

Chapter 8

MASSIVE TRANSFUSION IN THE FIELD

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INTRODUCTION

“The advantage of the direct transfusion of human blood in cases of severe haemorrhage which we encounter in the emergencies of military surgery cannot to our minds, be overestimated.”¹

The above comment, from a paper presented by Lieutenant Colonel A Primrose of the Canadian Army Medical Corps in 1916, remains as pertinent today as during those earlier days of military transfusion medicine.¹ Hemorrhage remains the most common cause of death in combat trauma and, more importantly, is the most frequent cause of preventable death.² On today's battlefield, advances in body armor, field resuscitation, and casualty evacuation have resulted in more potentially salvageable patients with massive trauma arriving alive at Role 2 and 3 care facilities. Such casualties, who in earlier conflicts likely would have died at or near the point of wounding, now often present to the combat support hospital (CSH) emergency department in the last few seconds of that “momentary pause in the act of death” that is severe shock.³ Massive transfusion is just one component in the multifaceted approach to managing the modern combat polytrauma patient.

The standard approach to casualties with major trauma is now termed damage control resuscitation (see Chapter 7, Damage Control Resuscitation), the aim of which is to “minimize blood loss, maximize tissue oxygenation and optimize outcome.”⁴ It encompasses rapid control of compressible hemorrhage in the field, swift retrieval with ongoing resuscitation during transport to the medical facility, focused airway management and oxygen therapy, hemostatic resuscitation, permissive hypotension, damage control surgery, and critical care. This chapter will focus on the interplay between hemostatic resuscitation, permissive hypotension, and massive transfusion. Hemostatic resuscitation is the proactive management of hemor-

rhage aimed at offsetting the effects of acute trauma coagulopathy before it is compounded by dilution of clotting factors and the development of acidosis and hypothermia. In the United Kingdom (UK) military, hemostatic resuscitation is initiated as early after wounding as possible by the Medical Emergency Response Team–Enhanced (MERT-E) and continued until surgical and microvascular hemorrhage is controlled.

In the more severely injured this approach involves the massive transfusion of blood products in, as near as possible, predetermined ratios that have been shown to improve outcome. For this approach to succeed, adequate quantities of blood products must be available and a pre-agreed massive transfusion protocol (MTP) must be in place to avoid delays in blood product administration and the use of unnecessary and potentially harmful crystalloids or colloids. The use of such MTPs has also been shown to improve outcomes.⁵

A major change in trauma patient transfusion medicine during the current conflicts is the administration of blood products in increased ratios of plasma and platelets to packed red blood cells (PRBCs). A retrospective study of combat casualties in Iraq demonstrated that survival is significantly improved with these increased ratios.⁶ As a result the UK military aims to transfuse severely injured casualties in a ratio of 1:1 PRBC to fresh frozen plasma (FFP), with platelet support as indicated, while the US policy is to use 1:1:1 PRBC to FFP to platelets.^{7,8}

Massive transfusion has been variously defined, but most definitions include the transfusion of 10 units of blood, or 1 to 1.5 times the patient blood volume, in 24 hours. Other criteria, more meaningful in acute major hemorrhage, include 4 units in 1 hour, 50% blood volume in 3 hours, or a rate of loss of over 150 mL/min.

INITIATION OF MASSIVE TRANSFUSION PROTOCOLS

A key factor in the effectiveness of the MTP is the timely and appropriate initiation of the protocol. Frequent inappropriate initiation of the MTP will likely result in diminished blood product supplies (particularly plasma) and greatly contribute to medical personnel fatigue. A number of authors have developed criteria for instituting an MTP. These tools use various combinations of mechanism of injury, vital signs, and laboratory results. Schreiber et al⁹ found that an international normalized ratio over 1.5, hemoglobin under 11g/dL and penetrating trauma mechanism independently predicted the need for MTP. McLaughlin et al¹⁰ used admission heart rate over 105 beats/min, systolic blood

pressure under 110 mm Hg, pH under 7.25, and hematocrit under 32%. These criteria demonstrated a positive predictive value of 66%. Revealingly, McLaughlin noted that some of the more severely injured requiring massive transfusion did not necessarily demonstrate these laboratory criteria on admission because they were diverted directly to the operating room. Larson et al,¹¹ who used a similar model, pointed out in their conclusions that the decision to activate the MTP is quite subjective, relying on experienced clinicians to assess the severity of injuries. It may well be that these models will prove their utility in the hands of the less experienced, under the stress of dealing with multiple

casualties and in the less clear cut cases.

In these models, waiting for laboratory results can result in decision delay. A scoring system described by Cotton et al,¹² referred to as the Assessment of Blood Consumption (ABC) score, eliminates these factors by using penetrating mechanism of injury, arrival systolic blood pressure less than 90 mm Hg, arrival pulse rate over 120 beats per minute, and a positive focused assessment with sonography for trauma (FAST) exam. One point is allocated for each of the four markers and a total score of 2 or more was shown to predict the requirement for MTP with 84% to 87% accuracy.

In combat, most severe injuries are penetrating in nature (primarily the result of blast but also gunshot wounds) so that if the ABC scoring system is applicable, the casualty would only have to demonstrate the falling blood pressure or tachycardia to be triaged to the MTP. This is in fact what happens currently in the prehospital phase in British combat operations: the MERT-E clinician identifies the mechanism of injury, checks for the presence of shock, and initiates the transfusion of blood and plasma in flight while at the same time passing a pre-agreed codeword on to the field hospital alerting the emergency department to the requirement for massive transfusion. With nonpenetrating injuries, the FAST examination is performed immediately on arrival at the CSH. It should be noted

that the ABC score was developed in civilian centers and needs to be validated in a military cohort.

In the civilian hospital, a high degree of specificity in predicting the need to initiate the MTP is ideal to avoid wasting blood products. During busy combat operations at the CSH, such specificity is less of a concern because prepared but unused blood products will most likely be required for other casualties before they need to be discarded. In these circumstances a high degree of sensitivity in prediction is of greater value in avoiding delays.

Other areas of concern include the over-transfusion of blood products (failing to recognize when hemorrhage is controlled and resuscitation efforts can be scaled back) and the recognized complications generally associated with blood transfusion. To avoid over-transfusion, it is essential to carefully monitor the patients' vital signs and laboratory indices. This monitoring includes recognizing a developing or resolving coagulopathy using clinical observation, standard coagulation tests, and, increasingly, thromboelastography (see below). Equally, close observation of the patient who has undergone large volume transfusion is required in the CSH intensive care unit, during repatriation flights, and in the Role 4 hospital intensive care unit, in anticipation of possible complications associated with massive transfusion.

COMPLICATIONS OF MASSIVE TRANSFUSION

Although massive transfusion can be life-saving, it is important to consider the possible complications that, left untreated, could be detrimental to the patient. Problems associated with massive transfusion cover a wide spectrum and include infections, immunologic changes, metabolic derangements, coagulopathies, and physiologic abnormalities. The majority of these complications can occur with transfusions of any magnitude; with some patients there is a significantly increased risk during large volume transfusion. The specific complications related to massive transfusion include hypocalcemia, hyperkalemia, acidosis, hypothermia, and dilutional coagulopathy.¹³ Considering the concomitant pathophysiology surrounding the initial traumatic injury, these complications can significantly worsen the clinical picture; therefore, it is imperative for the clinician to be vigilant with respect to these complications and understand how to prevent and treat them.

Hypocalcemia

Hypocalcemia is commonly seen in massive transfusion due to the anticoagulant citrate used in blood

products, which binds to ionized calcium. Plasma and platelets have the highest citrate level; therefore, these products have a higher risk. Since citrate is usually rapidly metabolized by the liver, the associated hypokalemia during standard transfusion is transient; however, when large volumes of blood products are administered against a background of impaired hepatic function due to hypothermia and hypoperfusion, the effect may be dramatic.¹³ For example, a healthy adult liver can metabolize 3 grams of citrate every 5 minutes, and one unit of PRBCs usually has about 3 grams of citrate. Therefore, if transfusion rates exceed one unit every 5 minutes, which is common in massive transfusion, citrate levels will increase and hypocalcemia will result.¹⁴ As the citrate level increases, signs of citrate toxicity and severe hypocalcemia can develop, including tetany, prolonged QT interval, decreased myocardial contractility, hypotension, narrowed pulse pressure, elevated end-diastolic left ventricular pressure, and elevated central venous pressure.¹⁵ Hypocalcemia can also predispose to hyperkalemia-related arrhythmias as well as pulseless electrical activity arrest and ventricular fibrillation.^{13,14} In addition, hypocalcemia has been implicated as a contributing factor in

the coagulopathy associated with massive transfusion. With this in mind, it is important to frequently monitor ionized calcium blood levels and treat low levels with intravenous calcium chloride or calcium gluconate to maintain levels within the normal range. Also, when possible, slowly infusing citrate-containing blood products can decrease the degree of citrate toxicity and hypocalcemia.¹³

Hypomagnesemia

Hypomagnesemia, which occurs with massive transfusion, is thought to result from the transfusion of large volumes of magnesium-poor fluids as well as the binding of magnesium to citrate.¹⁴ This effect of citrate explains why hypocalcemia, hypomagnesemia, and citrate toxicity are often seen concurrently. Low levels of magnesium can lead to QT prolongation and ventricular arrhythmias, and may contribute to the coagulopathy associated with massive transfusion.¹⁶ For these reasons, it may be important to monitor magnesium levels during trauma resuscitation and administer intravenous magnesium when indicated.

Hyperkalemia

Hyperkalemia is commonly seen during massive transfusion. Extracellular potassium increases as red blood cells (RBCs) are stored, which is attributed in part to inactivation of RBC membrane adenosine triphosphatase pumps.¹⁴ The average extracellular potassium level in blood after 7 days of storage is 12 mmol/L, increasing to 32 mmol/L after 21 days.¹⁷ After a unit has been transfused, the extracellular potassium is taken into RBCs as adenosine triphosphatase pump activity is restored. The increase in plasma potassium levels is therefore typically transient and without physiologic effect. However, during massive transfusion, large volumes of RBCs are typically administered through central venous catheters, so that a large extracellular potassium bolus may reach the right heart prior to intracellular uptake or dilution in the total blood volume. It is this delivery of extracellular potassium to the right heart that results in ventricular arrhythmias and cardiac arrest.¹⁸ As mentioned above, simultaneous hypocalcemia can further predispose patients to potentially dangerous dysrhythmias. Methods to reduce the risk of hyperkalemia include using fresh blood (less than 14 days old), transfusing blood products through lines further away from the right atrium, and using washed RBCs.^{13,14} In addition, correcting acidemia will prevent the extracellular shift of potassium. It is important to frequently check plasma potassium levels to detect hyperkalemia and treat

elevated levels appropriately with standard therapies such as insulin with dextrose, β -2 (adrenergic) agonists (when blood pressure allows), bicarbonate, and intravenous calcium.

In addition to the effect on potassium level and pH, the storage of RBCs alters two other properties that change the ability of transfused cells to deliver oxygen to tissues. RBC deformability, which allows RBCs to navigate microvasculature, decreases with storage. In addition, 2,3-diphosphoglycerate decreases in stored RBCs, therefore effectively increasing hemoglobin's affinity for oxygen and decreasing the unloading of oxygen at tissues.¹³ During massive transfusion in trauma, it is important to realize that older units of RBCs will not deliver oxygen to hypoperfused tissues as well as newer ones.

Although severely traumatized patients may present with an endogenous coagulopathy due to the nature of their injury and hypoperfusion, now referred to as acute traumatic coagulopathy, resuscitative efforts and the combination of acidosis, hypothermia, and coagulopathy (often referred to as the "bloody vicious cycle") may also contribute to the overall trauma-induced coagulopathy.¹⁴ It is therefore essential that each of these components be carefully monitored and any problems promptly treated.

Acidosis

During trauma-related hemorrhage, acidosis mainly results from hypoperfused tissues, producing lactate. However, massive transfusion can worsen this acidemic state because stored RBCs are acidic due to the citrate phosphate dextrose adenine (anticoagulant) solution in which they are suspended, as well as the accumulation of the products of continuing cellular metabolism.¹⁴ Stored RBCs have a pH of 7.16 at the time of collection and progressively become more acidic, with a pH of 6.87 at 21 days and 6.73 at 35 days. Once transfused, the acid present in blood products is immediately metabolized by the liver, but this typically rapid process may be impaired and overwhelmed during massive transfusion in the face of hemorrhagic shock. The injudicious administration of large volumes of nonbuffered crystalloid solutions may also lead to worsened acidemia, because the hydrogen ion is dissociated from water due to high levels of chloride relative to sodium. The physiologic consequences of acidemia include dysrhythmias, decreased cardiac contractility, hypotension, and decreased response to catecholamines. In addition, acidosis has been found to independently lead to coagulopathy because an acidic environment in the blood leads to decreased enzymatic activity of clotting factors, reduced thrombin genera-

tion, and impaired platelet aggregation.¹³ For example, it has been shown that at a pH of 7, the activity of factor VIIa, VIIa/tissue factor complex, and factor Xa/Va complex decreases by 90%.¹⁹ Acidosis attributable to massive transfusion can be lessened by using fresher blood and treated with alkalinizing solutions, such as sodium bicarbonate or tromethamine although the use of these agents is contentious in terms of both efficacy and necessity. Tromethamine is currently licensed and widely used in the United States but not in the United Kingdom.

Hypothermia

Hypothermia, defined as core body temperature below 36°C, is commonly seen in trauma patients and is associated with an increased risk of uncontrolled bleeding and mortality. Patients can become hypothermic from the environmental conditions at the time of injury, during evacuation, and during exposure for examination and surgery. Also contributing to hypothermia is the impaired thermoregulation related to shock and anesthesia.¹³ In addition, infusing large volumes of inadequately warmed intravenous fluid and blood products will contribute to the dangerous hypothermia that is too often seen in trauma. Blood products are normally stored between 1°C and 6°C, and for this reason it is imperative that fluid warmers be used during transfusion.¹⁴ Because serious physiologic effects of hypothermia include impaired oxygen delivery by hemoglobin, decreased cardiac output, increased risk of cardiac dysrhythmias, and increased cardiac toxicity from electrolyte derangements, maintaining normothermia is essential. In addition, hypothermia contributes to coagulopathy, affecting both platelet function and the coagulation cascade. Platelet dysfunction occurs as hypothermia leads to reduced thromboxane A₂ production, impaired platelet adhesion and aggregation, and decreased generation of thrombin on platelets.¹³ The coagulation cascade is affected as reduced temperatures impair the activity of coagulation enzymes, resulting in a 10% reduction in coagulation factor activity for each 1°C reduction in temperature.¹⁹ These platelet and coagulation derangements are resolved as the temperature returns to 37°C, emphasizing the importance of being vigilant with respect to patient temperature during massive transfusion.²⁰

Dilutional Coagulopathy

In addition to the detrimental effects on coagulation of acidosis, hypothermia, and the consumption of clotting factors, massive transfusion of blood products

can itself contribute to coagulopathy. This dilutional component of coagulopathy is the result of replacing lost blood with large volumes of stored RBCs and fluids that do not contain clotting factors or platelets. Dilutional thrombocytopenia associated with massive transfusion was seen in both the Korean and Vietnam conflicts because stored whole blood, which does not have functional platelets, was used extensively. In addition to low platelets, labile clotting factors such as V and VIII deteriorate with blood storage times.^{13,21}

Today, fractionated component transfusions are most commonly used and involve the transfusion of PRBCs, FFP, and platelets. Although this practice has been proven to result in less dilution when compared to transfusing PRBCs alone or stored whole blood, the risk of thrombocytopenia, hemodilution, and a resulting coagulopathy still exists. The reason for the continued risk of coagulopathy with blood component therapy is that when whole blood is used to make these three components, RBCs, platelets, and factors are diluted through processing and the addition of preservatives.¹³ The resulting 660 mL achieved when recombining one unit of each component results in a net deficit, with the reconstituted “whole” blood having a hematocrit of 29%, a mean platelet count of 85,000/ μ L, and a mean coagulation factor activity of 62%.¹⁴ During the current conflicts interest has resurged in the use of fresh whole blood (FWB) for resuscitating combat casualties; 6,000 units of FWB were administered by the US military to casualties in Iraq and Afghanistan, and many practitioners would argue for its use in cases of refractory coagulopathy.

In addition to issues with blood component therapy, infusing crystalloid or colloid into the bleeding patient results in the further dilution of cells and clotting factors, contributing to coagulopathy. Colloids such as hydroxyethyl starch have been shown to impair von Willebrand factor activity in plasma.²² As a result it is now standard in military practice to limit crystalloid or colloid infusion as much as possible.

Because conventional coagulation tests were not designed for monitoring transfusions and are time-consuming relative to the rapidly changing situations in casualty resuscitation, the use of real time thromboelastometry (ROTEM; TEM UK Ltd, Hartlepool, UK) may help to assess the patient’s current coagulation state and guide further transfusions. The potential value of ROTEM is under evaluation.

Immunologic Complications

Immunologic complications of massive transfusion include acute hemolytic reactions, which are very rare when units of “trauma blood” (uncross-matched

type O) are used. However, acute hemolytic reactions can be observed after patients have received large amounts of type O whole blood and then receive type-specific blood. This is due to transfused isoagglutinins from whole blood reacting against type A or B antigens found in type-specific blood.²³ Microchimerism (the harboring of small numbers of cells that originated in a genetically different individual) is another immunologic-related complication and involves the persistence of allogeneic cells for years posttransfusion. It can be seen in up to 10% of trauma patients receiving transfusions, but its clinical significance remains unknown. Another immune-related process is immunomodulation. Although its exact mechanism of action remains unclear, immunomodulation has been associated with an increased risk of bacterial infection (especially with older PRBC units), acute lung injury or acute respiratory distress syndrome, systemic inflammatory response syndrome, and multiple organ failure.^{13,24}

The leading cause of transfusion-related death, with

a reported mortality rate of about 25%, is transfusion-related acute lung injury (TRALI).^{19,25} TRALI typically occurs within 6 hours after transfusion, but can occur up to 24 hours later. The type of blood product transfused determines the risk of TRALI, which has been found to be 1 case per 5,000 units of PRBCs, 1 per 2,000 units of FFP, and 1 per 400 units of platelets.¹⁴ Clinically, it is indistinguishable from acute respiratory distress syndrome and involves acute onset of noncardiogenic pulmonary edema; severe hypoxia; and bilateral, fluffy infiltrates on chest radiograph. It is thought to be an immune-mediated process, wherein donor antibodies activate recipient leukocytes, causing pulmonary injury through microvascular occlusion, endothelial damage, and capillary leakage.²⁵ Treatment is supportive critical care including mechanical ventilation, fluids, and inotropes as needed.²⁵ TRALI should be distinguished from transfusion-associated circulatory overload (although the distinction is sometimes unclear), which is hydrostatic pulmonary edema occurring in approximately 1% of transfusions.^{14,19}

PRINCIPLE CONSIDERATIONS IN MASSIVE TRANSFUSIONS DURING MILITARY OPERATIONS

Given the risks outlined above, the overarching goal in managing massive transfusions for combat casualties must be to prevent the exacerbation of coagulopathy while avoiding unnecessary use of blood products. To this end the UK and US military have both published documents laying out the principles involved in damage control resuscitation in general and massive transfusion in particular. These are the *UK Armed Forces Surgeon General's Policy Letter on the Management of Massive Hemorrhage On Operations* (dated 27 February 2009)⁷ and the *US Joint Theater Trauma System Clinical Practice Guideline on Damage Control Resuscitation At Level IIb/III Treatment Facilities* (dated 10 August 2011).⁸

UK Operational Massive Transfusion Protocol

The 2009 UK policy letter describes the massive transfusion protocol adopted for UK military operations as an "aggressive massive transfusion protocol based on a 1:1 ratio of red cell concentrate (RCC) to FFP with platelet component support when needed" (Exhibit 8-1). It differs from the US equivalent in that platelets and cryoprecipitate are administered only on an as required basis. The policy outlines the following approach to massive transfusion:

1. Avoid hypothermia by using fluid warmers and rapid infusion devices.
2. Maintain hematocrit at 35%.
3. Use FFP and RCC in a 1:1 ratio as soon as

practicable.

4. Use cryoprecipitate early to maintain the level of fibrinogen above 1.0 g/L.
5. Initiate early intervention with platelet support to maintain the platelet count above $100 \times 10^9/L$ using UK-derived (or more local source if appropriate) platelet components, or platelets donated using field apheresis, both in preference to whole blood from the emergency donor panel (a group of preidentified and screened blood donor volunteers readily available to the field hospital).
6. Frequently take a full blood count and conduct coagulation studies to confirm successful application of the MTP.
7. Frequently measure potassium and calcium levels to identify the presence of hyperkalemia or hypocalcemia, followed by appropriate therapy as needed.
8. Use appropriate intervention with recombinant factor VIIa in accordance with current military guidelines.
9. Regularly assess the base deficit (along with hypothermia and coagulopathy) to monitor the lethal triad associated with massive trauma.

US Military Massive Transfusion Protocol

Not surprisingly, the US military has focused an enormous amount of time and research on developing

MTPs during the wars in Iraq and Afghanistan. Much of this research was done at the US Army's Institute of Surgical Research (USAISR) at Fort Sam Houston, Texas, which has the mission of "providing requirements-driven combat casualty care medical solutions and products for injured soldiers." Among much of the valuable literature published by the USAISR are the Central Command/Joint Theater Trauma System

Clinical Practice Guidelines (http://www.usaistr.amedd.army.mil/clinical_practice_guidelines.html). These generally evidence-based guidelines represent the US military's current thinking on a host of medical issues, including massive transfusion. The Clinical Practice Guideline covering damage control resuscitation and massive transfusions⁸ includes as an appendix the example of an MTP for a CSH (Exhibit 8-2).

FIBRINOLYTICS AND RECOMBINANT FACTOR VIIA

The use of antifibrinolytics such as tranexamic acid should also be considered to counter the hyperfibrinolysis that can be a feature of an acute traumatic coagulopathy. A randomized controlled trial of tranexamic acid, called CRASH-2, revealed a significant decrease in all-cause mortality and death due to bleeding in bleeding trauma patients treated with the drug; the effect was most apparent in patients administered the drug less than 3 hours after injury. As a result the investigators recommended that tranexamic acid be administered as soon as possible after injury²⁶; the drug is available for use in the prehospital phase of resuscitation in Afghanistan by UK MERT-E clinicians.

When coagulopathy persists despite appropriate blood product therapy, the use of recombinant factor VIIa has been considered to initiate a thrombin burst at the sites of injury. The safety of this off-label use of factor VIIa approach has, however, been questioned.²⁷ A study of 328 massively transfused trauma patients revealed a significantly improved 24-hour survival but no benefit in late survival to discharge.²⁸ In the authors' opinion, the use of factor VIIa has decreased as the use of higher ratios of FFP to PRBC has become standard, although there may be a place for factor VIIa on military operations where there is limited transfusion capability. The initial dose is 10 µg/kg IV, which may be repeated after 15 to 20 minutes.

MILITARY USE OF FRESH WHOLE BLOOD

FWB has been used in the trauma setting since World War I, serving as an ideal resuscitation fluid, intuitively appealing in that it "replaces what is bled." However, with the development of fractionation of whole blood into PRBCs, platelets, FFP, cryoprecipitate, and various concentrated coagulation factors, component therapy (CT) supplanted the use of whole blood in the operating room. The use of CT over FWB in the trauma setting therefore developed in part as an untested extension of CT's widespread use in the elective surgical world, and to preserve valuable resources. Trauma resuscitation strategies using CT were extrapolated from studies of euvolemic patients undergoing elective surgeries, resulting in unproven blood product recipes that relied heavily on crystalloid fluids and front-loaded PRBCs, preserving more precious blood products such as FFP and platelets until blood samples, often drawn during a hectic resuscitation, demonstrated their need.

Blood fractionation capabilities are not always in place in an austere combat theater of operation at the time of arrival of troops and casualties, as was the case in the wars in Iraq and Afghanistan, where trauma resuscitation early in the conflict included the use of both CT and FWB. At the time many surgeons and anesthesiologists using FWB were impressed with its efficacy and convenience. Favorable editorials and research

supporting the use of FWB for trauma ensued, such as a retrospective analysis by Spinella et al, which looked at 354 US combat casualties comparing two groups: (1) those who received warm FWB, RBCs, and plasma, but not apheresis platelets, and (2) the CT group, who received RBCs, plasma, and apheresis platelets, but not warm FWB. This study found improved 24-hour (96% vs 86%, $P = 0.018$) and 30-day survival (95% vs 82%, $P = 0.002$) among the FWB group.²⁹

"Walking blood banks" (ie, using FWB taken directly from volunteer donor soldiers) became commonplace in US CSHs in Iraq and Afghanistan, and by the summer of 2007 over 6,000 units of FWB were transfused to combat casualties. The procedures for walking blood banks differ depending on the level of care and within military medical facilities themselves. In general, however, donor pools consist of local service members within the hospital or at nearby military units. Military medical facilities that anticipate large transfusion requirements often develop lists of pre-screened potential donors based on blood type. When the walking blood bank is activated, donors are gathered, rescreened for recent changes to their medical history, tested for anemia using a copper sulfate test, and then cross-matched to the recipient's blood. Blood is then collected into 400- to 500-mL bags containing citrate phosphate dextrose adenine and imme-

EXHIBIT 8-1

UNITED KINGDOM OPERATIONAL MASSIVE TRANSFUSION PROTOCOL

Step 1. Primary clinical assessment of a casualty at risk of requiring massive transfusion support
If patient has:

- severe injury (eg, bilateral proximal amputations or truncal bleeding and one proximal amputation) OR clinically obvious massive trauma or hemorrhage,
- PLUS either temperature < 96°F or 35°C or systolic blood pressure < 90 mmHg or abnormal mental status,

then proceed to Step 2. (Secondary laboratory assessment criteria are INR > 1.5, base deficit of > 6 and Hb < 11 g/dL. These results support the requirement for massive transfusion but are not required to activate the protocol.)



Step 2. Activate massive transfusion protocol



Step 3. Action

Clinicians:

- Demand issue of a “shock pack.”
- Send samples for FBC, PT, APTT, fibrinogen, cross match, U&E, calcium, blood gases, and base deficit testing.
- Actively avoid hypothermia by passing all replacement fluids to be given through a blood warmer or rapid infusion device.
- Monitor the FBC, coagulation, blood gases, U&E, calcium (and lactate) closely once the patient is out of the “shock phase.” In the meantime, the calcium and potassium levels should be aggressively managed.

Laboratory (upon receipt of shock pack request):

- Issue four units compatible RCC¹ (group O Rh D-negative unless lab testing for casualty was previously undertaken) and four units of FFP (group AB).²
- Ensure sufficient numbers of staff are in the laboratory to provide a rapid response to the developing situation.³
- Defrost and store at 4°C six more units of FFP.
- Prepare to issue a further six units of RCC (either group-specific or fully cross matched depending on the time scale available).



Step 4. Continuing requirement for massive transfusion

Laboratory issues:

- six units of RCC (preferably group-specific or fully cross matched, depending on time frame), and
- six units of FFP (group selected).

Laboratory prepares to issue:

- cryoprecipitate if required,⁴
- platelets (to maintain platelet count above $100 \times 10^9/L$),⁵ and
- six units of FFP (unless the EDP has been used to supply whole blood).



Step 5: Requirement for massive transfusion support continues

Laboratory issues:

- six units of group selected RCC,⁶
- six units of FFP.
- platelets (dosage is dependant on FBC results; each adult equivalent dose of platelets can be expected to increase the platelet count by 30 to $40 \times 10^9/L$), and
- cryoprecipitate (dosage is dependent on fibrinogen results or clinical assessment).

Consider use of rVIIa.
Laboratory actively manages blood stocks and requests urgent resupply if appropriate.



Step 6. Requirement for massive transfusion support continues⁷

Repeat Step 5.

Consider giving one unit FFP, one pool of cryoprecipitate, one unit of platelets and rVIIa ("Bastion glue"), or using of cross-matched fresh whole blood derived from the EDP.

1. The first 10 units of RCC issued must, as soon as possible, be retrospectively cross-matched.
2. It may be appropriate, during high-tempo operations or following notification of the imminent arrival of a severely injured casualty, for the laboratory to anticipate the need for a massive transfusion and defrost four units of FFP (and hold them for up to 5 days at 4^o C). This approach will result in more waste but support the aggressive treatment required.
3. The laboratory may well need to suspend nonurgent testing during a massive transfusion situation.
4. The dosage of cryoprecipitate given should, when possible, be modified depending upon the results of fibrinogen tests to avoid unnecessary donor exposure.
5. In severe trauma one unit of platelets may be required for every 2.5 units of red cells given.
6. There is no requirement to fully cross match RCC after the first 10 units have been transfused in a massive transfusion situation UNLESS the patient has a clinically significant antibody. All patients should be converted to Rh D-positive units at this stage (to conserve Rh D-negative stock) UNLESS they are female of child-bearing age. If the patient has a clinically significant antibody, it may be necessary to deliberately select incompatible units during the mid-phase of a massive transfusion in order to preserve the compatible blood for use once hemostatic control has been achieved.
7. There is no clear threshold beyond which blood usage is futile. There is, however, a need to ensure that blood stocks are not exhausted in a futile effort to save a life. Close liaison, detailed attention to stock management, and effective communication is essential.

APTT: activated partial thromboplastin time

EDP: emergency donor panel

FBC: full blood count

FFP: fresh frozen plasma

Hb: hemoglobin

INR: international normalized ratio

PT: prothrombin time

rVIIa: recombinant factor VIIA

RCC: red cell concentrate

U&E: ureas and electrolytes

Reproduced from: UK Ministry of Defence. *Management of Massive Haemorrhage on Operations*. Surgeon General's Operation Policy Letter DMSD/29/15/01. London, England: MOD; 2009.

diately transfused to the patient. In ideal conditions, a military medical facility with a well-rehearsed walking blood bank program can have warm FWB transfused within 20 to 30 minutes of activation.³⁰

The risk of infection using walking blood banks is thought to be minimized by the reliance on service members, who are screened for HIV every 2 years (and often retested prior to deployment), must be vaccinated for hepatitis B, and undergo routine screening for illicit drug use. In an effort to further diminish the infectious risk, some military medical facilities in Iraq and Afghanistan with high-volume FWB requirements sent samples from potential donor pools back to the US for formal screening for transfusion-associated diseases before collecting blood.³¹

Despite these efforts, the risk of transfusion-acquired infection is inherently higher with FWB compared to the more rigorously screened CT blood products, and for this reason the Food and Drug Administration does not approve the use of FWB in the United States. In 2011, a study undertaken by

the US Armed Services Blood Program Office (and other institutions) looked at blood samples from 761 service members taken before and after they received emergency transfusions of FWB in Afghanistan and Iraq. The study determined that one service member acquired a hepatitis C infection from a transfusion and four service members had hepatitis C infections prior to their injuries and subsequent transfusions. Because these four service members were themselves potential donors, the finding suggests that the service-member donor pool was not as safe as first thought.³²

The USAISR annually reviews and modifies its Clinical Practice Guidelines for the use of FWB (originally released in 2006). The current guidelines describe the advantages of FWB as providing blood product in a favorable 1:1:1 ratio, its availability in austere conditions, and that it has no loss of clotting factor, platelet activity, or RBC "storage lesion" compared to CT. Among the principal disadvantages of FWB are that it must be ABO-type specific because it contains both RBCs and plasma, which creates a greater op-

EXHIBIT 8-2

EXAMPLE OF A MASSIVE TRANSFUSION PROCEDURE AT A US CENTRAL COMMAND ROLE 3 FACILITY

The following flexible massive transfusion (MT) procedure can be used in the emergency department (ED), operating room (OR), or intensive care unit (ICU). It may be initiated or terminated by the site-specific provider as dictated by the patient's needs in each specific venue. It consists of batches or packs, as defined below, which vary in composition but should approximate a 1:1:1 ratio of packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets, and cryoprecipitate.

Pack One: Four units of PRBC and four units of FFP. Additionally, consider using six packages of platelets, one 10-unit bag of cryoprecipitate, and possibly factor VII (obtained from the pharmacy). Use emergency release blood. Strongly consider the early use of tranexamic acid: infuse 1 g of tranexamic acid in 100 mL of 0.9% normal saline over 10 minutes intravenously (IV) in a separate IV line from any containing blood and blood products. (More rapid injection has been reported to cause hypotension.) Hextend (Hospira, Lake Forest, IL) should be avoided as a carrier fluid. Infuse a second 1-g dose intravenously over 8 hours infused with 0.9% NS carrier.

Pack Two: Four units of PRBC and four units of FFP.

Pack Three: Four units of PRBC, four units of FFP, six packages of platelets, one 10-unit bag of cryoprecipitate, and consider factor VII (obtained from the pharmacy).

Pack Four: Four units of PRBC and four units of FFP.

Pack Five: Four units of PRBC, four units of FFP, six packages of platelets, and one 10-unit bag of cryoprecipitate. At this time, providers should reassess the progress of the resuscitation, hemostasis, and the need to continue the MT procedure.

Packs Six, Seven, Eight and Nine are identical to **Packs Four and Five**.

Emergency release: four units of uncross-matched PRBC (two units of O+ and two units O-) and four units of AB or A FFP. (A FFP is not a universal donor product, but its use in MT patients when supplies of AB FFP are limited or absent may improve survival and help preserve resources, with a low risk to the patient. The decision to use A FFP or to switch from AB FFP to A FFP in the same patient should be made by the medical and surgical staff in concert with laboratory staff. Once the patient's type has been identified, type-specific plasma should be given as soon as possible.)

Pack: A single group of type-specific, cross-matched PRBC and FFP (four units of each), which later in the procedure may also include cryoprecipitate, platelets, and/or factor VII.

portunity for clerical errors. Moreover, the collection of FWB usually creates diminished exercise tolerance in donors, who may be members of the wounded soldier's own unit (and thus may still be needed in ongoing combat). For these reasons and the known increased risk of transfusion-acquired infections, the Joint Theater Trauma System Clinical Practice Guideline recommends that FWB be reserved for severe casualties expected to need massive transfusions (10 or

more units within 24 hours) with clinically significant shock or coagulopathy, when other blood products are not available, are not effective, or cannot be delivered rapidly enough to resuscitate an actively bleeding patient.⁸ Meanwhile, until the appropriate place for FWB in massive transfusion has been established, UK military policy is to confine its use to situations where full CT is not yet available in theater or when coagulopathy persists despite targeted CT.

SUMMARY

Hemorrhage remains the most common cause of death in combat, and in many cases these deaths are preventable with clinical vigilance and proactive care. Massive transfusion of blood products is a key part of the damage control resuscitation paradigm conceived to manage these severely injured casualties from point of wounding to critical care (described in Chapter 7, Damage Control Resuscitation). The earlier the appropriate transfusion of blood products is initiated, the

better the chance of survival; however, prediction tools are not yet adequately sensitive or specific, so when to initiate MTPs remains a clinical decision, particularly during the prehospital phase.

Lieutenant Colonel Primrose noted during World War I that the first result of blood transfusion in the treatment of hemorrhage is that "it increases the power of coagulation of the blood."¹ This lesson has been relearned in recent conflicts so that now the purpose of transfusion

is not merely the replacement of volume and oxygen-carrying capacity, but also the active prevention or treatment of coagulopathy. The complications of transfusion

described above are those most likely to be of concern during or soon after initial resuscitation, requiring attentive monitoring and treatment in the field hospital.

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