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BACKGROUND

The approach to transfusion in emergent situations varies dramatically depending on the clinical scenario. The primary guiding determinant is the clinician's assessment of the rapidity of bleeding, the severity of hemorrhage or amount of blood lost, and the clinical stability of the patient.

Hemodynamically stable patients with slow to moderate bleeding, chronic bleeding, or contained blood loss can usually be managed conservatively with crystalloid to maintain intravascular volume, when necessary. In these patients, transfusion decisions should be guided by the clinical status of the patient. Numerous studies have established that, in terms of morbidity and mortality, a restrictive (70 to 80 g/l) red blood cell transfusion strategy is superior or equivalent to a liberal strategy (90 to 100 g/l) in critically ill patients.¹ Patients exhibiting symptoms of inadequate oxygen delivery should be transfused one red blood cell unit at a time and reassessed.

On the other hand, hemodynamically unstable patients with rapid bleeding must be managed completely differently. Management of massive hemorrhage, as seen with severely injured trauma or obstetrical patients, has changed dramatically over the past 10 to 20 years. The recognition that trauma patients are often profoundly coagulopathic at the time of presentation has refocused energy and clinical research into redefining how we manage these patients. Using the severely injured trauma patient as a case study, this chapter will discuss the principles of massive hemorrhage and resuscitation, with the inclusion of special situations such as obstetrical hemorrhage, where data are available. Extension of practices from the trauma literature to other bleeding critically ill patients is not always appropriate^{2, 3}; however, most clinical studies and experience have come from trauma patients, and some general principles of emergency transfusion and bleeding management apply.

Successful management of massive hemorrhage and emergency transfusion requires the coordinated effort of clinicians, transfusion medicine specialists, and blood bank representatives to come up with an institution-specific massive transfusion protocol (MTP) that is executable, and that incorporates the basic principles for management of rapidly bleeding patients.⁴

IDENTIFICATION OF MASSIVE HEMORRHAGE

Early recognition and identification of the patient that will go on to require a massive transfusion is critical to successful resuscitation. Many definitions of massive transfusion exist, such as the replacement of one (or more) blood volume in 24 hours, 10 or more units of red blood cells in 24 hours, or replacement of more than 50 per cent blood volume in four hours.⁵ Unfortunately, these definitions are retrospective, and not helpful when faced with a bleeding patient. Other definitions such as the requirement for more than four units of red blood cells in one hour, or a rate of blood loss greater than 150 ml/min with ongoing hemodynamic instability are more helpful. Additional assessment tools, such as the Assessment of Blood Consumption (ABC) score⁶, may help the clinician to identify the patient requiring a massive transfusion (Table 1).

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Table 1. ABC Score for Early Assessment of the Acutely Injured Trauma Patient. Adapted from Nunez et al.⁶

Score		Odds ratio for predicting massive transfusion
ED SBP ≤ 90 mmHg	No = 0; Yes = 1	13.0
ED HR ≥ 120 bpm	No = 0; Yes = 1	3.9
Positive FAST	No = 0; Yes = 1	8.2
Penetrating mechanism	No = 0; Yes = 1	1.9
	ABC score = sum of the four scores described above	ABC score ≥ 2 is 75% sensitive and 86% specific for prediction of massive transfusion requirement.
ED = emergency department; SBP = systolic blood pressure; HR = heart rate; bpm = beats per minute; FAST = focused assessment with sonography for trauma		

ESTABLISHMENT OF AN INSTITUTIONAL MASSIVE TRANSFUSION PROTOCOL (MTP)

A massive transfusion protocol (MTP) is a locally-derived set of principles and practices that facilitates early provision of blood products to critically injured or massively hemorrhaging patients. Development of the MTP is ideally a multi-disciplinary process that accounts for local practice, logistics, and human resource considerations. Bedside clinicians (e.g. anesthesiologists, trauma surgeons, emergency physicians, obstetricians), transfusion medicine specialists (hematology, pathology and hematopathology) and blood bank representatives should be included in the MTP development process to ensure that the MTP is appropriate for a given institution. An effective MTP engages everyone on the clinical team, encourages communication with standardized language both between and within the clinical and laboratory teams, and standardizes transfusion best practices. Having clear protocols for blood product management, bedside testing, and transfusion decisions allows practitioners to focus on other aspects of patient care. Implementation of MTPs has been associated with less overall blood product utilization, cost savings, and improved patient outcome in trauma⁷⁻⁹; studies in obstetrics are ongoing.

Guidelines for development of MTPs are available on the Australian National Blood Authority website.⁴ Tertiary care centres within a health authority often have an established MTP that can be modified and adopted for smaller centres. MTPs should be reviewed regularly to ensure that they continue to incorporate best practices.

TRAUMA INDUCED COAGULOPATHY (TIC)

In severely injured trauma patients, exsanguinating hemorrhage is the most common cause of death in the first hour, and accounts for 50% of deaths in the first 24 hours.¹⁰ Historically, it was assumed that trauma patients became coagulopathic during the course of their resuscitation due to dilution, depletion, and dysfunction of procoagulant factors as they received progressively more crystalloid, and became increasingly cold and acidemic. It has now been well established that a significant proportion (25 – 40%) of severely injured trauma patients are already coagulopathic at the time of presentation to hospital, and that this coagulopathy is associated with an increased risk of mortality.¹¹ TIC is characterized by endothelial dysfunction, dysfibrinogenemia, platelet dysfunction and an imbalance of pro- and anticoagulant factors with systemic anticoagulation. This process is exacerbated by hypothermia, acidemia, and resuscitation with hypocoagulable fluids, the so-called “lethal triad” of trauma coagulopathy.¹²

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The recognition that TIC presents very early has dramatically changed the approach to the severely injured trauma patient, and, by extension, the management of massive bleeding in other populations. Attempts to ameliorate the coagulopathy of acute trauma have led to the development and proliferation of massive transfusion protocols, a focus on damage control resuscitation, and ratio driven resuscitation with an emphasis on early provision of frozen plasma, platelets and procoagulant factors. The appropriateness of whether trauma resuscitation principles should extend to non-trauma populations will be revisited later in the chapter.

DAMAGE CONTROL RESUSCITATION (DCR)

Damage control resuscitation comprises a set of resuscitation principles with the goal of arresting or limiting TIC and the physiologic consequences associated with resuscitation.^{13, 14} It applies only to the most seriously injured trauma patients that are approaching physiologic exhaustion. DCR is defined by the employment of four simultaneous strategies:

- 1. Avoidance or strict limitation of crystalloid use.** Traditional trauma resuscitation was initiated with large volumes of crystalloid, followed by 6 to 10 units of red blood cells, prior to consideration of other blood products. Crystalloid resuscitation is no longer recommended because it exacerbates coagulopathy and is associated with several deleterious side effects including tissue edema, acidosis, reperfusion injury and multiorgan failure.
- 2. Target resuscitation to low normal blood pressure to limit hemorrhage** and prevent rebleeding from recently clotted sites.
- 3. Employment of a massive transfusion protocol** that provides rapid delivery of pre-determined, fixed ratio blood products to the bedside. Modern MTPs aim to provide blood product therapy in a ratio that approximates whole blood (i.e. one unit of red blood cells: one unit of plasma: one unit of platelets). Early military studies demonstrated a significant survival benefit to soldiers with severe traumatic injury receiving a higher plasma : red blood cell ratio during the early phase of resuscitation.¹⁵ The Pragmatic Randomized Optimized Platelet and Plasma Ratios (PROPPR) trial is the most recent, multicentre prospective randomized trial aimed to definitively answer this question in civilian patients. Though there was no overall survival benefit demonstrated with provision of a 1:1:1 (as compared to a 1:1:2) blood product strategy, there was a reduction in bleeding and exsanguination in the first 24 hours.¹⁴
- 4. Early hemorrhage control** in the form of damage control surgery or interventional radiology. When the risk of ongoing shock and TIC is high, limit surgical intervention and delay definitive management in order to restore metabolic homeostasis and reverse coagulopathy.

At the moment, the optimal ratio of product is unknown. We know that early, aggressive resuscitation with non-crystalloid product, with early introduction of non-red blood cell products in a relatively balanced approach can limit the extent of TIC and its associated mortality. These principles are also used to guide the resuscitation of less severely injured trauma patients, and often massively bleeding non-trauma patients. However, caution must be exercised when extending what is learned from resuscitating the trauma patient to the non-trauma patient, as they are likely to have different mechanisms of injury, and thus different pathophysiology of tissue injury and coagulopathy. The few studies available suggest that the aggressive 1:1:1 (or near 1:1:1) transfusion approach is not necessary in non-traumatic bleeding such as that seen in GI bleeds or perioperative bleeding.^{2, 3} In these populations, an aggressive 1:1:1 resuscitation strategy is likely not necessary, and in some studies has been associated with harm.^{2, 3}

For each of these scenarios, the ideal transfusion strategy is not known. It is reasonable to start with red blood cell transfusion for resuscitation of the unstable bleeding non-trauma patient. Consideration of frozen plasma,

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platelets and/or fibrinogen supplementation will depend more on early and frequent assessment of coagulation parameters including fibrinogen concentration and platelet count. In these scenarios, a careful history will also account for the presence of platelet inhibiting medications or other anticoagulants.

Resuscitation of the massively bleeding patient is not easy. There are many factors that contribute to confusion and complexity – patient factors, human resources, practitioner availability and bias, hospital and blood bank resources, and system factors. Likely the most meaningful and effective impact that can be made is the development and successful implementation of a protocol to manage bleeding patients.

ADDITIONAL ADJUNCTS FOR MANAGEMENT OF THE BLEEDING PATIENT

Tranexamic acid (TXA)

Early provision of TXA to the traumatically injured patient improves outcomes. The largest study of TXA in trauma patients (CRASH-2) revealed that TXA administration improved both all-cause mortality, and mortality related to bleeding. Benefit was also seen in patients *at risk* for bleeding, in whom subsequent “massive transfusion” was not required. Follow up analyses of CRASH-2 have demonstrated that the majority of the benefit occurs when TXA is administered within three hours of injury. Based on these findings, most jurisdictions have included TXA administration in their pre-hospital algorithm or early in their MTP for all trauma patients deemed at risk for bleeding.^{16, 17}

TXA has also been shown to reduce bleeding in multiple surgical settings¹⁸ and in postpartum hemorrhage¹⁹, in addition to some limited data demonstrating benefit in traumatic brain injury.²⁰ There are multiple ongoing clinical trials looking at TXA use in traumatic brain injury (CRASH-3), intracranial hemorrhage and subarachnoid hemorrhage.

Fibrinogen supplementation

Fibrinogen is critically important in hemostasis. Due to consumption, dilution, fibrinolysis and fibrinogenolysis, fibrinogen levels can fall to critically low levels early after injury in the massively bleeding patient. A prospective analysis has demonstrated that a low fibrinogen level in trauma patients was associated with coagulopathy on hospital presentation and a higher injury severity score, and was an independent predictor of mortality. Several observational studies have also demonstrated that a higher fibrinogen : red blood cell transfusion ratio in trauma patients is associated with improved outcomes (reviewed by Curry et al. in 2014).¹³ Observational studies in cardiac surgery demonstrate that patients coming off of cardiopulmonary bypass with fibrinogen levels below 2.0 g/l are at increased risk of bleeding requiring large volume transfusion.²¹ Similarly, obstetric patients with lower fibrinogen levels are at a higher risk of postpartum hemorrhage.²² Contemporary appreciation of the importance of adequate fibrinogen replacement in bleeding patients is reflected by recent changes to many guidelines recommending a fibrinogen level of at least 1.5–2.0 g/l in the context of bleeding^{23, 24}, with higher, as yet undefined targets in the context of postpartum hemorrhage.²⁵

APPROPRIATE SELECTION OF PRODUCTS FOR TRANSFUSION

Clinical assessment of the urgency for red blood cell transfusion will determine whether the patient receives unmatched emergency Type O red blood cells, group-specific red blood cells, or a fully cross-matched red blood cell unit. In all cases, a pre-transfusion sample of appropriately identified and labelled blood should be obtained from the patient and sent to the blood bank for typing and initiation of compatibility testing. Risks of potentially fatal ABO transfusion errors are high in urgent clinical situations involving multiple-trauma patients. Particular

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care and attention must accompany patient identification procedures in this setting.

Type O unmatched red blood cells should be used if the patient's blood group is unknown and transfusion is immediately required. In this scenario, Type O Rh-positive red blood cells can be transfused to males who have no prior history of transfusion with Rh-positive blood. Type O Rh-negative red blood cells should be reserved for females of child-bearing age, children, and others suspected or known to be alloimmunized to the D antigen.²⁶ Type-specific unmatched blood can usually be provided within 10 minutes; however, completion of an antibody screen and crossmatch often takes 30–60 minutes. In the setting of an emergency transfusion that is initiated with emergency supply Type O blood, a switch to group-specific product should happen as soon as the patient's blood type is known, regardless of the number of Type O units the patient has received. Transfusing physicians should familiarize themselves with the policies and procedures of their local hospital blood bank in providing blood for emergency use.

RISKS AND COMPLICATIONS ASSOCIATED WITH LARGE VOLUME RESUSCITATION WITH BLOOD PRODUCTS

1. Hypothermia

Massive transfusion can easily result in clinically significant hypothermia (body temperature below 35°C). Hypothermia dramatically worsens platelet and coagulation function, decreases citrate metabolism, increases hemoglobin-oxygen affinity (decreasing oxygen release to the tissues), and decreases myocardial function. Aggressive temperature management is imperative to successful treatment during massive transfusion. This can be accomplished by warming of the resuscitation bay or operating room, infusion of all products through an approved blood warming device, and employment of external warming devices. The patient's temperature should be actively monitored. Precautions for avoidance of air embolism must be considered with the use of pressurized infusion systems.

2. Impaired hemostasis

Patients that present with trauma or tissue injury can have significant coagulation defects at presentation. This coagulopathy is exacerbated by resuscitation with both crystalloid and starches (e.g. hydroxyethyl starch). Large volume resuscitation with blood products is more favorable but dilution of platelets and clotting factors, particularly fibrinogen, can still occur. In the early phases of resuscitation when bleeding is rapid, transfusion should be guided by the institution's MTP, with replacement of blood products (red blood cell, plasma, and platelets) in a predetermined ratio, with early consideration for the addition of fibrinogen replacement (fibrinogen concentrate or cryoprecipitate). As time permits, transfusion can then be guided by either standard laboratory tests or viscoelastic tests of whole blood clotting (ROTEM® or TEG®).

3. Hypocalcemia and citrate toxicity

Blood products are anticoagulated with sodium citrate. Transfused citrate binds calcium and magnesium, and suboptimal citrate metabolism in the context of massive transfusion may lead to citrate toxicity and hypocalcemia. Hypocalcemia can lead to hypotension, impaired coagulation, reduced ventricular function and increased neuromuscular excitability. Metabolic alkalosis may occur, particularly in children, from accumulation of bicarbonate, which is the metabolic by-product of citrate. Calcium monitoring and replacement are essential and their inclusion in the MTP should be considered.

4. Hyperkalemia

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Potassium leaks from red blood cells during storage and occasionally reaches levels of up to 80 mmol/l. In rare cases, hyperkalemia can result in cardiac arrhythmias, myocardial depression, or cardiac arrest.

5. Volume overload/over transfusion

Massively transfused patients, particularly those with ongoing hemorrhage, are vulnerable to extremes of intravascular volume (hypovolemia to hypervolemia) and myocardial depression. Physical examination may be inadequate to guide management of these patients; invasive monitoring methods (central venous pressure, pulmonary artery catheter, echocardiography) may be required.

6. Alloimmunization

In cases where uncrossmatched blood is used, there is a risk of alloimmunization. Development of red blood cell antibodies to foreign antigens (alloimmunization) puts female patients at risk for future hemolytic disease of the fetus or newborn, renders a patient more difficult to crossmatch in the future, increases the risk of transfusion reactions, and complicates matching for solid organ transplantation.

7. Risk of transfusion reaction

The potential for triggering a transfusion reaction in a patient with unidentified antibodies with the use of uncrossmatched blood is a concern. The prevalence of alloantibodies in patients that present to hospital is approximately 3%, and the presence of clinically significant antibodies is approximately 2%. Antibody incidence is higher in females, and increases with age.²⁷ However, the risk of a clinically significant delayed hemolytic transfusion reaction is very low — in the order of 0.02%.^{28, 29}

CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to **two credits**.

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We're here to answer your questions about the Clinical Guide to Transfusion. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the [Clinical Guide feedback form](#).

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