

# BLOOD BULLETIN

VOL. 9, NO. 2

FEBRUARY 2008



Community Blood Center  
Community Tissue Services

PROVIDED BY YOUR INDEPENDENT,  
NONPROFIT COMMUNITY BLOOD CENTER  
in conjunction with America's Blood Centers ®

## Massive Transfusion in Trauma

By Edahn Isaak, MD, Community Blood Center/Community Tissue Services (Dayton, Ohio) and the Scientific Publications Committee, America's Blood Centers

**Massive Transfusion: Definition and Incidence in Trauma Patients.** In trauma, massive transfusion is defined in several different ways. Most commonly, definitions are based either on the replacement of a fraction of the patient's blood volume within a given time period or on the transfusion of a given number of red blood cells (RBC) within a given time period. Definitions based on patient blood volume stipulate either the replacement of one blood volume in 24 hours or the replacement of 50% of one blood volume within three hours.<sup>1</sup> Definitions based on the absolute number of transfused RBC stipulate either the transfusion of 10 units or more of RBC in 24 hours or the transfusion of 20 units of RBC or more in the course of the hospital admission.<sup>2</sup> Other studies have used operational definitions such as the transfusion of 10 units or more of RBC from the time of admission to the hospital trauma bay to the time of admission to the intensive care unit.

Most trauma patients who are transported to the hospital emergency center do not require massive transfusion. There is a range of reported incidence of trauma patients requiring this intervention. At the lower end of this range, Como *et al.* reported 2.6%<sup>3</sup> and Malone *et al.* reported 2.7%.<sup>4</sup> At the higher end of this range, Huber-Wagner *et al.* reported an incidence of 13%.<sup>2</sup>

**Pathophysiology of Trauma.** Beyond their anatomic injuries, seriously injured trauma patients face several physiological hurdles. They suffer an initial hypoxic insult followed by reperfusion injury.<sup>5</sup> The hemorrhage also leads to an acquired coagulopathy caused by the cumulative effects of hypovolemia, hypothermia and acidosis.<sup>6,7</sup> These changes are interrelated, so it is necessary not only to analyze the effects of each component, but also to understand how these components interact with one another.

The initial anoxic injury, followed by reperfusion, results in a predictable clinical progression beginning with the systemic inflammatory response syndrome (SIRS), followed by the compensatory anti-inflammatory response syndrome (CARS), and potentially culminating in multi-system organ failure (MOF).<sup>8</sup> SIRS is a pro-inflammatory, prothrombotic response with activation of neutrophils, activation of complement and production of inflammatory cytokines such as IL-1, IL-6 and TNF-alpha. Over several days SIRS progresses to CARS, characterized by significant shifts in the inflammatory milieu and coagulation profile. There is increased production of IL-4, IL-10, TGF-beta and endogenous corticosteroids. Although the exact pathophysiology of this progression has not been elucidated, the result is an immunocompromised patient who becomes susceptible to a wide

**Table 1: Complications of Massive Transfusion**

**Rate-related complications:**

- Hypocalcemia
- Hyperkalemia
- Hypomagnesemia
- Hypothermia
- Acidosis

**Volume-related complications:**

- Dilutional thrombocytopenia
- Dilution of procoagulant factors
- Dilution of anticoagulant factors

array of opportunistic and nosocomial infections. These infections contribute to MOF.

Once the traumatic injury has taken place, hypovolemia, coagulation factor consumption, colloid and crystalloid infusion, hypothermia and acidosis intervene against the SIRS backdrop and create a clinical picture characterized by diffuse thrombosis and concurrent fibrinolysis. This clinical picture has been called a "disseminated intravascular coagulation (DIC)-like" state.<sup>9-11</sup> Several elements contribute to the coagulopathy in this setting. In addition to the consumption, dilution and dysfunction of the serine proteases involved in clot formation, there is a decrease in platelet count, a deterioration in platelet function and an abnormal formation of platelet clumps in the hepatic sinusoids.<sup>12</sup> One additional factor is the loss of red blood cells and their ability to modulate platelet behavior through hydrodynamic effects on platelet margination and the secretion of mediators such as cyclooxygenase and thromboxane A2.

**Complications of Massive Transfusion.** The administration of large volumes of blood components further complicates the clinical picture. These complications may be divided into those that are rate-related and those that are volume-related (Table 1).<sup>13</sup> Each complication has a standard definition and a predictable clinical presentation. In general, rate-related complications are characterized by an approximate infusion rate, while volume-related complications are characterized by a triggering volume.

Rate-related complications occur because citrate is used as the anticoagulant during the collection procedure, the blood components are acidic and become more acidic during storage and some blood components are refrigerated. Because citrate chelates calcium and magnesium, hypocalcemia may occur when the rate of citrate infusion exceeds the rate at

(continued on next page)

which it is metabolized and excreted. The pH of an RBC is approximately 7.0 at collection, then decreases during storage with the continuous production and accumulation of lactic acid. This acidic environment leads to transmembrane egress of potassium ions – producing hyperkalemia in the extracellular fluid. Clinical acidosis and hyperkalemia can result when the rate of infusion exceeds the capacity of the patient to metabolize or excrete it. RBC and thawed plasma products are stored at 1-6°C. Hypothermia can result during rapid transfusion unless these products are administered through a blood warmer.

Volume-related complications occur when the transfusion of RBC, plasma and other intravenous fluids cause hemodilution of platelets, procoagulant and anticoagulant factors. The point at which this dilution manifests itself as a coagulopathy depends on many clinical variables. In general, the minimum threshold for platelets is 50,000/microliter, the minimum threshold for fibrinogen is 100 mg/dL and the minimum threshold for each of the serine proteases varies by factor. There is no published literature at this time on the minimum levels of anticoagulant factors.

**Management of Transfusion Therapy in Trauma.** Massive transfusion protocols have been developed by the military and at trauma centers associated with academic institutions. These algorithms have several common components – a procedure for initial resuscitation, a procedure for transfusion therapy while hemorrhage is ongoing, a procedure for laboratory monitoring and, in some, guidelines for governing the timing and dosage of recombinant activated Factor VII in selected patients. The aims of these protocols include volume resuscitation and prevention and treatment of coagulopathy. Despite the common features and aims of these protocols, there is no consensus on optimal laboratory monitoring, the exact mix of components to be administered or the order of their transfusion. Nevertheless, a growing body of evidence suggests that in the population with high Injury Severity Scores, survival is associated with prevention or control of the coagulopathy. This control may be optimized by the earlier routine transfusion of fresh frozen plasma (FFP), plasma frozen within 24 hours of phlebotomy or thawed plasma, and platelets.<sup>14</sup> (The literature does not indicate a difference between plasma products in the trauma setting.<sup>15</sup>)

Despite the emerging importance of the control of coagulopathy as a clinical priority, there is no consistent literature on an appropriate trigger for a massive transfusion protocol. In general, the definition of massive transfusion itself has served as the trigger. Most investigators concentrate instead on the issues related to the selected ratio of blood components and to the timing of transfusion. Using a mathematical model that considered the rate of volume infusion and the loss of coagulation factors through bleeding, Ho *et al.* conservatively concluded that control of coagulation factor levels would necessitate a ratio of at least one unit of FFP for every RBC transfused, and that this ratio is probably even higher.<sup>16</sup> Malone *et al.* reviewed the massive transfusion protocols at several institutions both within the United States and abroad and concluded that the ideal protocol should consist of FFP, RBC and platelets.<sup>17</sup> These should be given in a ratio of 1:1:1 when random donor platelets are used. When apheresis platelets are used, FFP and RBC components should be given alternately until ten of each have been transfused; at this point a unit of apheresis platelets should be transfused. This proposed protocol may serve as the standard against which future modifications may be compared, but at this point there is no established standard.

## References

1. Hardy JF *et al.* Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth.* 2004;51:293-310.
2. Huber-Wagner S *et al.* Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. *Vox Sang.* 2007;92:69-78.
3. Como JJ *et al.* Blood transfusion rates in the care of acute trauma. *Transfusion.* 2004;44:809-813.
4. Malone DL *et al.* Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma.* 2003;54:898-905; discussion 905-7.
5. Spahn DR and Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesth.* 2005;95:130-139.
6. Cosgriff N *et al.* Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. *J Trauma.* 1997;42:857-61; discussion 861-2.
7. Ferrara A *et al.* Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg.* 1990;160:515-518.
8. Mannick JA *et al.* The immunologic response to injury. *J Am Coll Surg.* 2001;193:237-244.
9. Gando S *et al.* Posttrauma coagulation and fibrinolysis. *Crit Care Med.* 1992;20:594-600.
10. Gando S *et al.* Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. *Thromb Haemost.* 1998;79:1111-1115.
11. Reiss RF. Hemostatic defects in massive transfusion: rapid diagnosis and management. *Am J Crit Care.* 2000;9:158-65; quiz 166-7.
12. Pina-Cabral JM *et al.* Platelet sequestration during hypothermia in dogs treated with sulphinpyrazone and ticlopidine--reversibility accelerated after intra-abdominal rewarming. *Thromb Haemost.* 1985;54:838-841.
13. Goskovic R. Perioperative Use of Anticoagulants and Thrombolytics. *Anesthesiology Clinics of North America.* 1999;17:959.
14. Gonzalez EA *et al.* Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma.* 2007;62:112-119.
15. Katz LM, Kiss JE. Plasma for transfusion in the era of transfusion-related acute lung injury mitigation. *Transfusion* 2008;48:393-7.
16. Ho AM *et al.* A mathematical model for fresh frozen plasma transfusion strategies during major trauma resuscitation with ongoing hemorrhage. *Can J Surg.* 2005;48:470-478.
17. Malone DL *et al.* Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma.* 2006;60:S91-6.



*Blood Bulletin* is issued periodically by America's Blood Centers. Editor: Louis Katz, MD. The opinions expressed herein are opinions only and should not be construed as recommendations or standards of ABC or its board of trustees. Publication Office: 725 15th St., NW, Suite 700, Washington, DC 20005. Tel: (202) 393-5725; Fax: (202) 393-1282; E-mail: [abc@americasblood.org](mailto:abc@americasblood.org). Copyright America's Blood Centers, 2008. Reproduction is forbidden unless permission is granted by the publisher. (ABC members need not obtain prior permission if proper credit is given.)