3.1 Introduction

Despite the word “war” refer to a bad feeling, it is undeniable that military conflicts have always driven innovation and technical advances in medicine and surgery. Accepted concepts of trauma resuscitation and surgery have been challenged in the recent wars, and novel approaches have been developed to...
address the current complexity and severity of not only military trauma but also civilian conflicts.

Damage control resuscitation (DCR) has become a topic of increasing relevance and popularity over the past several years. Hemorrhage secondary to trauma accounts for 40% of trauma fatalities and comprises the leading cause of preventable death in trauma [1]. Research in military and civilian populations regarding DCR has focused on ways to improve survival in patients with severe hemorrhage. It should be mentioned that the majority of trauma patients do not require DCR and that its techniques should be reserved for those who are the most severely injured [2]. For these patients the rapid and effective use of techniques to control bleeding and correction of this hemostatic derangement coined as acute coagulopathy of trauma shock (ACoTS) is essential. The perpetuating combination of acute coagulopathy, hypothermia, and acidosis seen in exsanguinating trauma patients is a well-recognized term known as lethal triad (Fig. 3.1). In a practical standpoint, the vicious cycle of acidosis/hypothermia/coagulopathy must be aimed as potential lethal cycle and corrected immediately.

Fig. 3.1 The lethal triad flowchart
DCR combines two seemingly diverse strategies—permissive hypotension and hemostatic resuscitation—with damage control surgery, integrating these three procedures in one dynamic process. Therefore, DCR is designed to proceed hand in hand with damage control surgery. The sequential strategy of operation followed by resuscitation has been replaced by an integrated approach so that resuscitation and surgery are undertaken simultaneously, with close communication and cooperation between surgeon and anesthetist [2–5].

### 3.2 Permissive Hypotension

The recognition that fluid resuscitation might interfere with hemostatic mechanisms, ultimately exacerbating blood and coagulation factors loss, led to a reevaluation of the former accepted concept that normal circulatory function is restored by aggressive crystalloids volume. The crystalloid fluid used in initial resuscitative efforts does not contain any clotting factors or erythrocytes. Its use may result in a dilution of clotting factors or role blood and therefore poorer control of bleeding and impaired oxygen transport to tissues causing further ischemic damage. Additionally, crystalloids have an acidic pH, and the administration of large quantities of isotonic or slightly hypertonic crystalloid solutions such as 0.9 % normal saline or lactated Ringer’s could cause or aggravate metabolic acidosis, another component of the “lethal triad” leading to a decrease in myocardial function and cell apoptosis [6–9].

Permissive hypotension, also known as hypotensive resuscitation, is a strategy of restricting crystalloids administration until the bleeding is controlled, while accepting a limited period of suboptimum end-organ perfusion.
3.2.1 Rationale

Following injury the otherwise healthy individual has a natural ability to clot off bleeding. The higher the vessel pressure, the harder it is for the bleeding to stop, since the fluid essentially “pushes” the clot out and consequently the bleeding resumes. In another words, it is reasonable to think that hypotension facilitates coagulation. Attempts to normalize blood pressure in case of uncontrolled bleeding as in victims of penetrating trauma may result in increased blood loss and worsen outcomes [10]. Another issue with aggressive fluid resuscitation is the potential for hypothermia if fluids that are stored at room temperature are used. If these fluids are not warmed prior to infusion, this can result in a significant drop in core body temperature. As exposed in Fig. 3.1, hypothermia is associated with many problems including bleeding disorder, organ failure, and hypotension and is one of the three components in the “lethal triad,” condition that must be feared and soon corrected by all trauma specialists [5–8].

It is important to remember that permissive hypotension is a temporizing measure to improve outcomes until the source of bleeding is controlled. There are consequences associated with prolonged permissive hypotension (>90 min) that must be taken into account. Prolonged permissive hypotension can lead to aggravated post-injury coagulopathy, ischemic damage secondary to poor tissue perfusion including the brain, mitochondrial dysfunction, and lactic acidosis. Permissive hypotension is currently contraindicated in the presence of traumatic brain injury suspicion.

No published evidence exists to support the strategy of permissive or controlled hypotension, although its usefulness has not been entirely ruled out either. Few would argue against replacing lost intravascular volume in patients with controlled or self-limiting hemorrhage. In patients with uncontrolled hem-
orrhage, particularly in the context of penetrating torso trauma, a strategy of permissive hypotension, together with expert resuscitation and rapid control of hemorrhage, might be more appropriate. It is conceivable that permissive hypotension is more applicable to the management of penetrating trauma, which is often characterized by the presence of major vascular injuries, than to blunt injuries.

Despite the lack of evidence, guideline recommendations for clinical practice point towards judicious administration of intravenous fluids. In recognition of the unique challenges posed by combat casualties, permissive hypotension has been incorporated into military medical doctrine and used widely during the recent war conflicts [4].

### 3.3 Hemostatic Resuscitation

Hemostatic resuscitation has also recently become a popular form of transfusion therapy. The concept of giving fractionated blood in an attempt to closely approximate whole blood makes a lot of sense. In this context, hemostatic resuscitation provides transfusions with plasma and platelets in addition to red blood cells in an immediate and sustained manner as part of the transfusion protocol for massively bleeding patients. Rapid and proactive treatment of the coagulopathy associated with major injury is now recognized as central to improve outcome. Although early and effective reversal of coagulopathy is documented, the most effective means of preventing coagulopathy of massive transfusion remains debated and randomized controlled studies are lacking [11–14].

With all this said, became clear that the high prevalence and profound impact of coagulopathy mandates timely treatment of trauma patients. Strategies to proactive action in the emergency room and operating room may include administration of packed
red blood cells, fresh frozen plasma, and platelets; use of recombinant factor VIIa, cryoprecipitate, and tranexamic acid; and calcium replacement.

Commonly available diagnostic tests—such as prothrombin time and activated partial thromboplastin time—are inappropriate for guiding treatment in trauma patients owing to their poor sensitivity and the delay in obtaining results, so the decision to initiate clotting factor replacement is a clinical one.

### 3.3.1 Massive Transfusion Protocol

Massive bleeding patients demand a massive transfusion protocol (MTP). The traditional definition of massive transfusion is 20 units red blood cells (RBCs) in 24 h, which corresponds to approximately 1 blood volume in a 70 kg patient. A commonly used definition in the trauma literature is >10 units RBCs in 24 h. Both of these definitions are reasonable for publications, but are not practical in an ongoing resuscitation. Other definitions are loss of 0.5 blood volume within 3 h, use of 50 units of blood components in 24 h, and use of 6 units RBCs in 12 h. From a practical standpoint, requirement for >4 RBC units in 1 h with ongoing need for transfusion or blood loss >150 ml/min with hemodynamic instability and need for transfusion are reasonable definitions in the setting of a MTP situation.

Once MTP is initiated, the target is to achieve a close ratio resuscitation with 1:1:1 of fresh frozen plasma (FFP), platelets (Plts), and packed red blood cells (PRBCs). The rationale behind early and sustained administration of FFP involves the replacement of fibrinogen and clotting factors [15]. In mathematical studies, Hirshberg et al. noted that resuscitation with more than 5 units of PRBCs will lead to a dilutional coagulopathy and that the ideal manner to correct for this coagulopathy would be to add FFP to PRBC in a 2:3 FFP:PRBC ratio [16]. Another study by Ho et al. noted that once excessive deficiency
of factors has developed, 1–1.5 units of FFP must be given for every unit of PRBCs transfused [17].

It should be emphasized FFP replacement alone does not address the coagulopathy seen in trauma patients with severe hemorrhage. A quantitative and qualitative platelet dysfunction has been shown to play a role as well in the mechanism of coagulation [18]. Although not as extensively as FFP, platelet replacement as a part of transfusion protocols has been studied to determine the most effective ratio of platelets to PRBC. Hirshberg et al. suggest a ratio of platelet:PRBC of 8:10 is effective in preventing dilution of platelets below the hemostatic threshold [16]. It should be noted, however, that both studies were theoretical models and did not take into account factors such as hypothermia, acidosis, thrombocytopenia, or ACoTS. These mathematical models for FFP and platelets set forth by Hirschberg and Ho have helped modify ratios used for MTPs throughout the world [13, 19].

Approximately 3–5 % of civilian adult trauma patients receive massive transfusion. Early identification of patients requiring MTP has been evaluated by assigning a value of 0 or 1 to the following four parameters: penetrating mechanism, positive FAST for fluid (focused assessment sonography in trauma), arrival blood pressure <90 mmHg, and arrival pulse >120 bpm. A score of 2 or more is considered positive [20–23]. The score is 75 % sensitive and 85 % specific. FAST examination identifies whether there is free fluid within the peritoneum, which could indicate organ rupture and internal bleeding. Patients receiving uncross-matched red cells in the emergency department are three times more likely to receive massive transfusion.

3.3.2 Recombinant Factor VIIa

Recombinant factor VIIa use in trauma emerged because of the additional necessity of correcting ACoTS. Researches sug-
gested that a pharmacological adjunct would be useful to treat-
ment of ACoTS and this could play an important outcome role.

Recombinant activated factor VII (rFVIIa) is a hemostatic
agent originally developed to treat hemophilia, FVII deficiency,
and Glanzmann thrombasthenia patients refractory to platelet
transfusion. The activation of platelets at the site of injury is the
reason for a localized action of rFVIIa, as it causes clotting at
the site of bleeding. The dose ranges from 60 to 200 g/kg; how-
ever, prospective randomized controlled clinical trials using
different doses of rFVIIa are needed to explore the potential
efficacy of lower doses in traumatic coagulopathy to reduce cost
and adverse effects, such as thromboembolic complications
[24]. The efficacy and safety of rFVIIa as an adjunct therapy for
bleeding control in patients with severe blunt and penetrating
trauma were evaluated in a parallel randomized, placebo-
controlled, double-blind clinical trial [25]. The authors compared
three doses of rFVIIa (doses of 200, 100, and 100 μg/kg) with
three doses of placebo in addition to standard treatment in
patients who received 6 units of RBCs within a 4-h period. In
blunt trauma (143 patients), RBC transfusion was significantly
reduced with rFVIIa compared to placebo, and the need for
massive transfusion (defined as 20 units of RBCs) was reduced
(14 % vs. 33 %, respectively). In penetrating trauma (134
patients), there was no reduction in mortality and complications
or reduction of PRBCs transfused in patients receiving rFVIIa.
Adverse effects, including thromboembolic events (a total of 12,
six in each group), were distributed equally between the groups.
The authors concluded that rFVIIa is safe within the investi-
gated dose and may be a promising adjunct to existing therapy
in trauma [25]. The effects of liberally administering rFVIIa in
hemorrhaging trauma patients are unknown because its proco-
agulant effect must be balanced against a real risk of thrombo-
embolic events. At present, the use of rFVIIa in correcting
coagulopathy from trauma is off-label and has not been
approved by the Food and Drug Administration [26].
3.3.3 **Fibrinogen and Cryoprecipitate**

Fibrinogen deficiency develops earlier than deficiency of other clotting factors. Fibrinogen is, therefore, an obvious target for replacement with either cryoprecipitate—which contains fibrinogen, factor VIII, factor XIII, and von Willebrand factor—or fibrinogen concentrate. Updated guidelines recommend giving either product if plasma fibrinogen levels fall below 1.0 g/l. Concerns about patient exposure to a large number of donors and the associated risk of blood borne virus transmission limit the use of cryoprecipitate to situations where conventional treatment has failed [5, 27].

3.3.4 **Tranexamic Acid**

Clot breakdown (fibrinolysis) is a normal response to surgery and trauma in order to maintain vascular patency and can become exaggerated (hyperfibrinolysis) in some cases. The anti-fibrinolytic drug tranexamic acid (TXA), a lysine analogue, interferes with the binding of plasminogen to fibrin, which is necessary for plasmin activation. Fibrinolysis consists of activated plamin cleaving fibrin. Antifibrinolytic drugs can prevent clot breakdown and thus reduce blood loss in trauma [28, 29]. TXA has recently been shown to reduce deaths in a large population of trauma patients. In 2011, the CRASH-2 investigators published an exploratory analysis of the previous trial that specifically evaluated the effect of tranexamic acid on death due to bleeding subdivided by time from treatment to injury. The results showed that earlier treatment with tranexamic acid is more effective in reducing the risk of death due to bleeding. Patients that received tranexamic acid within 1 h of injury had a death rate due to bleeding of 5.3 % versus 7.7 % for placebo (RR 0.79, CI 0.64–0.97; p < 0.0001). Similarly, patients that received
treatment between 1 and 3 h from injury also had a significantly lower risk of death due to bleeding. However, patients receiving tranexamic acid >3 h from injury had a significantly increased risk of death compared to placebo, 4.4 % versus 3.1 %, respectively (RR 1.44, CI 1.12–1.84; \( p=0.004 \)) [28].

Current recommendations for the use of TXA are the following [29]:

1. Tranexamic acid should be routinely used in trauma patients with evidence of bleeding.
2. Tranexamic acid should be included in transfusion protocols for trauma.
3. Tranexamic acid should be given within 3 h of injury.
4. Administer 1 g of TXA intravenously (bolus over 10 min) followed by the infusion of 1 g over 8 h.

### 3.3.5 Calcium Administration

Ionized hypocalcaemia is common in critically ill patients and is associated with increased mortality. Calcium is an important cofactor to many components of the coagulation cascade. Citrate, used as an anticoagulant in many blood components, chelates calcium and exacerbates hypocalcaemia. The dose–response effect of hypocalcaemia on coagulation is difficult to measure. A recent nonsystematic review, however, extrapolated that ionized calcium concentrations of less than 0.6–0.7 mmol/l could lead to coagulation defects and recommended maintaining a concentration of at least 0.9 mmol/l [5, 14].

### 3.3.6 Aged Packed Red Cells

The transfusion of red cells with a high storage age has been associated with increased rates of infective complications and
multiple organ failure. Although the shelf life of packed red cell units is around 6 weeks, adverse effects of administration—which are thought to be mediated by passenger leukocytes—have been shown with units at a storage age of about 2 weeks. When blood is stored, the level of antioxidants decreases, resulting in oxidative damage that converts hemoglobin to methemoglobin, which cannot bind to oxygen. If blood is stored for more than 7 days, it loses 2,3-DPG. Without 2,3-DPG, the hemoglobin-oxygen dissociation curve shifts to the left and less oxygen moves into the tissues. Storage also promotes hemolysis and acidosis. Researchers have found that transfused blood is an independent predictor of multisystem organ failure and death [14, 19].

A recent large retrospective cohort study of trauma patients showed that transfusion of red cells stored for longer than 2 weeks was associated with significantly increased odds of death. This finding was observed despite leukoreduction but was apparent only among patients who received at least 6 units of packed cells. Recently donated red cells are, therefore, preferable for trauma patients requiring massive transfusion, although such a practice has obvious logistical and resource implications.

### 3.4 Damage Control Surgery

The concept of damage control surgery arose from the realization that the massively traumatized patient lacked the physiological reserve to survive the rigors of complex and prolonged definitive or reconstructive surgery. It is now an accepted part of the trauma surgeon’s armamentarium and viewed as a component of damage control resuscitation. The aim of damage control surgery is to stop hemorrhage and minimize contamination. Temporary clamping, packing, shunting, or ligation controls
hemorrhage, and hollow viscus injuries are either closed or resected without anastomosis. On completion of the procedure, the abdomen is temporarily closed using an improvised or commercially available topical negative pressure dressing, which saves time, helps to minimize the risk of intra-abdominal hypertension, and facilitates observation of the volume and nature of drainage from the abdomen. Planned reoperation to restore anatomy and achieve definitive repair is carried out on return to normal physiology. Damage control surgery is associated with potential morbidity, should be employed judiciously, and should not be practiced in isolation [2, 6, 30].

3.5 Evidence-Based Current Recommendations

3.5.1 Level I Recommendations

An FFP to PRBC ratio of 1:1 is associated with less transfusions. Sufficient evidence does exist for showing that transfusion with FFP will decrease the number of transfusions needed. It should be noted that there are no randomized, prospective, class I trials. Conducting such trials in the future will be essential to continuing to understand the ideal manner to transfuse during trauma.

Class I evidence supports use of antifibrinolytics in massive transfusion. The recently completed CRASH-2 trials demonstrate improved all-cause mortality as well as mortality due to hemorrhage. Further class I, II, and III studies should be performed to further support these findings.
3.5.2 **Level II Recommendations**

A MTP will improve outcomes for trauma resuscitations. There are many logistical challenges associated with this strategy. Many civilian institutions, even level I trauma centers, have yet to adopt a MTP. However, simple ratios such as 1:1 FFP:PRBC have the benefit of ease of use, and the relatively higher plasma doses appear to be associated with improved outcome. Such a standard protocol can foster multicenter research on resuscitation and hemorrhage control.

High FFP:PRBC is supported by class II and class III evidence and should be considered in the treatment of massively transfused coagulopathic trauma patients. Class II and class III data demonstrates the potential for severe complications such as ARDS/acute lung injury, increased hospital and ICU LOS, and increased ventilator time; however, most studies demonstrate improved mortality, suggesting an overall improvement in the use of these therapies.

3.5.3 **Level III Recommendations**

Increased FFP to PRBC ratio leads to improved outcomes in massive transfusion with the potential for severe complication. MTP implementation and adherence yields improved results with decreases in mortality and complication rates.

The use of high ratio platelets:PRBC is supported by some class II studies and several class III studies. Increased platelets:PRBC has become an integral part of DCR in recent years.

Several class III studies demonstrate mortality improvement with the use of fibrinogen concentrate. The use of fibrinogen in trauma-induced coagulopathy and DCR should be studied further in class I and class II trials.
Increased FFP to PRBC ratio administered early leads to improved outcomes in massive hemorrhage. This benefit is believed to be extended to patients undergoing transfusion with increased FFP:PRBC ratios due to lower transfusion requirements, less risk of complications secondary to the transfusions, and better ability to compensate for the coagulopathy of trauma. Although there is not yet a consensus regarding mortality reduction from increased FFP:PRBC ratios, there does appear to be a trend towards decreased mortality. Likely optimized protocol guidelines will contribute to standardizing variations among current practices.

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