol activation. Additional blood product administration was given algorithmically based on abnormal lab values in the context of ongoing hemorrhage, with additional massive transfusion protocol (MTP) packages delivered as needed. The California Maternal Quality Care Collaborative Task Force collated best practices from nine maternal hemorrhage protocols derived from expert opinion in obstetrics and hematology[89]. Common elements between these protocols included: (1) partnership between obstetric teams and transfusion services for rapid release of 'obstetrical hemorrhage packs' to include RBC, platelets, plasma and cryoprecipitate; (2) availability of a local expert (hematologist or transfusion medicine physician) for consultation as needed; and (3) a scripted protocol for maternal hemorrhage response which is periodically practiced and assessed. In addition, laboratory assessment of hemoglobin, platelet count, PT/aPTT and fibrinogen is recommended to be performed every 30 minutes until the patient is stabilized.

These published obstetric hemorrhage MTPs bear similarities to trauma MTPs in their higher plasma : RBC ratios (both published protocols having no lower than a 2 : 3 ratio) and early incorporation of platelets and cryoprecipitate. Despite this, creation of obstetric transfusion protocols based on the current trauma data should be approached with a sense of caution for several reasons. Current data on the use of high plasma : RBC ratios in trauma settings are entirely derived from observational studies. Numerous potential sources of bias have been identified in these studies, such as survivor bias, failure to include other pro-hemostatic therapies (such as recombinant factor VIIa) in data interpretation, and lack of standardization between treatment groups[66,72]. Moreover, the majority of trauma data are collected from male patients, particularly those data from military settings. Significant baseline hematologic differences exist between this mostly male cohort and pregnant females, particularly in the coagulation system where pregnant women have significantly higher levels of fibrinogen, factors VII, VIII and IX, and protein S[80] as well as significant expansion of plasma volume. Additionally, higher plasma doses during massive transfusion could potentially be associated with a greater risk of acute respiratory distress syndrome, as suggested by a prospective study of over 1100 adults with blunt trauma[90].

A collaborative review of observational studies to date by the AABB Clinical Transfusion Medicine Committee and subject matter experts recommends neither for nor against use of plasma : RBC transfusion ratios of 1 : 3 or more[91]. Nevertheless, the panel noted that both the death rate and the risk of multiorgan failure were both reduced by 60% as compared to controls, and strongly urged that the question of high plasma : RBC transfusion ratios be addressed in randomized controlled trials. However, until such studies are performed in patients suffering from obstetric hemorrhage, questions will remain regarding the fundamental pathophysiologic difference between trauma and obstetric massive transfusion[64].

Antifibrinolytic therapy

Pharmacologic therapy has shown promise in serving as an adjunct to transfusion in PPH management. Antifibrinolytics may be a particularly useful therapy in light of the increased fibrinolysis which occurs during the third stage of labor and persists for several hours after delivery[92]. Tranexamic acid (TXA), a lysine analogue which competitively blocks plasminogen binding to fibrin, has garnered attention for its use in both preventing and treating PPH[93,94]. A recent multicentered randomized trial examined use of high-dose TXA in treating acute PPH as defined by blood loss exceeding 800 ml within 2 hours after vaginal delivery[95]. Women were randomized to receive either placebo or 4 g TXA given over 1 hour followed with 1 g infused over 6 hours, with transfusion limited to pRBC units until blood loss exceeded 2500 ml ($n = 72$ for each group). Blood loss in the 6 hours following delivery was significantly lower in the TXA group than in the control group (median 170 ml; first to third quartiles, 58–323 ml) than in controls (221 ml; first to third quartiles 110–543 ml) ($p = 0.041$). Additionally, the duration of severe PPH was significantly shorter (median 30 minutes (first to third quartile, 15–40 minutes) compared to median 30 minutes (first to third quartile, 20–93 minutes) ($p = 0.001$), and the overall amount of either plasma transfusion or fibrinogen concentrate administration was significantly less in the TXA group as compared to controls ($n = 1$ versus $n = 7$, $p < 0.001$).

A further large-scale investigation of TXA is currently enrolling subjects: the World Maternal Antifibrinolytic (WOMAN) trial, sponsored by the London School of Hygiene and Tropical Medicine[96,97]. This 15,000 subject multicenter randomized controlled trial will be investigating whether TXA reduces mortality, rate of hysterectomy and other morbidities in PPH following vaginal or cesarean delivery, as well

as examining critical safety issues such as thromboembolic events after its use in the setting of PPH. The impact of maternal treatment with TXA on the rate of thromboembolism in breastfed babies will also be monitored. The current literature is encouraging for use of TXA to reduce PPH severity and the overall exposure to allogeneic transfusion. The results of the WOMAN trial will help provide definitive evidence regarding incorporation of tranexamic acid in PPH protocols.

COMPLICATIONS OF TRANSFUSION

Transfusion complications are similar to the potential deleterious effects of organ transplantation in that they often derive from immunologic complications or contamination with infectious agents. A comprehensive review of all adverse transfusion reactions is beyond the scope of this chapter, but transfusion management of obstetric hemorrhages requires familiarity with acute transfusion reactions which may complicate therapy and require rapid intervention (Table 2).

Acute hemolytic transfusion reaction

Acute hemolytic transfusion reactions are one of the most serious complications of transfusion and remain one of the leading causes of transfusion-related mortality worldwide[98]. They result from RBC lysis or accelerated clearance by the reticuloendothelial system resulting from RBC transfusion into a recipient with pre-formed antibodies directed against donor erythrocytes. Only rarely have plasma-rich blood products been implicated in hemolytic reactions directed against recipient erythrocytes[55,56]. Antibodies directed against ABO antigens are the most frequent source of incompatibility, but occasionally alloimmunization against other antigens such as RhD, Duffy, Kidd and Kell is also implicated. The most frequent causes of hemolytic transfusion reactions are clerical errors in patient identification (either at the time of pretransfusion sample collection or at the point of transfusion) or laboratory errors during compatibility testing[99].

Signs and symptoms of acute hemolysis are not specific, and may include one or more of the following: fever, hypotension, chills/rigors, pain at the infusion site, flank/back/chest pain and coagulopathic bleeding. While these findings are potentially confounded in patients suffering from PPH, hemoglobinemia and hemoglobinuria are the most reliable clues that intravascular hemolysis has transpired. Complement cascade activation by hemolytic antibodies precipitates the lysis of erythrocytes, as well as generating bradykinin, histamines and anaphylatoxins, which may result in shock and DIC[99]. As hemolytic transfusion reactions have been reported after transfusion volumes as small as 30 ml[100], clinicians must maintain constant vigilance for early indicators and immediately terminate any transfusion when such a reaction is first suspected. Rapid notification of the blood bank is essential for serologic compatibility investigation as well as for confirming accuracy of patient identification. Patients may develop hemolytic transfusion reactions after receiving pRBC units having undergone mechanical or osmotic hemolysis due to mishandling, infusion through small-bore IV needles, or co-infusion through IV lines containing incompatible patient support should be directed towards early treatment of hypotension and maintenance of urine output with intravenous fluids, diuretics, inotropes and vasopressors. Patients should also be assessed for the development of DIC with clotting factor replacement as required with platelet, plasma and either cryoprecipitate or fibrinogen concentrate administration (see Blood component administration box below).

Table 2 Acute versus delayed adverse transfusion reactions

Acute (onset <24 h post-transfusion)	*Delayed (onset >24 h post-transfusion)*
Acute hemolysis	Delayed hemolysis
Febrile non-hemolytic	Post-transfusion purpura
Bacterial contamination	Iron overload
Transfusion-related acute lung injury (TRALI)	Graft-versus-host disease
Allergic/anaphylactic	Transfusion-related immunomodulation
Volume overload	Infectious disease*
Metabolic derangement	HIV
Hypocalcemia/citrate toxicity	Viral hepatitis
Hyperkalemia	HTLV
Hypothermia	Cytomegalovirus
Acidosis	Syphilis
	West Nile virus
	Trypanosoma cruzi
	Creutzfeld-Jacob disease
	Malaria

*Note: This is a partial list of transfusion-transmitted infections. Potentially, a multitude of infectious diseases may be transfusion transmissible
HTLV, human T-cell lymphotropic virus

Septic transfusion reaction

In most countries, bacterial contamination of blood products remains the leading infectious complication of transfusion. Sources of bacterial contamination most commonly are the donor's skin and blood, but loss of blood product sterility can occur at any step from the point of collection to the moment of bedside infusion. Gram-positive skin commensal organisms such as *Staphylococcus epidermidis* are the most frequent contaminants, but Gram-negative bacteria are also implicated, particularly in severe reactions resulting from endotoxin accumulation in the contaminated blood products[105]. The most commonly affected products are platelet concentrates due to their requirement for storage at room temperature, occurring in up to 1 : 2000 platelet units[106]. While 1 : 2000 platelets are contaminated, the incidence of septic reactions is much lower (around 1 : 12,000 units). Incidence of reactions is dependent upon the bacterial burden in the unit at the time of transfusion and the immune state of the recipient. Many countries, including the US, have culture-based bacterial screening of platelet concentrates. Such procedures have significantly decreased, but not entirely eliminated, the risk of

BLOOD COMPONENT ADMINISTRATION

Protocols and procedures for blood administration are the last line of defense in preventing errors which can lead to potentially fatal transfusion reactions. The following list describes critical steps in bedside safety; failure to ensure any of these should prompt withholding of transfusion and return of the blood product to the blood bank[101,102]:

(1) *Positive patient identification* Confirmation of at least two independent patient identifiers (such as full name and date of birth or medical record number) should be performed at the bedside with a second health care provider or barcoding system.

(2) *Component identification* The compatibility tag attached to the unit must be compared to the patient's identification to confirm the unit has been crossmatched to the patient. Spelling discrepancies or omissions in identifier data are contraindications for proceeding with transfusion.

(3) *Medical order* Verify that the patient has a transfusion order by a licensed medical professional for the specific component. Also confirm ordered modifications of the blood product have been performed by inspecting the label (i.e. leukoreduction or irradiation).

(4) *Blood type* Confirm compatibility of the component's ABO group and Rh type with that of the recipient.

(5) *Visual inspection* Blood components should not be transfused if there are visible abnormalities, such as discoloration, clots, or loss of bag integrity.

(6) *Blood product expiration* The expiration date of the component must be confirmed. In addition, blood components should be infused within 4 hours of time of dispense from the blood bank.

Filters and infusion sets

Blood components are administered through IV tubing sets with filters designed to remove harmful clots and debris. Standard sets contain filters with pore sizes between 170 and 260 μm, while microaggregate filters (most frequently used during cardiac bypass blood recirculation) have pore sizes of 20–40 μm. Separate filters specifically designed for leukocyte removal are required for bedside leukoreduction of blood components, if pre-storage leukoreduced blood products are not available and leukoreduction is indicated. Manufacturer's instructions should be followed for proper use.

Intravenous solutions and medications

With the exception of 0.9% normal saline (USP), no medications or solutions should be administered simultaneously with blood components through the same tubing[101]. Co-infusion of non-approved solutions or medications may results in reversal of blood component anticoagulation (resulting in clotting) or hemolysis.

Rapid infusion and blood warmer devices

Non-emergent transfusions of single units in adults are typically completed in between 30 and 120 minutes. In patients with massive PPH, significantly faster transfusion rates may be required. A combination of pressure infusion devices and large bore intravenous tubing designed for rapid infusion can achieve transfusion rates as fast as 1500 ml/min[102]. Such flow rates require appropriate filters, as filters with small pore size can significantly slow transfusion rates or cause hemolysis. Since rapid transfusion of chilled blood components has been associated with hypothermia and cardiac arrest[102], the use of rapid infusers has been coupled to the use of blood warmers, devices which safely warm blood components. Indications for use of blood warmers include massive transfusion and an administration rate of more than 50 ml/ min for 30 minutes or more[103]. Blood warmers should be used and maintained according to manufacturer's instructions, with validation of protocols derived from these instructions, and warming of blood components should only be performed in equipment specifically licensed for such use[103]. Non-approved devices for blood warming (such as microwave ovens or immersion in hot water) may result in thermal hemolysis with resultant severe hemolytic transfusion reactions and should not be used. Most rapid infusion devices do not induce significant mechanical hemolysis, but manufacturer inserts should be reviewed to confirm approval for use with specific blood products. Hyperkalemic cardiac arrest has been associated with use of rapid infusion devices, and patients with hemorrhagic shock may have metabolic disturbances (such as acidosis, hypocalcemia and hyperglycemia) which exacerbate hyperkalemia[104].

septic transfusion reactions in either platelets or unscreened blood products such as pRBC units[105,107].

Unlike other transfusion-transmitted infectious diseases, bacterial contamination of blood products can result in rapid and potentially fatal reactions. Signs and symptoms of septic shock (such as fever, rigors, dyspnea and hypotension) can develop within minutes of starting a transfusion, or can manifest hours or days later[107]. Initial clinical suspicion of a septic transfusion reaction should prompt immediate cessation of the transfusion, along with aggressive supportive therapy and immediate administration of broad-spectrum

antibiotics. The suspected blood product should be returned to the blood bank immediately for investigation, including inspection for visible abnormalities such as discoloration or hemolysis as well as Gram stain and culture of the implicated product.

Febrile non-hemolytic transfusion reaction

Febrile non-hemolytic transfusion reactions (FNHTR) represent an essentially benign, albeit unpleasant, transfusion reaction most notable for development of fever, defined as a temperature elevation of more than 1°C or 2°F above pre-transfusion temperature. Such patients may also experience chills, rigors, nausea and vomiting, and occasionally manifest these signs and symptoms in the absence of fever. The underlying pathophysiology is believed to be primarily caused by pyrogenic cytokines, such as interleukin (IL-1), IL-6, or tumor necrosis factor (TNF)-α, which accumulate in blood products during storage[108]. Onset of symptoms can occur during transfusion, typically toward the end of transfusion due to the increasing level of cytokine exposure; rarely they will present up to 1–2 hours after transfusion due to the increasing level of cytokine exposure. Diagnosis of FNHTR is one of exclusion, having ruled out other causes of febrile reactions such as hemolytic transfusion reactions, septic reactions or contributions from co-morbidities or medications. It is important to note that FNHTR and acute hemolytic or septic reactions cannot be distinguished by clinical presentation alone; therefore, every febrile transfusion reaction should be acted upon with immediate cessation of transfusion and swift investigation. Treatment for FNHTR is supportive, including antipyretics such as acetaminophen.

Transfusion-related acute lung injury (TRALI)

Transfusion of plasma-containing blood products – which would account for all blood products except washed cellular blood products – may result in a syndrome of non-cardiogenic pulmonary edema and acute respiratory distress. Clinical findings that define this transfusion-related acute lung injury (TRALI) include: (1) onset during or within 6 hours of transfusion; (2) severe hypoxemia, such as less than 90% oxygen saturation of room air; (3) diffuse bilateral pulmonary infiltrates on chest X-ray; (4) absence of evidence suggesting volume overload; and (5) no pre-existing acute lung injury[109]. TRALI may also manifest with fever, chills, hypotension and transient leukopenia. TRALI is the leading cause of transfusion related mortality in the US as well as in Western Europe, with incidences reported as high as one in every 5000 transfusions[110].

The primary suspected pathophysiology of TRALI is believed to be a reaction between donor antileukocyte antibodies and recipient leukocytes resulting in leukocyte activation, sequestration and infiltration into the pulmonary capillary bed. Granulocyte activation results in pulmonary microvascular injury and capillary leakage with influx of proteinaceous fluid into the alveolar space[111]. Female donors sensitized to human leukocyte antigens (HLA) by pregnancy are most frequently implicated as the source of blood products which have been linked to TRALI cases. As a result, many blood collection agencies in the US and Europe limit or prohibit collection of plasma-rich blood products from female donors[112].

The diagnosis of TRALI is clinical and not based on the results of laboratory investigations for the presence of anti-leukocyte antibodies in the donor[109]. Although cognate leukocyte antibody–antigen matches are often seen in TRALI cases, their absence does not rule out TRALI[113–115]. Careful patient evaluation must be undertaken by the clinical team and transfusion service in the wake of a suspected TRALI, including post-transfusion chest X-rays, measures of oxygenation and evaluation for volume overload. Treatment is supportive and includes supplemental oxygen or mechanical ventilation. The pulmonary pathology of TRALI is not responsive to diuretics, and the role of corticosteroids remains unclear. The majority of patients recover with supportive care[109].

Allergic/anaphylaxis

Allergic reactions to blood products are one of the most common adverse complications of transfusion, with incidence rates estimated between 1 and 3%[116]. The spectrum of presentation varies widely, with the majority manifesting with solely cutaneous symptoms, such as pruritis, urticaria, erythema and angioedema[117]. These minor allergic reactions are thought to be most often mediated by recipient IgG or IgE directed against plasma proteins[99]. It is therefore not surprising to find that allergic reactions occur most frequently with plasma-rich products (including platelets), but reactions can also occur in plasma-deplete products such as red cell units. Treatment for minor allergic reactions includes cessation of transfusion and administration of an antihistamine such as diphenhydramine.

Rarely, patients present with moderate or severe allergic reactions with the potential to escalate to anaphylactic shock within minutes after symptom onset. These reactions are characterized by their systemic impact, including wheezing, bronchospasm, hypotension, nausea and vomiting, chest pain and tachycardia[116]. IgA-deficient patients who have developed class-specific anti-IgA are at risk for such severe allergic reactions; however, this group only represents a fraction of anaphylactic transfusion reactions[118]. Causative agents vary widely from anti-haptoglobin antibodies to passive transfer of allergens to which a patient is already sensitized, such as recently ingested foods (i.e. peanuts)[116,119]. Ultimately, anaphylaxis is a mostly unpredictable and potentially fatal transfusion outcome, and clinicians should be aware of this risk and act swiftly should it be encountered. Severe allergic reactions or anaphylaxis should be managed in a similar fashion to anaphylaxis from other causes, with

administration of epinephrine (with or without other vasopressors), maintenance of a patent airway and crystalloid infusion to support blood pressure.

Volume overload

Transfusion-associated circulatory overload (TACO) occurs when the rate of transfusion exceeds the recipient's cardiovascular system adaption to the additional workload[99]. The rapid infusion of excessive volume can result in dyspnea, hypoxemia, elevated central venous pressure and pulmonary edema – and in the worst case scenario, congestive heart failure. The initial presentation has significant overlap with TRALI, including similar chest X-ray findings of bilateral infiltrates. Unlike TRALI, however, TACO shows symptomatic improvement with dieresis. Patients at highest risk for TACO are those with diminished cardiovascular function, relatively small intravascular volumes as compared to transfused volumes (e.g. the elderly and young pediatric patients), and severe compensated anemia such as seen in patients with chronic hemolytic anemias. Patients with suspected TACO should have any ongoing transfusion paused to establish the diagnosis, with supportive care and diuretics administered as indicated before attempting further transfusion. Resumption of transfusion should be approached with a slower infusion rate and careful vigilance for recurrent symptoms.

Metabolic complications and hypothermia

As all blood products are collected and stored in citrate-based anticoagulants, large volume transfusions have the potential to be complicated by hypocalcemia. Citrate binds divalent cations such as calcium and magnesium, and is rapidly metabolized by the liver. Whereas citrate is easily cleared during non-urgent transfusions, citrate load during massive transfusion may overwhelm this clearance mechanism. Parturients with liver dysfunction, such as acute fatty liver of pregnancy or hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome, may be particularly vulnerable to this complication. Hypocalcemia presents initially with chills, tingling, dizziness and tetany; continued progression of citrate toxicity can lead to prolonged QT interval, decreased left ventricular function and cardiac arrhythmias[120]. Typically, hypocalcemia can be managed by slowing the rate of transfusion[99]. However, in ongoing massive transfusion or in patients with liver dysfunction, calcium replacement therapy as guided by the patient's ionized calcium concentration may be required[120].

The occurrence of hypocalcemia during massive transfusion can exacerbate another potential complication: hyperkalemia. During pRBC unit storage, potassium accumulates in the supernatant secondary to impaired function of the transmembrane sodium–potassium ATP pump[120]. This potassium accumulation rarely increases to a clinically significant level. However, large volume transfusions, particularly those complicated by use of malfunctioning blood warmer or rapid infusion devices (see text box above), can rarely result in fatal hyperkalemia in adult recipients. Patients with underlying cardiac, hepatic, or renal dysfunction are especially vulnerable and should be closely monitored during massive transfusion.

Rapid infusion of refrigerated blood products may lead to hypothermia, and can worsen existing hypothermia in obstetric patients undergoing cesarean section or hysterectomy during management of PPH. Hypothermia can lead to multiple systemic derangements, including peripheral vasoconstriction, cardiac dysfunction, acidosis and coagulopathy[120]. The effects of hypothermia and acidosis on coagulation have been observed both clinically and *in vitro*. Decreases in core temperature to less than 34°C and pH less than 7.1 after massive transfusion are predictive for development of coagulopathy[117]. Activity of factor VII–tissue factor and factor Xa–Va (prothrombinase) complexes is directly dependent on temperature, with both showing a 1.1-fold loss of activity at 33°C as compared to 37°C[118]. Even more dramatically, FVIIa–tissue factor and FXa–FVa show sharp decreases in activity in acidic environments, with activity decreasing by 55% and 70% at pH 7.0, respectively[122].

The most effective treatment for hypothermia is also the best prevention: warming the room, warming the patient with blankets and heating lamps, and use of approved blood and fluid warming devices (see text box above). Restoration of tissue perfusion is the definitive therapy for acidosis in massive transfusion, but alkalinizing agents such as sodium bicarbonate can assist in increasing the blood pH during the resuscitation to improve hemostasis[120].

CONCLUSION

Following Blundell's first experiments in the 19th century, the use of blood products has become a life-saving strategy in management of obstetric hemorrhage in general and PPH in particular. Continued advances in blood banking procedures and technology in the second half of the 20th century, including component therapy, infectious disease screening and careful pre-transfusion compatibility testing, have resulted in enormous improvements in safe transfusion practices. Having acknowledged this, transfusion remains associated with numerous risks, and clinicians should be aware of them.

As we progress further into the 21st century, many questions about proper transfusion management remain unanswered. These include but are not limited to: 'What are the risks in transfusing red blood cells or platelets which may have functional changes induced by storage conditions?' and 'What is the best approach for blood product administration during massive hemorrhage?' Such questions remain highly debated among those who practice transfusion medicine, and are even more debatable with regard to obstetric transfusion because of a virtual absence of reliable data for this unique patient population.

An exception to the latter generality is the near consensus of the benefits of having and using an obstetric hemorrhage protocol which is known and available to the entire hospital staff[8,123]. These protocols effectively reduce maternal morbidity and mortality from PPH[124] and are recommended by the American College of Obstetrics and Gynecology[125], the UK Confidential Enquiry into Maternal and Child Health (CEMACH)[8] and the Joint Commission in the United States[126]. CEMACH and other academic bodies recommended that massive hemorrhage protocols should be rehearsed in conjunction with transfusion services[8]. Transfusion protocols not only provide more rapid blood product delivery and laboratory assessment of coagulopathies, but also greatly reduce clinician anxiety by creating a predictable framework for obstetric hemorrhage management[127]. Clinical laboratories and hospital blood banks are critical partners in the care of obstetric hemorrhages, and should be included in the establishment of management protocols or alerted regarding high risk obstetric patients. Active partnership and communication between obstetricians and transfusion medicine experts can help protect mothers' lives and well-being.

PRACTICE POINTS

- Transfusion is a life-saving strategy in the management of obstetric hemorrhage
- Separation of whole blood into components allows for transfusion to treat specific hematologic deficiencies in patients
- Massive transfusion in PPH may benefit from higher ratios of pro-coagulant components (such as plasma, platelets and cryoprecipitate or fibrinogen concentrates) to red blood cell components, but definitive data are lacking for obstetric patients and benefits have been extrapolated from military or civilian trauma data
- Transfusion carries risk; clinicians should be aware of how acute transfusion reactions present and be prepared rapidly to assess and treat these reactions
- All transfusion reactions should be reported to the blood bank or transfusion service at the point of recognition to allow for rapid laboratory investigation
- Multidisciplinary protocols for PPH management should actively include local transfusion medicine experts.

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