Damage Control Resuscitation
Permssive Hypotension and Massive Transfusion Protocols

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Abstract: Evidence for changes in adult trauma management often precedes evidence for changes in pediatric trauma management. Many adult trauma centers have adopted damage-control resuscitation management strategies, which target the metabolic syndrome of acidosis, coagulopathy, and hypothermia often found in severe uncontrolled hemorrhage. Two key components of damage-control resuscitation are permissive hypotension, which is a fluid management strategy that targets a subnormal blood pressure, and hemostatic resuscitation, which is a transfusion strategy that targets a coagulopathy with early blood product administration. Acceptance of damage-control resuscitation strategies is reflected in recent changes in the American College of Surgeons’ Advanced Trauma Life Support curriculum; the most recent edition has decreased its initial fluid recommendation to 1 L from 2 L, and it now recommends early administration of blood products without specifying any specific ratio. These recommendations are not advocated in adult settings, but represent an initial step toward limiting fluid resuscitation and using blood products to treat coagulopathy earlier. Evidence for permissive hypotension exists in animal studies and few adult clinical trials. There is no evidence to support permissive hypotension strategies in pediatric trauma patients with severe hemorrhage. Additional studies on the management of children with severe uncontrolled hemorrhage are needed.

Key Words: hemorrhagic shock, damage-control resuscitation, permissive hypotension, coagulopathy, massive transfusion protocol

(Pediatr Emer Care 2014;30: 651–659)

TARGET AUDIENCE
This CME activity is intended for prehospital providers, pediatric emergency physicians, emergency nurses, pediatricians, trauma surgeons, trauma nurses, and any practitioners caring for pediatric patients in a trauma setting.

LEARNING OBJECTIVES
Upon completion of this article the reader should be able to:

1. Define damage-control resuscitation, permissive hypotension, acute coagulopathy of trauma, hemostatic resuscitation, massive transfusion protocol, and balanced resuscitation.
2. Describe rationale for changes in the Advanced Trauma Life Support (ATLS) curriculum.
3. Identify limitations of damage-control resuscitation in pediatric trauma.

CLINICAL SCENARIO
You are the emergency physician in charge when a 13-year-old girl presents to your emergency department (ED) after a high-speed motor vehicle collision in which she was an unbelted front seat passenger. She has a heart rate of 120 beats per minute, a respiratory rate of 30 breaths per minute, a blood pressure of 80/40 mm Hg, and a Glasgow Coma Scale (GCS) score of 15. She is complaining of shortness of breath and diffuse abdominal pain. Breath sounds are absent on the left, and her trachea is deviated to the right. After placement of a left-sided thoracostomy tube, her breathing becomes less labored, but she remains tachycardic, tachypneic, and hypotensive with a capillary refill of 3 seconds. Her abdomen is distended and tender. She has received an initial isotonic fluid bolus of 20 mL/kg over 10 minutes when your colleague suggests that while waiting to transfer her to the operating room, you stop rapid administration of crystalloid fluids, permit her to remain relatively hypotensive, and initiate the hospital’s recently established massive transfusion protocol.

Damage-Control Resuscitation
 Damage-control resuscitation is a management strategy used to treat hemorrhagic shock in severe traumatic injury. It has been used in recent military conflicts with reported success and has been incorporated into management in many civilian trauma centers. Damage-control resuscitation differs from the traditional management of hemorrhagic shock by limiting isotonic fluid resuscitation and by transfusing blood components empirically before coagulopathy is identified by laboratory tests.

The widespread acceptance of damage-control resuscitation is reflected in recent changes in the ATLS curriculum. The initial ATLS fluid recommendation has changed from 2 L liters of isotonic fluid to only 1 L, and the curriculum also now recommends early use of blood and blood products, without recommending any specific ratio of plasma and platelets. Both of these recommendations reflect damage-control resuscitation management strategies.

Damage-control resuscitation is intended for patients with severe hemorrhage, which is not controlled and which may require large-volume blood transfusion. It is not intended for patients with hemorrhage that has been controlled or for patients who respond to initial administration of fluids without further need for intervention. Patients with physiologic extremis from hemorrhage develop a metabolic syndrome that includes the triad of acidosis, hypothermia, and coagulopathy, referred to as the lethal triad in trauma management. Large volumes of isotonic fluids and packed red blood cells (PRBCs) can exacerbate the...
condition of these patients by causing hemodilution and hypothermia, which worsens coagulopathy and causes more bleeding.3

Before damage-control resuscitation, damage-control surgery was developed to address the physiologic derangement that occurs in severe hemorrhage. This intervention strategy includes initial operative control of bleeding, followed later by more definitive repair of injuries once the patient has been fully resuscitated.4 The concept of an initial abbreviated surgery for the patient with hemorrhagic shock was introduced in the 1980s by and Stone et al5 and Burch et al.6 This technique was refined and named damage-control surgery by Rotondo et al7 in 1993 in their landmark article showing a 7-fold improvement in mortality. This approach has improved outcomes for trauma patients and has been applied to other surgical patients in physiologic extremis.8 Reversal of hemorrhagic shock will not occur until the bleeding is stopped, operatively or with interventional radiology. Damage-control resuscitation also encompasses management interventions before and after interventions to control bleeding (operative and interventional radiographic controls) by minimizing iatrogenic injury from fluids and treating the coagulopathy, which occurs with hemorrhagic shock.

The focus of this review is on care of the pediatric patient in hemorrhagic shock in the ED setting. We will discuss several management strategies and concepts that are key components of damage-control resuscitation. We will first discuss *permissive hypotension*, which is a management strategy used in severe uncontrolled hemorrhage in which fluid resuscitation is limited to keep systolic blood pressure at subnormal levels. Next, we will focus on coagulopathy. *Acute coagulopathy of trauma* is a term used to describe the coagulopathy that is present shortly after injury in severe hemorrhage, before any resuscitation measures. This is followed by a discussion of hemostatic resuscitation and massive transfusion protocols, which have been advocated to treat acute coagulopathy of trauma. *Hemostatic resuscitation* is a management strategy that targets coagulopathy by early transfusion of blood products. *Massive transfusion protocols* are predefined multidisciplinary transfusion protocols designed to provide hemostatic resuscitation in an efficient manner. We will show that insufficient evidence supports the use of permissive hypotension in pediatric trauma; however, evidence does support the presence of coagulopathy in pediatric trauma, and there are limited data to support the use of massive transfusion protocols in this setting.

### Permissive Hypotension

The use of permissive hypotension is based on the observation that patients with shock from uncontrolled hemorrhage may worsen with intravenous fluid resuscitation.9 Permissive hypotension, also known as hypotensive resuscitation or controlled resuscitation, refers to a strategy of withholding or minimizing intravenous fluids to keep systolic pressures at a subnormal value until definitive management of bleeding can be obtained by surgical treatment or selective embolization. Limitation of fluids must be balanced with provision of enough fluid resuscitation to maintain end-organ perfusion.

Despite concerns as early as 1918 that aggressive fluid resuscitation may worsen hemorrhage, isotonic crystalloid fluid resuscitation after injury became widespread beginning in the 1950s.8,9 This change followed animal research published in the 1950s and 1960s suggesting that crystalloid resuscitation in trauma would improve survival.9,10 Based on this work, investigators concluded that fluid resuscitation equal to at least 3 times blood volume loss was needed to replace both intravascular volume loss and interstitial deficits in patients with uncontrolled hemorrhage. Patients with hemorrhage often receive large volumes of fluids resuscitation to maintain perfusion.

Before its 9th edition, ATLS curriculum recommended administration of 2 L of crystalloid fluid followed by PRBC transfusion for patients in shock. The emphasis of ATLS on early fluids administration was based on animal studies and a single small clinical observational study.11,12 This recommendation has been extrapolated so broadly that many trauma patients are given 2 L of fluids regardless of their hemodynamic status.13 A Cochrane review published in 2003 reviewed the timing and volume of fluid resuscitation in patients with hemorrhage.14 The authors of this review found no convincing evidence for or against early aggressive fluid resuscitation for uncontrolled hemorrhage. With this lack of evidence to support aggressive fluid resuscitation for trauma and evolving evidence to support permissive hypotension, the American College of Surgeons’ Committee on Trauma has modified recommendations in its latest version of the ATLS manual. The 9th edition of the ATLS manual recommends a balanced resuscitation strategy for traumatic shock, which includes less initial fluid resuscitation and the early use of blood and blood products.2 Several explanations may potentially explain why fluid resuscitation may be harmful for patients with uncontrolled hemorrhage. The most obvious is that increasing hydrostatic pressure disrupts any clot formation that may have formed since the injury.15 Fluids also worsen coagulopathy by diluting coagulation factors and causing hypothermia.16 Finally, fluids may contribute to mortality by causing damage at the molecular level. Large volumes of fluid administration, for example, can cause imbalance in intracellular and extracellular osmolality. Cellular swelling results in disruption of numerous regulatory mechanisms in the inflammatory cascade, resulting in activation of phospholipase A2, tumor necrosis factor α, and interleukin 6. These inflammatory changes may also contribute to common complications of fluid resuscitation in trauma such as acute respiratory distress syndrome, abdominal compartment syndrome, and multiorgan system failure.17

A multicenter epidemiologic study of mixed population of critically ill adults showed that more than 60% of patients with intra-abdominal hypertension had received massive fluid resuscitation.18 Intra-abdominal hypertension, also called abdominal compartment syndrome, is the pathologic elevation of intra-abdominal pressure resulting in organ dysfunction.19 Abdominal compartment syndrome in critically ill children is associated with fluid resuscitation for the treatment of shock from multiple etiologies, including trauma.20–22 Morrell et al22 describe 6 trauma patients, ages 4 to 17 years, who received up to 25 L of fluid and developed abdominal compartment syndrome within 12 hours from injury. Of note, all the patients reported in this case series lived. Practitioners should be aware of the potential complications from aggressive fluid resuscitation, but it is not known if these patients would have tolerated a permissive hypotension strategy. Additional evidence to support improved outcomes from permissive hypotension in children is needed before changes in practice in can be strongly recommended.

Several animal studies support permissive hypotension by showing that intentional hemorrhage followed by resuscitation to subnormal blood pressures was associated with lower mortality rates.15,23,24 A systematic review of these and other animal trials examined permissive hypotension for evidence of efficacy. Nine studies compared hypotensive resuscitation with normotensive resuscitation and found that hypotensive resuscitation was associated with a reduced risk of mortality (relative risk, 0.37; 95% confidence interval, 0.27–0.50). In addition, 44 studies compared no fluid resuscitation with fluid resuscitation. The authors of the systematic review found that when hemorrhage is severe, fluid resuscitation reduces risk of death but that when hemorrhage is less severe, then risk of death was increased with fluid resuscitation.25
These associations imply that efficacy of fluid resuscitation is related to the severity of hemorrhage.

Limited clinical data support the use of permissive hypotension in uncontrolled hemorrhagic shock. A large prospective trial published in 1994 by Bickell et al.26 randomized adults with penetrating torso injuries and hypotension to delayed or immediate fluid resuscitation. The investigators found significantly improved survival in the delayed fluid resuscitation group (70% vs 62%, P = 0.04). This work brought new attention to the topic of permissive hypotension but did little to change standards in trauma management.27 In 2002, Dutton et al.28 attempted to replicate and expand on the study of Bickell et al. In this study, the investigators included patients initially presenting to their trauma center with evidence of ongoing hemorrhage and a systolic blood pressure less than 90 mm Hg within the first hour of evaluation. They randomized patients to low (70 mm Hg) or conventional (100 mm Hg) systolic blood pressure targets for fluid resuscitation. They found no difference in mortality or duration of active hemorrhage. In 2011, Morrison et al.29 reported preliminary findings of a large randomized controlled trial of intraoperative permissive hypotension management in adults requiring surgery for thoracic or abdominal trauma with shock, defined by a systolic blood pressure less than 90 mm Hg or by clinical assessment. They found that permissive hypotension was associated with a slightly higher intraoperative mortality but a trend toward decreased 30-day mortality. None of these studies showed conclusive evidence to support permissive hypotension.

Evidence supporting the use of permissive hypotension comes from animal studies and from a few adult studies, which show contradictory results. No pediatric studies to date have evaluated permissive hypotension. Children have a physiology different from that of adults when presenting with hypovolemic shock. Because they have much greater cardiac reserve, they are able to compensate for up to 45% of blood loss before shock is reflected in low blood pressure.29 Permissive hypotension may therefore not be as applicable to pediatric trauma patients.

Finally, it is important to note that permissive hypotension is contraindicated in head injury, as cerebral perfusion pressure is imperative for these patients. Data from the Traumatic Coma Data Bank, for example, found that among patients with head injuries, the presence of a single measurement of systolic blood pressure less than or equal to 90 mm Hg from the accident scene through resuscitation doubled mortality and decreased likelihood of satisfactory recovery in survivors.30 If future studies show more convincing evidence to support permissive hypotension, it will only be applicable to trauma patients without any evidence of head injury.

Coagulopathy in Trauma

The management of coagulopathy in trauma currently has a more direct application in pediatric trauma than permissive hypotension. Coagulopathy in trauma may evolve because of dilution from intravenous fluids and blood products, consumptive coagulopathy, and exacerbation from hypothermia and acidosis often found during resuscitation.1 Acute coagulopathy of trauma is a separate entity that is present at initial injury before resuscitative efforts. It is present in 24% to 28% of adult trauma patients at presentation to the ED.16,31 Acute coagulopathy of trauma is associated with mortality independent of fluid resuscitation and injury severity.31,32 Several theories have been hypothesized to explain this initial coagulopathy including tissue factor release, activation of protein C and anticoagulation, and hyperfibrinolysis.33-36 Identification of patients with coagulopathy at presentation followed by appropriate early management may improve morbidity and mortality.

Several studies report the presence of coagulopathy in pediatric trauma patients as well (Table 1). Studies by Hendrickson et al.37 and Holmes et al.39 evaluated initial coagulation studies in low blood pressure.39 Permissive hypotension may therefore not be as applicable to pediatric trauma patients.

### TABLE 1. Pediatric Studies Supporting Presence of Coagulopathy in Trauma

<table>
<thead>
<tr>
<th>Study</th>
<th>Population of Trauma Patients</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Hendrickson et al, 2012</td>
<td>102 patients, mean [SD] age of 6 [5] y, who required blood transfusion within the first 24 h of admission</td>
<td>• Coagulopathy was present in 77%, on arrival to the ED.</td>
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<tr>
<td></td>
<td></td>
<td>• Coagulopathy was significantly associated with severity of injury, morbidity (intensive care unit days and ventilator days) and mortality.</td>
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<tr>
<td>Talving et al, 2011</td>
<td>320 hospitalized patients, age &lt; 18 y, with isolated traumatic brain injury</td>
<td>• Coagulopathy was present in 40%, during hospitalization.</td>
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<tr>
<td></td>
<td></td>
<td>• Coagulopathy was associated with severity of injury and age.</td>
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<tr>
<td></td>
<td></td>
<td>• Adolescent patients had a statistically significant increase in coagulopathy compared with patients 3 y and younger.</td>
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<tr>
<td>Holmes et al, 2001</td>
<td>830 patients, age &lt; 15 y, hospitalized for blunt trauma to head or torso</td>
<td>• Coagulopathy was present in 28%, on initial ED screening tests.</td>
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<tr>
<td></td>
<td></td>
<td>• GCS score &lt; 13, low systolic blood pressure, open or multiple bony fracture, or major tissue wounds is significantly associated with abnormal coagulation results.</td>
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<tr>
<td>Hymel et al, 1997</td>
<td>147 patients, age 2 wk to 3 y, hospitalized for head trauma associated with nonaccidental trauma</td>
<td>• Prothrombin time was prolonged in 54% of patients with parenchymal brain injury.</td>
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<tr>
<td></td>
<td></td>
<td>• Prothrombin time was prolonged in 20% of patients without parenchymal brain injury.</td>
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<td></td>
<td></td>
<td>• Among patients with parenchymal brain injury that did not survive, prothrombin time was prolonged in 94%.</td>
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<tr>
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<td></td>
<td>• Coagulopathy noted by at least 1 abnormal test result was present in 87%.</td>
</tr>
<tr>
<td>Miner et al, 1982</td>
<td>87 patients age 2–18 y hospitalized for traumatic head injuries diagnosed by clinical examination and computed tomographic scan</td>
<td>• Disseminated intravascular coagulation was present in 32%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mortality rates were 4 times greater in those with DIC.</td>
</tr>
</tbody>
</table>

DIC indicates disseminated intravascular coagulation.
pediatric trauma patients with different study objectives. Holmes et al identified characteristics of trauma patients that were associated with coagulopathy with the goal of reducing the laboratory testing of all pediatric trauma patients with low suspicion of coagulopathy. In contrast, Hendrickson et al narrowed their sample of pediatric trauma patients to include only those requiring blood transfusion, thus selecting a more severely injured sample of patients. The study of Hendrickson et al highlights the presence of acute coagulopathy of trauma with the suggestion that further study in this area may inform evidence-based transfusion guidelines.

Three of the studies on coagulopathy in pediatric trauma listed in our table focus on coagulopathy associated with head trauma in pediatric patients without addressing coagulopathy at initial presentation (Table 1). The other 2 studies described in our table support the association of coagulopathy and head trauma by reporting that coagulopathy was associated with GCS score (Table 1). An association between coagulopathy and traumatic brain injury may be separate from the association between coagulopathy and trauma. Further studies of the pathophysiologic causes for these coagulopathies will help determine the relationship between these groups.

A final study of interest that reflects the importance of coagulopathy in the treatment of pediatric trauma is by Borgman et al. They developed and validated a mortality prediction score for children with traumatic injuries, the pediatric “BIG” score. They found that base deficit, international normalized ratio, and GCS score were independently associated with mortality in a derivation set of 707 patients treated in combat-support hospitals as well as in a validation set of 1101 patients in the German Trauma Registry. As new information is discovered about the role of coagulopathy in trauma, management strategies targeting this coagulopathy will become more prominent in trauma practice.

Hemostatic Resuscitation and Massive Transfusion Protocols

Hemostatic resuscitation is the use of fresh frozen plasma (FFP), platelets, and PRBCs to empirically treat coagulopathy before laboratory values are available to direct management. Controversy exists regarding the best ratio of FFP/platelet/PRBC, but before laboratory values are available to direct management. Controversy exists regarding the best ratio of FFP/platelet/PRBC, but controversy exists regarding the best ratio of FFP/platelet/PRBC. Borgman et al reported that soldiers who received higher ratios of FFP and platelets compared with those who had medium (1.2.5) or low (1.8) ratios. Mortality was also associated with FFP/PRBC ratios with 65% in the low group, 34% in the medium group, and 19% in the high group despite similar injury severity. In 2008, Holcomb et al studied data from 16 civilian level I trauma centers and found that high FFP and platelet–to–PRBC ratios improved survival at 6 hours and 30 days. Several other studies in this period found similar associations between higher FFP and platelet–to–PRBC ratios, but the findings were not consistent. Scalea et al for example, prospectively collected data on 806 consecutive trauma patients admitted to the intensive care. They found no significant difference in outcome when comparing patients who had 1:1 FFP/PRBC ratio and patients who did not receive any FFP. One criticism of the initial studies on blood product ratios is the presence of survival bias, the observation that only patients who survived long enough to get transfusions were included in the study, effectively excluding the sickest patients. The Prospective Observational Multicenter Major Trauma Transfusion (PROMTT) group evaluated data from 10 level I trauma centers to assess the association between blood product ratio and mortality prospectively accounting for time, a strategy intended to address survival bias. The PROMTT group found that higher plasma and platelet-to-PRBC ratios were associated with decreased early mortality but did not affect mortality at 30 days. Further studies are needed to define the ideal blood product ratios.

Hemostatic resuscitation has been extended to pediatric patients without injury (eg, uncontrolled bleeding in the operative setting). Massive transfusion protocols have been developed at several pediatric centers, and case reports support their usefulness in surgery. Two case reports of severe uncontrolled intraoperative hemorrhage treated with massive transfusion protocol had successful outcomes. The authors attribute this success to the use of a massive transfusion protocol. The first case report was a resection of a ruptured intracerebral arteriovenous malformation in a 5-year-old girl. Massive transfusion protocol was initiated upon decision to bring the patient to the operating room; she received 13 U of PRBCs, 8 U of FFP, 4 U of platelets, and 1 dose of factor VIIa. She had a normal coagulation profile postoperatively, was extubated on postoperative day 2, and recovered with only mild neurologic sequelae. The second case report was a liver resection in a 9-year-old boy, for whom the massive transfusion protocol was initiated because of bleeding from the liver bed. The patient received a total of 10 U of PRBCs, 14 U of FFP, and 15 U of platelets as well as replacement of calcium. The patient maintained normal base deficit values, was extubated on postoperative day 1, and was discharged home on postoperative day 14. Both cases report successful use of a massive transfusion protocol in pediatric patients.

Massive transfusion protocols have also been implemented for use in pediatric trauma. Hendrickson et al describe implementation of a pediatric massive transfusion protocol for trauma patients at their institution. They found that massive transfusion protocol increased FFP/PRBC ratios and decreased length of time to FFP transfusion in coagulopathic children. In this study, they did not meet their goal of 1:1 FFP/PRBC transfusion ratio and did not improve mortality. Patients meeting predefined severe trauma criteria and receiving blood transfusions were compared before (pre–massive transfusion protocol [MTP]) and after (MTP) implementation of the protocol. The ratio of blood products was 1:1.8 in the MTP group and 1.3:6 in the pre-MTP group. Chidester et al also described pediatric massive transfusion protocol implementation, for both surgical and trauma patients. In the patients studied, 8 were surgical and 47 were traumatic. They found that the FFP/PRBC ratio was not significantly different between patients who received massive transfusion protocol and those who received blood according to physician discretion. The average ratio of FFP/PRBC overall was 1:3. Unlike the study of Hendrickson et al, they compared cohorts during the same period instead of preprotocol and postprotocol implementation. Failure of these studies to find decreased mortality with massive transfusion protocols could be in part due to the small size of the samples or to difficulty in achieving the goal 1:1 FFP/PRBC ratio. Massive transfusion protocols have the potential to improve outcomes in severe hemorrhage in pediatric trauma based on pediatric.
operative case reports and adult trauma data. Massive transfusion protocols in pediatric trauma settings have not yet shown evidence of decreased mortality or morbidity.

**CONCLUSIONS**

Damage-control resuscitation is intended for the most severely injured patients who account for less than 10% of adult trauma. Changes in the American College of Surgeons’ ATLS curricula reflect current damage-control resuscitation strategies by recommending less fluid resuscitation with crystalloid and earlier transfusion of blood products. Nonetheless, permissive hypotension does not have sufficient evidence to support its use in children. The presence of coagulopathy associated with severe hemorrhage in children is well documented, and massive transfusion protocols are currently being initiated in many pediatric trauma centers. Changes in adult trauma management often precede changes in pediatric trauma management without conclusive supportive evidence. Additional studies on management of children with severe uncontrolled hemorrhage are needed.

**REFERENCES**


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