

Fluid Resuscitation and Trauma Management: Permissive Hypotension, Restricted Volume, and Beyond

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Uncontrolled hemorrhagic shock is responsible for 40% of deaths among those under the age of 35, making it the primary cause of mortality in this age group. An optimal fluid therapy strategy can restore tissue perfusion and oxygenation in trauma patients. However, excessive fluid resuscitation can result in glycocalyx shedding, which leads to globally increased permeability syndrome, leading to complications such as changes in tissue perfusion, abdominal compartment syndrome, and respiratory distress syndrome. Permissive hypotension is a resuscitation strategy that aims to maintain systolic blood pressure below the normal threshold. Restricted volume replacement or restricted fluid resuscitation is a resuscitation principle that limits the amount of fluid used to prevent the worsening of diluted coagulopathy, hypothermia, and acidosis. This review article aims to discuss the recent concept of fluid therapy in trauma and to connect the understanding of fluid therapy in trauma with related topics such as trauma-induced coagulopathy and damage control resuscitation.

Keywords: *Permissive Hypotension; Restricted Fluid; Trauma-Induced Coagulopathy; Damage Control Resuscitation*

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INTRODUCTION

Uncontrolled hemorrhagic shock is responsible for 40% of deaths among those under the age of 35, making it the primary cause of mortality in this age group [1,2]. Fluid resuscitation is the initial step in the treatment of catastrophic hemorrhagic shock, aimed at restoring the hemodynamics [3].

The metabolic response to trauma can be categorized into three distinct phases: the ebb phase, characterized by a drop in metabolic rate during the first shock period;

the flow phase, also known as the catabolic phase; and the anabolic phase [4]. Certain patients are unable to naturally progress through the “flow” phase and instead experience a chronic condition of globally increased permeability syndrome with ongoing fluid accumulation [5]. Globally increased permeability syndrome refers to a condition characterized by an excessive accumulation of fluid in the body, which is accompanied by the sudden failure of one or more organs. This condition is also known as “the third hit of shock” [6].

Death can occur in both the acute and subacute phases after hemorrhagic shock. In the acute phase, the inability to control bleeding can lead to the heart's failure to maintain the minimum cardiac output, resulting in death. During the subacute phase, resuscitation and surgical interventions successfully stop the bleeding, allowing for sufficient blood supply to the brain and heart. However, the build-up of ischemia eventually leads to fatal consequences within a matter of days, weeks, or months because of multiple organ failure [7].

Previously, aggressive fluid resuscitation was a frequently employed approach to revive trauma victims [8]. Recent investigations have demonstrated that employing the principles of permissive hypotension and limiting

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volume yields superior outcomes. This article reviews the concept of permissive hypotension and restricted volume in fluid management for trauma.

PERMISSIVE HYPOTENSION AND RESTRICTED VOLUME RESUSCITATION

Permissive hypotension is a resuscitation approach that seeks to keep the systolic blood pressure (SBP) below the usual threshold. This approach is also referred to as “hypotensive resuscitation,” “controlled resuscitation,” and “balanced resuscitation.” Restricted volume replacement, also known as restricted fluid resuscitation, is a resuscitation strategy that aims to limit the quantity of fluid administered in order to prevent the exacerbation of diluted coagulopathy, hypothermia, and acidosis. The approach to managing hypotension caused by trauma by restricted volume replenishment or permissive hypotension was initially influenced by a study conducted by Bickell et al. in 1994 [9]. The study conducted at a single facility examined the effects of immediate and delayed fluid resuscitation in patients with low blood pressure (≤ 90 mm Hg) caused by penetrating injuries to the torso. The study found that delaying vigorous fluid resuscitation until surgical intervention resulted in significantly greater survival rates (70% vs. 62%; $p = 0.04$) [9]. In 2015, Schreiber et al. found that in blunt trauma patients the use of 1 liter of crystalloid resulted in a 24-hour mortality rate of 3%, whereas the use of 2 liters of crystalloid resulted in a mortality rate of 18% [10]. In 2016, Carrick et al. [11] compared the outcomes of trauma-penetrating patients using minimum mean arterial pressure (MAP) targets of 50 mm Hg and 60 mm Hg. The study found that hypotensive resuscitation with MAP targets of 50 mm Hg resulted in significantly lower 30-day mortality rates [11]. Similar results were also reported by Morisson et al. in 2011; the trauma patients using the 50 mmHg MAP target had significantly better 30-day morbidity and mortality rates and required fewer blood products than those using the 65 mm Hg MAP target [12].

At present, multiple systematic review studies and meta-analyses demonstrate the benefits of employing the notion of permissive hypotension resuscitation [13–16]. In 2018, Owattanapanich et al. [14] discovered that hypotensive resuscitation results in reduced quantities of fluid resuscitation and packed red cell transfusion, along with a decreased occurrence of acute respiratory distress syndrome and multiple organ failure. The study also concluded that there was no notable disparity in resuscitation techniques in terms of the occurrence of acute renal damage [14]. According to the study by Albreiki and Voegeli in 2017, low-volume resuscitation resulted in a lower death rate than big-volume resuscitation, with values of 21.5% and 28.6%, respectively [17].

A meta-analysis conducted by Safienjko et al. in 2022 demonstrated that the use of hypotension fluid

resuscitation is associated with reduced mortality and comorbidities [15]. Among the twenty-eight studies analyzed, the mortality rate for hypotension fluid resuscitation was found to be 12.5%, but for traditional fluid resuscitation it was 21.4%. The incidence of complications with hypotension fluid resuscitation is 10.8%, but in traditional resuscitation it is 13.4%. The primary distinction in the risk of complications between hypotensive and conventional fluid resuscitation is in the occurrence of acute respiratory distress syndrome (ARDS), with rates of 7.8% and 16.8%, respectively, as well as multiple organ damage syndrome (MODS), with rates of 8.6% and 21.6%, respectively.

The effectiveness of limited volume replacement in trauma was also documented in pediatric instances. In a study conducted by Mbadiwe et al. in 2021, it was found that administering resuscitation fluid of more than 20 cm³/kg in cases of pediatric trauma is linked to higher fatality rates. This association is determined by the dosage, meaning that the higher the dosage, the more significant the impact on mortality [17].

Permissive hypotension and restricted volume replacement are not recommended for patients with severe brain damage and spinal cord injury. This concerns the ideal concentration of blood flow required to guarantee sufficient oxygen supply to the impaired central nervous system. Stable fluid infusions above 80 mm Hg are recommended for severe cerebral hemorrhagic damage that raises intracranial pressure. This prevents arterial ischemia and maintains cerebral perfusion pressure at 60 mm Hg [18]. Revised guidelines have been issued for the management of SBP in adult patients with traumatic brain injury (TBI), taking into account their age. The age-based guidelines set by the Brain Trauma Foundation exceed the acceptable thresholds for hypotension. The recommended blood pressure levels for those aged 15 to 49 are 110 mm Hg, for those aged 50 to 69 they are 100 mm Hg, and for patients aged 70 years and above they are 110 mm Hg [19,20].

The optimal approach to attain sufficient perfusion pressure through volume resuscitation and vasopressors remains a subject of ongoing research without a definitive solution. Geriatric patients and patients with chronic hypertension, in addition to situations of severe head injuries and spinal cord injuries, should be given additional care and may be considered a contraindication for permissive hypotension [21].

OVERVIEW OF FLUID MANAGEMENT: LIBERAL, STANDARD, AND RESTRICTIVE

In 2014, the acronyms ROSE and SOSD were introduced as concepts in fluid treatment. The acronym ROSE was introduced at the International Fluid Academy Day (IFAD) to represent the four phases of fluid therapy: Resuscitation, Optimization, Stabilization, and Evacuation [22]. On the other hand, the concept of SOSD

(Salvage, Optimization, Stabilization, De-escalation) was proposed by The Acute Dialysis Quality Initiative (ADQI) group [23]. During the Resuscitation or Salvage phase, the treatment focuses on restoring or correcting shock conditions by aiming for an appropriate perfusion pressure. During this stage, a fast infusion of fluid with a volume of 3–4 ml/kg is administered for 10 to 15 minutes (which can be repeated if necessary), typically accompanied by vasopressors. During the Optimization phase, the patient's hypovolemia is no longer severe, but their hemodynamics are still unstable. The objective of therapy in this phase is to prevent or minimize the risk of organ damage. The stabilization phase commences once the patient has achieved a condition of stability and continues for several days. During this stage, the goal is to achieve a fluid balance of zero or slightly negative. The evacuation or de-escalation phase is the final stage that seeks to eliminate surplus fluid. Typically, this stage happens naturally as the patient recovers. However, diuretics or ultrafiltration can be employed if necessary.

The terms liberal, standard, and restrictive are often used to compare fluid therapy regimens. Usually, researchers use their approach as a standard therapy and compare it with restrictive or liberal concepts that they define themselves. Even differences in definition make a restrictive group a liberal group in other studies [24]. The study of the comparison between restrictive and liberal is also sometimes more accurately seen as hypovolemia vs. normovolemia [25].

Definitions of liberal, standard, and restrictive fluid therapy vary widely across studies. The definition of this term probably should not only relate to the volume of fluid given but also to when to start and stop fluid therapy performed [26].

FLUID RESUSCITATION AND ENDOTHELIAL GLYCOLALYX

The fluid displacement between plasma and interstitium is an important concept that must be understood regarding fluid resuscitation in trauma situations. One of the earliest basic concepts of plasma and interstitial fluid transfer was proposed by Starling in 1896, that the movement of fluid across capillary membranes depends on a net imbalance between the osmotic absorption pressure of plasma proteins [colloidal osmotic pressure (COP)] and the capillary hydraulic pressure generated by the heartbeat [27]. The understanding of the existence of glycocalyx structures on the endothelial surface of blood vessels prompted Levick and Michel [28] to revise the concept proposed by Starling.

The endothelial glycocalyx is essential for controlling the permeability of blood vessels. The disruption of the glycocalyx increases the permeability of blood arteries, allowing for the facilitated passage of water, proteins, and other substances from the bloodstream to the external environment [29]. The molecular sieve effect

of the glycocalyx structure determines the permeability of blood arteries. Additionally, the negatively charged nature of glycocalyx creates a charge barrier in blood vessels [30].

The type of resuscitation fluid used is known to affect the integrity of glycocalyx after hemorrhagic shock [31]. Crystalloids are reported to be associated with higher glycocalyx shedding than colloids [32,33]. Several different results regarding the relationship of resuscitation fluid with glycocalyx shedding have been reported, such as the type of fluid affecting post-hemorrhage glycocalyx thickness [34], but other studies report that such thickness changes do not affect membrane permeability [35].

An optimal fluid therapy strategy can effectively restore tissue perfusion and oxygenation in the body. However, excessive fluid resuscitation can result in glycocalyx shedding, which leads to globally increased permeability syndrome, which can lead to complications such as changes in tissue perfusion, abdominal compartment syndrome, and respiratory distress syndrome [3,36,37].

FLUID RESUSCITATION AND TRAUMATIC-INDUCED COAGULOPATHY

Excessive fluid resuscitation in trauma patients can trigger traumatic-induced coagulopathy. Overly administering fluids through crystalloids can lead to a decrease in the amount of oxygen that can be carried and a reduction in the concentration of substances that help with blood coagulation. Administering fluids at a temperature lower than the body's normal temperature worsens heat loss in the body due to bleeding, low energy levels, and exposure to the environment. It also reduces the effectiveness of enzymes involved in the clotting process [38]. Excessive administration of acidic crystalloid solutions will worsen the acidosis induced by reduced blood flow, leading to a decline in the effectiveness of clotting factors. This will result in a dangerous combination of coagulopathy, hypothermia, and acidosis, which can be fatal [39].

Trauma-induced coagulopathy (TIC) is the term used to describe the abnormal formation of blood clots that happens due to physical damage. During the early phases of TIC growth, there is typically a state of diminished hemostatic capacity, resulting in hemorrhaging. As TIC advances, there is a noticeable rise in blood clotting, which is linked to the development of venous thromboembolism and organ failure. Generally, TIC can be a mixed phenotype, including the bleeding and thrombogenic phenotypes [40].

Viscoelastic measures (VEM) are used frequently in the detection of traumatic-induced coagulopathy. These assays are whole blood tests that offer data on the speed at which a clot forms (fibrin cross-linking), reaches its maximum strength (platelet function), and ultimately breaks down (fibrinolysis). VEM tests can be employed

at the point of care, providing available data promptly within 5 minutes that can effectively guide resuscitation. Thromboelastography (TEG, Haemonetics) and thromboelastometry (ROTEM, Tem International GmbH) are the two main platforms used for these examinations.

Tissue injury and shock synergistically stimulate the activation of the endothelium, immune system, platelet, and clotting processes. The presence of the “lethal triad”, which includes coagulopathy, hypothermia, and acidosis, significantly intensifies these activations [41].

Insufficient oxygen availability for aerobic metabolism leads to a shift towards anaerobic metabolism at the cellular level [42]. Consequently, this results in heightened lactic acid build-up, inorganic phosphates, and oxygen radicals [43]. Furthermore, on a cellular level, damage-associated molecular patterns (referred to as DAMPs or alarmins), such as mitochondrial DNA and formyl peptides, are released. These substances then initiate a widespread inflammatory response throughout the body [44].

The hemorrhaging also triggers significant alterations in the vascular endothelium across the body [45]. The endothelium and blood work together at the bleeding site to enhance the formation of a blood clot. However, the accumulation of oxygen debt and sudden increases in catecholamine levels eventually lead to the development of endotheliopathies, which occur when the protective glycocalyx barrier is shed systemically [32].

During severe hemorrhage, adaptive and maladaptive alterations occur either at the bleeding site or in tissues throughout the body. Hemostatic plugs form at the bleeding site [46]. There is an increase in fibrinolytic activity in tissues that are distant from the site of bleeding, potentially as a protective reaction to avoid the formation of blood clots in small blood vessels [47]. Nevertheless, an overabundance of plasmin activity and auto-heparinization caused by glycocalyx shedding might result in hyperfibrinolysis and widespread coagulopathy [48].

RESUSCITATION USING DAMAGE CONTROL TECHNIQUES

The word “damage control” originates from naval warfare. The word refers to a method of handling warships that have been damaged, with the goal of preserving the ship’s ability to sail and operate rather than fully repairing all of the damage [49,50]. Subsequently, this concept was incorporated into the field of medicine as a strategy for treating patients who have sustained multiple and serious traumas [51].

Discussing damage control resuscitation (DCR) is essential when explaining the rationale and benefits of permissive hypotension in trauma resuscitation. Permissive hypotension, one component of DCR, aims to maintain a low but adequate blood pressure to reduce

bleeding until bleeding control can be achieved, avoiding excessive fluid resuscitation that could dislodge clots and exacerbate hemorrhage. DCR integrates a broader strategy that includes rapid hemorrhage control, limited fluid resuscitation, and preventing coagulopathy [52]. By incorporating permissive hypotension within DCR, the patient’s physiological condition is optimized during the critical pre-operative phase, minimizing the risk of worsening hemorrhage while maintaining vital organ perfusion [53]. Crystalloids are restricted in DCR to prevent dilutional coagulopathy, whereas hypotensive resuscitation is employed until significant bleeding is under control. Tranexamic acid is used empirically, and acidosis and hypothermia are prevented [54].

Rapid control of bleeding in non-compressible hemorrhage can be achieved by damage control surgery (DCS) or through Endovascular Resuscitation and Trauma Management (EVTM) [55], which is defined as “a term that represents a modern, multidisciplinary approach that integrates minimally invasive endovascular techniques to manage severe trauma, particularly in patients with hemorrhagic shock” [21,56]. In most simple terms, endovascular resuscitation can be defined as the use of catheter-based therapies to achieve rapid bleeding control, such as Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) [57–59]. REBOA is utilized to stabilize patients at high risk of death from build-up torso bleeding, but it is not a device for definitive hemorrhage control. Its use should be integrated into a comprehensive system that includes DCR, definitive hemorrhage management, and postoperative critical care [60,61].

The use of crossmatched packed red blood cells (pRBCs) is ideal in trauma resuscitation. However, when crossmatched blood is unavailable, type O pRBCs are recommended for patients experiencing exsanguinating hemorrhage. In situations requiring massive transfusion, early administration of pRBCs, plasma, and platelets in a balanced 1:1:1 ratio can improve survival by minimizing the need for excessive crystalloid resuscitation [62]. Recently, whole blood has re-emerged as a viable option for resuscitation in hemorrhagic shock [63]. However, clear guidelines regarding when to opt for whole blood over individual blood components remain absent.

The administration of blood products in the pre-hospital setting is also possible, although studies have produced mixed outcomes [64–68]. Currently, there are no definitive recommendations supporting or opposing prehospital blood product administration [21].

ATLS AND EUROPEAN GUIDELINES

In 2013, the Advanced Trauma Life Support (ATLS) course implemented multiple modifications to its resuscitation method. The adjustments involved eliminating the term “aggressive resuscitation” and suggesting permissive hypotension prior to bleeding control. Additionally, the advice is now to reduce the amount

of crystalloids from 2 liters to 1 liter and to administer plasma and platelets early in patients who need extensive transfusions [69]. The 2013 European guidelines on the management of bleeding and coagulopathy included a recommendation regarding hypotensive resuscitation [72]. According to this recommendation, the target SBP should be maintained between 80 and 90 mm Hg until major hemorrhage can be controlled in cases of traumatic injury without brain damage. The 2023 European guidelines for managing bleeding and coagulopathy recommends a limited volume replacement strategy with a blood pressure target of 80–90 mm Hg (MAP 50–60 mm Hg) until major bleeding is controlled and there is no clinical evidence of brain injury in patients with severe head trauma. If the Glasgow Coma Scale (GCS) score is less than or equal to 8, it is advised to maintain a MAP of at least 80 mm Hg. Table 1 compares the ATLS and European Guidelines on fluid resuscitation on trauma.

VASOPRESSORS AND FLUID RESUSCITATION IN TRAUMA

In trauma resuscitation, rapid hemorrhage control and restoration of adequate tissue perfusion are the primary goals to prevent further organ damage and mortality. Vasopressors, commonly used in non-trauma shock management, are not recommended for initial use in trauma resuscitation due to the risk of exacerbating hypoperfusion, as vasoconstriction can impair oxygen delivery to tissues already compromised by hemorrhagic shock [73]. The European guidelines on trauma management highlight that vasopressors may delay the recognition of bleeding by artificially maintaining blood pressure without addressing the underlying cause of hypovolemia [73]. Their inappropriate use can lead to a worsening of tissue ischemia, particularly in situations where vasoconstriction compounds existing circulatory compromise [74]. However, vasopressors may be indicated in cases of neurogenic shock or in patients with traumatic brain injuries where maintaining cerebral perfusion pressure is critical [71]. According to the ATLS guidelines, fluid resuscitation and hemorrhage control must be prioritized before considering the cautious use of vasopressors in trauma patients [71,75].

The 10th edition of ATLS suggests administering warm saline as resuscitation fluids up to a volume of 1 liter in patients with class I or II bleeding. In cases of hemorrhage classified as class II or higher, it is advisable to utilize blood products rather than adding more crystalloid or colloidal fluids. The ATLS guidelines do not include detailed advice for the use of vasopressors [71]. According to the recommendation of the European guidelines, vasopressors should be used when fluid resuscitation fails to achieve SBP objectives of 80–90 mm Hg or when severe hypotension caused by bleeding results in SBP below 80 mm Hg. Noradrenaline is a recommended

vasopressor in situations where there is no dysfunction of the heart, whereas dobutamine is the recommended vasopressor in situations when there is dysfunction of the heart. If the amount of bleeding is too much and if the combination of crystalloids and vasopressors cannot adequately maintain the basic flow of blood to the tissues, colloid infusions might be considered as an additional alternative to restore blood flow [21].

Hemorrhagic shock is also reported to be related to a deficiency of arginine vasopressin. In 2019, Sims et al. [76] demonstrated that administering a low dose of arginine vasopressin (a surge of 4 IU followed by 0.04 IU/min) reduces the need for blood products. A previous double-blind randomized trial evaluated the safety and effectiveness of including vasopressin in resuscitative fluid, and the results are consistent with that study [77].

Ethical Approval and Informed Consent

Ethical approval was not required. Written informed consent was not required.

CONCLUSION

In conclusion, fluid resuscitation strategies in trauma management have shifted from traditional aggressive approaches to more refined methods such as permissive hypotension and restricted volume resuscitation. These strategies aim to limit the adverse effects of fluid overload, such as coagulopathy, hypothermia, and acidosis, while optimizing tissue perfusion and reducing mortality. Permissive hypotension has demonstrated significant survival benefits by maintaining lower SBP until definitive hemorrhage control can be achieved. Furthermore, restricted volume resuscitation minimizes glycocalyx shedding and prevents complications associated with excessive fluid administration.

The integration of these principles into DCR protocols has further improved trauma outcomes by reducing the need for large volumes of crystalloid solutions and emphasizing the early use of blood products. This approach aligns with contemporary guidelines such as those provided by ATLS and European trauma management, which advocate limited fluid use and hypotensive resuscitation in non-head trauma patients.

Despite these advances, the use of permissive hypotension and restricted volume resuscitation must be carefully tailored to individual patients, particularly those with traumatic brain injuries or spinal cord injuries, where higher perfusion pressures may be required. Further research is needed to refine the optimal resuscitation strategies for specific patient populations, especially in geriatric trauma and those with pre-existing chronic conditions. Overall, permissive hypotension and restricted fluid resuscitation represent key components of modern trauma care, contributing to improved survival and reduced morbidity in hemorrhagic shock management.

Table 1 ATLS and European Guidelines of fluid resuscitation on trauma.

Parameters	ATLS 8th (2008) [8]	ATLS 9th (2013) [69,70]	ATLS 10th (2018) [62,71]	European guidelines (2013) [72]	European guidelines 6th (2023) [21]
Volume	Up to 2 liter	Up to 1 liter	Up to 1 liter	1–1.5 liter	1–1.5 liter
Target of blood pressure without TBI	Systolic of ≥90 mm Hg	Support for hypotensive resuscitation	Support for hypotensive resuscitation	Systolic of 80–90 mm Hg (MAP 50–60 mm Hg)	Systolic of 80–90 mm Hg (MAP 50–60 mm Hg)
Target of blood pressure with TBI	Systolic of ≥90 mm Hg	15–49 y.o: 110 mm Hg 50–69 y.o: 100 mm Hg, ≥70 y.o: 110 mm Hg	15–49 y.o: 110 mm Hg 50–69 y.o: 100 mm Hg, ≥70 y.o: 110 mm Hg	GCS ≤ 8: MAP ≥ 80 mm Hg	GCS ≤ 8: MAP ≥ 80 mm Hg
Type of fluid	Warm isotonic electrolyte solution Ringer lactate is the initial fluid of choice Normal saline is the second choice	Class II hemorrhage: NaCl 0.9% (normal saline), resuscitation with blood and blood product for patient with transient- or non-responders Class III and IV hemorrhage: Early resuscitation with blood and blood products Class IV: Massive transfusion protocol	Class II hemorrhage: NaCl 0.9% (normal saline), resuscitation with blood and blood product for patient with transient- or non-responders Class III and IV hemorrhage: Early resuscitation with blood and blood products Class IV: Massive transfusion protocol	NaCl 0.9% or balance crystalloid Avoid ringer lactate in severe head trauma	NaCl 0.9% or balance crystalloid Avoid ringer lactate in severe head trauma

European guidelines on the management of bleeding and coagulopathy. ATLS, Advance Trauma Life Support; NaCl, sodium chloride; TBI, traumatic brain injury; MAP, mean artery pressure; y.o., years old; GCS, Glasgow Coma Scale.

Ethics Statement

- (1) All the authors mentioned in the manuscript have agreed to authorship, read and approved the manuscript, and given consent for submission and subsequent publication of the manuscript.
- (2) The authors declare that they have read and abided by the JEVTM statement of ethical standards including rules of informed consent and ethical committee approval as stated in the article.

Conflicts of Interest

All authors declare no conflicts of interest.

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