CHAPTER 3

Exsanguination in trauma: a review of diagnostic and treatment options

L.M.G. Geeraeds Jr
H.A.H. Kaasjager
A.B. van Vugt
J.P.M. Frölke

Abstract

Trauma patients with hemorrhagic shock who only transiently respond or do not respond to fluid therapy and/or the administration of blood products have exsanguinating injuries. Recognition of shock due to (exsanguinating) hemorrhage in trauma is about constructing a synthesis of trauma mechanism, injuries, vital signs and the therapeutic response of the patient. The aim of pre-hospital care of bleeding trauma patients is to deliver the patient to a facility for definitive care within the shortest amount of time by rapid transport and minimize therapy to what is necessary to maintain adequate vital signs. Rapid decisions have to be made using (trauma) regional triage protocols that have incorporated patient condition, transport times and the level of care than can be performed by the prehospital care providers and the receiving hospitals. The treatment of bleeding patients is aimed at two major goals: stopping the bleeding and restoration of the blood volume. Fluid resuscitation should allow for preservation of vital functions without increasing the risk for further (re) bleeding. To prevent further deterioration and subsequent exsanguinations ‘permissive hypotension’ may be the goal to achieve. Within the hospital, a sound trauma team activation system, including the procedure for logistics as well as activation criteria, is essential for a fast and adequate response. After determination of hemorrhagic shock, all efforts have to be directed in order to stop bleeding to prevent exsanguinations. A simultaneous effort is made to restore blood volume and correct coagulation. Coagulation management with pharmacotherapeutic interventions may be a promising concept to limit blood loss after trauma. FAST has replaced diagnostic peritoneal lavage for detection of hemoperitoneum. With the development of sliding-gantry based computed tomography diagnostic systems, rapid evaluation by CT-scanning of the trauma patient is possible during resuscitation. The concept of damage control surgery, the staged approach in treatment of severe trauma, has proven to be of vital importance in the treatment of exsanguinating trauma patients and is adopted worldwide. Selection of suitable patients for this approach is a continuing challenge. During these procedures, a predetermined fixed ratio of blood components ('blind' transfusion or ‘damage control resuscitation’) may result in the administration of higher plasma and platelets doses and may improve outcome. The role of thromboelastography and thromboelastometry as point-of-care tests for the coagulation status in massive blood loss is emerging, providing information about actual clot formation and stability, shortly (10 min) after the blood sample is taken. Thus, therapy can be directed by the test results allowing for administration of specific coagulation factors that may be depleted despite administration with fresh frozen plasma during massive transfusion of blood components.
Introduction

Death due to traumatic injury is the leading cause of life years lost throughout the world.\textsuperscript{1} Recently, the impact of hemorrhage on trauma outcome has been well described by Kauvar \textit{et al.}\textsuperscript{2} Hemorrhage is responsible for 30 to 40\% of trauma mortality and of these deaths, 33-56\% occur during the pre-hospital period. Only central nervous system injury, which also has a high rate of pre-hospital mortality, is consistently more lethal. However, in contrast to hemorrhage and hemorrhagic shock, possibilities for life-saving interventions are very limited in CNS injury. The significant contribution of hemorrhagic shock to brain injury mortality further illustrates the role of hemorrhage control in reducing mortality in trauma patients.\textsuperscript{2} Hemorrhage accounts for almost 50\% of deaths in the first 24 hours of trauma care. After day one, very few hemorrhagic deaths occur. Delayed death in trauma patients is caused by late sequelae as multi-organ failure. The proportion of trauma deaths with multi-organ failure remains unchanged: 7\% in the early 1990’s and 9\% ten years later.\textsuperscript{3,4} This paper was written to summarize what’s new in the care of the injured concerning the diagnosis and treatment of life-threatening bleeding. An attempt is made to describe the state of the art in managing the exsanguinating trauma patient. New insights, concepts and treatment modalities are discussed as well as potential new therapies for pre-hospital as well as in-hospital situations.
PRE-HOSPITAL TREATMENT

Concepts

Recognition of shock due to (exsanguinating) hemorrhage in trauma is about constructing a synthesis of trauma mechanism, injuries, vital signs (blood pressure, pulse rate, respiratory rate and if available end-tidal carbon dioxide) and the patient’s response to fluid therapy. Estimations of unknown amounts of blood loss will be inaccurate.\(^5\) Shock classifications as proposed by the worldwide-accepted Advanced Trauma Life Support (ATLS®) /Pre-hospital Trauma Life Support (PHTLS®) guidelines may be helpful,\(^6\) although this classification has never been validated. More important, patients with ongoing bleeding and/or imminent exsanguination do not or only transiently respond to standardized fluid therapy (ATLS®-guidelines). Recognition can be difficult by only relying on a sole parameter as blood pressure as for example automated non-invasive blood pressure measurements are not reliable in hypotensive patients.\(^7\) Also, variability in physiologic reserves (sports), age, co-morbidity and medication within the patient population may challenge the recognition of shock. A promising adjunct now available to evaluate shock in the field may be the measurement of venous lactate as a point of care test adequately reflecting arterial lactate.\(^8,9\) Its role still has to be evaluated in randomized studies. The aim of pre-hospital care of bleeding trauma patients is to deliver the patient to a facility for definitive care within the shortest amount of time by rapid transport and minimize therapy to what is necessary to maintain adequate vital signs. The order and way of treatment of bleeding patients may differ between patients in the pre-hospital phase. Entrapped patients (for example in vehicles or under buildings) implicate a different approach then bleeding patients than can be ‘scooped and runned’ to the hospital. Also, in bleeding patients with airway compromise due to concomitant brain injury or maxillofacial injuries, establishment of a patent airway may take priority prior or during transport to the hospital. However, within the military environment and even in the case of penetrating injury, the A (airway), B (breathing), C (circulation) paradigm may be changed into C, A, B as heavy external bleeding from high velocity gunshot wounds and blast injuries may cause rapid deterioration and death. Rapid decisions have to be made using (trauma) regional triage protocols that have incorporated patient condition, transport times (i.e. distances) and the level of care than can be performed by the pre-hospital care providers and the receiving hospitals. In the case of a physician-staffed pre-hospital care system, the responsible doctor at the scene may even facilitate strategic planning of diagnostic and treatment process in the hospital by direct communication with the receiving trauma surgeon advising on the patient’s injuries and condition.
Time may be saved in selected trauma cases of imminent exsanguinations when the Emergency Department (ED) is bypassed at arrival and the patient is directly transported to the operating room. Thus, a differentiated pre-hospital approach is needed for patients with exsanguinating injuries depending on trauma mechanism, entrapment, injuries, shock grade, transport times, distribution of adequate facilities, and professional level of pre-hospital care providers.
Finding and stopping the bleeding

Compressible bleeding
The treatment of bleeding patients is aimed at two major goals: stopping the bleeding and restoration of the blood volume. A third goal that can be added is restoration of coagulation in order to achieve final hemostasis. Bleeding in the pre-hospital phase can be caused by injuries resulting in either ‘compressible’ and/or ‘non-compressible’ bleeding. Normally, compressible bleeding in the pre-hospital phase can effectively be dealt with direct, manual pressure on the bleeding (one bleeding, one swab, one finger) to limit external blood loss. However, as manual compression cannot be maintained constantly as the care provider has to continue his efforts for further stabilization and transportation, hands-free techniques are needed. Manual compression achieves the highest average pressure (180 mmHg) on the wound when compared to standard field dressing (33 mmHg) and elastic adhesive dressing (88 mmHg). Thus, as a hands-free technique, elastic adhesive dressing may be the method of choice. However, for anatomical sites as for example the neck, groin, axilla and shoulder, compressive bandages and even tourniquets are impractical. The use of tourniquets to control external blood loss in extremity injury has been controversial as injudicious and/or prolonged use may cause limb paralysis either by ischemia or direct nerve injury. However, within the military pre-hospital setting it is a known means to stop bleeding because its application technique is far less demanding and time consuming than application of a proper compressive bandage under battlefield conditions. In a retrospective analysis, Lakstein et al. showed a 78% success rate in a group of 91 patients with a higher success rate for the upper limb (94%) than lower limb (71%). Neurological complications were encountered in 5.5% of the cases. The mean ischemic time in uncomplicated cases was 78 minutes and longer than 150 minutes in the complicated cases. Even in selected cases in the civilian situation, application of tourniquets may be a fast and easy lifesaving method to prevent exsanguinations from limb injury. Ischemic time should be as short as possible and conversion to pressure bandages should always be considered. Newer developments consist of advanced hemostatic products that can be used as adjuncts to the direct compressive techniques in severe external bleeding through local application on and/or in the wound. Especially in controlling bleeding from injuries in anatomical areas such the groin, axilla or neck, these products may be of promising advantage. Pusateri et al. have put forward that of the four most promising products only the chitosan dressing (HemCon®, Tigard OR) and QuickClot® (Z-Medica, Wallingford, CT) are currently used on the battlefield. Chitosan, a polysaccharide polymer, adheres
strongly to tissue, sealing the wound site and may accelerate concentration of red blood cells and platelets at the bleeding site. QuickClot® is a granular zeolite, which absorbs water, concentrating red blood cells, clotting factors, and platelets at the bleeding site in an exothermic reaction. Pusateri et al. advise that chitosan dressing should be the first choice as it has been proven to control high-pressure/high flow bleeding in animal models and has no known adverse effects. In contrast, QuickClot® may cause thermal injury and should be used as a last resort. In an observational study, 64 uses of chitosan dressing in the combat environment resulted in cessation of bleeding or improvement of hemostasis in 97%. However, there are no clinical (field) reports yet validating the efficacy of both products. In the pre-hospital environment, depending on the available expertise, uncontrolled bleeding from large scalp lacerations can be stopped more effectively with rapid suturing or stapling of the wounds prior to the application of a pressure bandage. Also, uncontrolled bleeding from maxillofacial injuries or skull base injuries can be temporarily dealt with gauze tamponade of mouth, nose and pharynx after intubation.
**Non-compressible bleeding**

Long bone fractures, especially fractures of the femur may cause significant blood loss. To reduce pain and facilitate transport, femur fractures are often treated with traction splints for example the Donway®, Sager® or Thomas-splint. Despite the theory that traction splinting may reduce blood loss by reducing the virtual soft tissue space around the actual fracture, there are no scientific reports on this subject. In the pre-hospital situation, temporary stabilization of pelvic fractures with some type of pelvic sling, belt or binder has become common practice in an effort to control hemorrhage.\(^{15-17}\) The theoretical advantages may be the prevention of clot dislodgement, compression of opposing bleeding bony surfaces and tamponade of low pressure (venous) bleeding by volume reduction of the pelvic cavity. However, there are still no clinical studies available confirming these effects on hemorrhage control or patient hemodynamics. Several effective, commercial devices have been developed in the past years, e.g. Trauma Pelvic Orthotic Device (T-POD® and SAM-sling ®). Therefore, improvised pelvic wrapping with a sheet should be only done when a device is not available. The ideal device has to be readily (re) adjustable for all patient sizes and easy to be applied in a minimum amount of time and should be radiolucent. In the past, pneumatic anti-shock garment (PASG) or medical anti-shock garment (MAST) has been used in the pre-hospital environment for shock management and temporary stabilization of pelvic and lower extremity fractures and/or tamponade of pelvic and abdominal bleeding. However, no benefit in hospital stay or mortality was demonstrated in a prospective randomized study.\(^{18}\) Also, when excluding the use of MAST for splinting, no beneficial effect on mortality, length of hospital stay or ICU stay was noted.\(^ {19}\) So, regarding these findings and because of potential adverse effects as extremity ischemia and MAST-associated compartment syndrome as well as the described alternatives for splinting of pelvic and femur fractures, the decision to use a MAST should be made very judiciously.\(^ {20}\) All treatment of bleeding patients should start straight away in the pre-hospital phase.\(^ {20}\) However, sources of non-compressible bleeding may be difficult to treat or not at all be treatable in the field. For instance, severe bleeding within the chest requires thoracotomy. A successful roadside resuscitative thoracotomy in which the descending aorta was digitally compressed in a case of exsanguinations from pulmonary vein injury has been described.\(^ {21}\) Athanasiou et al. report of emergency thoracotomy performed by pre-hospital care providers.\(^ {22}\) In a 9-year period, 31 emergency thoracotomies were performed on the scene. However, these interventions were indicated by suspicion of obstructive tamponade and the need for more effective internal cardiac massage, but not for hemorrhage control. Intrathoracic bleeding will normally require in-hospital operative procedures. Nowadays, intra-abdominal bleeding can be
diagnosed in the field by ultrasound examination (Focused Assessment with Sonography for Trauma; FAST). However, the bleeding can only be stopped in the hospital by means of operative or angiographic procedures. Nevertheless, the management of abdominal bleeding in trauma might be improved using pre-hospital FAST. In a prospective, observational study, Walcher et al. showed that the results of FAST at the scene changed pre-hospital therapy in 21% (reducing intravenous fluid therapy) and pre-hospital management (accelerating the pre-hospital process and transport to shorten time to surgery) in 30%. In 22% the choice of the receiving hospital was changed and in many cases early pre-hospital FAST reports allowed trauma teams to timely prepare the operating room for urgent laparotomy. However, beneficial effect of pre-hospital FAST on outcome still has to be scientifically proven. In the future, a potential method of controlling intra-abdominal bleeding temporarily, which could be used in the field, might be abdominal insufflation. In an animal model of liver injury, blood loss and mortality was significantly reduced by abdominal insufflation. Blood loss was reduced in an animal model of severe splenic injury. Intracavitary deposition of high-pressure fibrin sealant foam might also be a potential means to limit intra-abdominal bleeding in the field before definitive care.
Resuscitation and coagulation management

In the pre-hospital care for the bleeding patient, especially when the patient is entrapped, and/or has a concomitant airway or breathing problem and the definitive care facility is not close by, administration of intravenous fluids for resuscitation and/or medication (analgesia, sedatives and muscle relaxants) is indicated. Insertion of intravenous catheters in a shocked patient in the pre-hospital environment or during transport can be challenging and time-consuming. Insertion of central venous catheters and venous cut down as alternatives are time consuming as well and depend on the availability of highly skilled pre-hospital care providers. Therefore, in recent years, the almost forgotten, but not in resuscitation of infants and small children, methods of intraosseous access have gained renewed attention. New developments have aimed at fast, easy and accurate insertion of intraosseous needles that can be used at various anatomical locations in adults such as sternum, proximal tibia, femur condyle, iliac crest, distal radius and humerus. The intraosseous needle has become the standard alternative in case of failed intravenous cannula insertion and may be the first choice in extreme cases of hemorrhagic shock and/or under austere or military tactical conditions. Several devices are nowadays available that are manually driven (e.g. threaded needles), mechanically driven (e.g. bone injection gun: BIG®, or even powered (e.g. battery-fed hand drill: EZ-IO®). Most methods are easy to learn and to apply. However, as some devices do not come with standard protection of the insertion site, improvised fixation may take more time. Also, in the last 10-15 years there has been some paradigm shift regarding optimal resuscitation of bleeding trauma patients before definitive hemorrhage control. Aggressive fluid resuscitation increases blood pressure, reverses vasoconstriction, dislodges early thrombus, increases blood loss and causes dilutional coagulopathy and metabolic acidosis in experimental studies. Sampalis et al. showed increased mortality in patients with fluid resuscitation in the field in combination with longer on scene times. To prevent further deterioration and subsequent exsanguinations permissive hypotension (allowing low blood pressure until hemorrhage is controlled) may be the goal in pre-hospital resuscitation. Bickell et al. conducted a prospective clinical trial in which fluid resuscitation was delayed in hypotensive patients with penetrating torso injuries until the time of operative intervention. In this selected patient group (mean age 31 years, penetrating torso injuries and short transport times) outcome was improved. Due to the heterogeneity of the trauma patient population regarding co-morbidity (elderly), trauma mechanism (blunt versus penetrating) and concomitant injuries (head injuries) and due to geographic/organizational differences in trauma areas
(longer versus shorter transport times) this practice could not be extrapolated straight away.\textsuperscript{37} Pre-hospital fluid resuscitation should allow for preservation of vital functions without increasing the risk for further (re)bleeding. Several strategies/field resuscitation protocols have been postulated but until now there are no outcome studies available regarding hypotensive resuscitation. Revell \textit{et al.} advises a \textit{permissive hypotension} regimen in which fluid administration is titrated to maintain a palpable radial pulse (indicative of a systolic blood pressure of 80-90 mmHg) in ongoing hemorrhage in soldiers.\textsuperscript{38} In penetrating torso trauma a palpable central pulse (indicative of a systolic blood pressure of 60 mmHg) is advised as resuscitation end point. In patients without head injury, the presence of effective mentation may also be useable. Krausz describes another military protocol for fluid resuscitation that differentiates between uncontrolled and controlled hemorrhagic shock and that takes into account the anticipated evacuation time.\textsuperscript{39} A dilemma exists in bleeding patients with head injury, as aiming for normotension or hypertension to maintain adequate cerebral perfusion will aggravate bleeding. A dogmatic (ABCD) approach suggests that prevention of secondary brain injury indicates that all efforts should primarily be pointed at stabilization of the circulation and hemorrhage control. However, Soreide \textit{et al.} advocate, in their differentiated approach for pre-hospital fluid resuscitation, to titrate systolic blood pressure to up and above 110 mmHg in blunt trauma patients with clinical suspicion of severe brain injury.\textsuperscript{40} In conclusion, as the differentiated approach for pre-hospital resuscitation of trauma patients will evolve further and decision making will be more complicated, the need for specialized pre-hospital care providers (specialized doctors in emergency medicine, anaesthesiology or critical care) on the scene is warranted in order to bear responsibility for critical decisions made in the field. The classic debate has been about the type of resuscitation fluid: crystalloids versus colloids. In the recent Cochrane Database Systemic Review, Perel \textit{et al.} conclude that as colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of randomized clinical trials.\textsuperscript{41} However, it remains difficult to conclude about advantages of one resuscitation fluid type over the other within different patient subgroups within different clinical scenarios. Nolan concludes that as long as the appropriate volume is given, the type of fluid may not be of importance since anemia is much better tolerated than hypovolemia.\textsuperscript{37} However, regarding bleeding, colloids may interfere with coagulation more than crystalloids. For instance, hydroxyethyl starch (HES) reduces clot strength due to impairment of fibrin polymerization.\textsuperscript{42} In recent years however, the promising role of hypertonic resuscitation fluids has become more evolved within pre-hospital trauma care.\textsuperscript{40,43} Resuscitation with hypertonic fluids improves
hemodynamics and rapidly corrects blood pressure. It improves tissue perfusion as drawing fluid from edematous endothelium enhances microcirculatory flow. In hypotensive patients with penetrating injuries as well as in hypotensive patients with head injuries, improvement of survival with the use of hypertonic saline/dextran has been described.\textsuperscript{44,45} Kreimeier \textit{et al.} have defined small-volume resuscitation as bolus infusion of 250 mL (for example 4 mL/kg body weight) of hypertonic colloid solution within 2-5 min through a peripheral vein for primary resuscitation from severe hypovolemia and shock, generally seen after severe trauma and hemorrhage.\textsuperscript{46} Use of hypertonic fluids in the field is advocated now for specific indications. However, the exact role of, for example, hypertonic saline-hydroxyethyl starch in combination with hypotensive resuscitation in different preclinical scenario's have to be defined.\textsuperscript{47} In severe hemorrhagic shock (ATLS shock classification: class III and class IV) initial resuscitation with blood is mandatory and should not be delayed.\textsuperscript{6} There are only very few reports on transfusion of blood in the pre-hospital setting. The use of blood transfusions by helicopter emergency medical services has been considered as safe.\textsuperscript{48} Barkana \textit{et al.} justified the use of pre-hospital blood transfusion in cases of long transport times.\textsuperscript{49} Although, in cases of severe hemorrhagic shock and/or entrapment and/or long transport times, pre-hospital blood transfusion seems to be a logical intervention, no clinical outcome studies have been done. Probably, the reasons must be the costs, storage and problems with logistics, medico-legal issues and lack of sufficient patient numbers. The search for artificial blood or so called oxygen therapeutics, as an alternative for pre-hospital blood transfusion, is everlasting. Such a product may have great potential in the pre-hospital treatment of bleeding patients. Two products are undergoing clinical trials. Polyheme® (pyridoxylated and glutaraldehyde-polymerized human haemoglobin) is undergoing a phase III study in trauma starting before hospitalization, with a planned enrolment of 720 patients, to evaluate 30-day survival.\textsuperscript{50} Safety and effectiveness of polymerized human hemoglobin have been shown in trauma in earlier studies.\textsuperscript{51-53} Coagulation management and/or pharmacotherapeutic intervention for coagulation in the pre-hospital phase of bleeding patients (for example before blood transfusion is started and/or definitive hemorrhage control) may be a promising concept to limit blood loss after trauma. In a swine model, Howes \textit{et al}, administered rFVIIa fifteen minutes (“pre-hospital phase”) after multiple blunt injuries consisting of a femur fracture, liver laceration and soft tissue crush injury.\textsuperscript{54} A significant decrease in blood loss was noted in these animals that had no previous coagulopathy. Further studies are needed regarding this interesting concept.
IN-HOSPITAL TREATMENT

Concepts

A well-established communication system between the hospital and the pre-hospital care providers is essential to prepare for timely, optimal preparation of the receiving team. Within the hospital, a sound trauma team activation (TTA) system, including the logistic procedure as well as activation criteria, is essential for a fast and adequate response. When the responsible (trauma) surgeon is not automatically part of the TTA, triage protocols for TTA should incorporate criteria to call-in the surgeon on-call. In managing trauma in general but especially in bleeding trauma patients, time is of essence. For example, Clarke et al. have found that the probability of death increases approximately 1% for each 3 minutes in the emergency department in patients with major injuries isolated to the abdomen. Therefore, critical decision makers, for example, the responsible trauma surgeon should be present in the resuscitation room upon arrival of the bleeding victim. Within high-volume trauma centers, the benefit of in-house trauma surgeons has been disputed. A system with an attending trauma surgeon (i.e. in-house 24/7) will reduce resuscitation time and reduce time to incision for emergent operations, especially in penetrating trauma but without impact on mortality when compared with an out-house trauma surgeon system. Helling et al. found that as long as the attending surgeon responds in a defined period of time (e.g. 20 min) if out-house to guide critical decision making, the in-house presence of an attending surgeon will not improve care. Advanced treatment algorithms for trauma teams have reduced mortality from 33.3% to 16.7% in a single center non-randomized study. Nowadays, trauma resuscitation according to ATLS® or similar (Emergency Management of Severe Trauma: EMST®) guidelines is well established. After securing the airway, (cervical) spine control and establishing of adequate ventilation and oxygenation, the circulation will be assessed. Arterial catheterization is an accurate method to measure systolic and mean arterial pressure and superior to non-invasive blood pressure measurement especially, in low flow states. However, the insertion of an arterial catheter can be time-consuming and must not interfere with the primary resuscitation efforts. As stressed earlier, the recognition of hypovolemic shock (hemorrhagic shock state) in trauma patients can be challenging. In-hospital, the role of other markers of shock, in addition to clinical signs and symptoms, have become more evolved and may be of benefit in early evaluation in the resuscitation room. Lactate has been used as a determinant of tissue hypoperfusion in hemorrhagic shock and predictor of outcome and hemorrhagic shock. New serum lactate analyzers offer point-of-care measurements within minutes and may be used to detect
tissue hypoperfusion prior to the onset of hemodynamic instability. Base deficit (BD), which can be also quickly obtained through bedside arterial blood gas analysis and, correlates well with serum lactate and may be used for the same reason and/or to guide resuscitation. Sublingual capnometry has been investigated recently in a prospective, observational study. It was found that sublingual capnometry is a rapid, non-invasive tool for the determination of hemorrhagic shock in trauma, correlating well with lactate and BD. However, its application in the future may be questionable because of the availability of bedside tests for lactate and BD nowadays and because of its limited feasibility in for example uncooperative patients or in patients with blood in the oral cavity. After determination of hemorrhagic shock, all efforts have to be directed in order to stop bleeding to prevent exsanguinations. A simultaneous effort is made to restore blood volume and correct coagulation. Trauma patients with hemorrhagic shock who only transiently respond or do not respond to fluid therapy and/or the administration of blood products have exsanguinating injuries.
Finding the bleeding and stopping the bleeding

To stop the bleeding, the location of the bleeding has to be identified. In exsanguinating patients with penetrating injury, operative treatment to stop the bleeding is guided by the anatomical location of entrance and exit wounds. In blunt trauma, hemodynamically unstable patients have to be subjected to rapid radiological screening for possible bleeding within the chest, abdomen and pelvic compartment. In addition, clinical assessment of the extremities for long bone fractures has to be performed as well as screening for sites of external blood loss from, for example, maxillofacial injuries. To identify abdominal bleeding, abdominal ultrasound (FAST) can be performed to screen for intra-abdominal free fluid (i.e. blood in most cases) rapidly. A positive FAST in the hemodynamically unstable patient mandates laparotomy. The use of ultrasound as the primary screening tool for blunt abdominal trauma is well established as an accurate, fast and non-invasive method that indicates the need for emergency laparotomy.\textsuperscript{62-64} Nowadays, FAST has replaced diagnostic peritoneal lavage (DPL) for detection of hemoperitoneum. Trained radiologists or non-radiologists who have become accredited by proctored training should perform FAST. If FAST is not available when evaluating a hemodynamically unstable patient, diagnostic peritoneal aspiration (DPA) may be the alternative to detect significant hemoperitoneum.\textsuperscript{65} Classically, computed tomography (CT)-scanning of hemodynamically unstable patients (for example transient- and non-responders in need of an emergency hemostatic intervention) has been considered not warranted and even dangerous because of the time-consuming process of patient transport to the CT-room and the limited possibilities to continue intensive care therapy within the CT-room. However, with the development of sliding-gantry based computed tomography diagnostic systems (i.e. CT-scanner in the trauma room) rapid evaluation by CT-scanning of the trauma patient is possible during resuscitation. When a trauma room with integrated multi-slice CT scanner is available, a management algorithm for trauma patients reduces the length of stay in the trauma room until relocating the patient to operating theatre or ICU from 87 to 38 minutes.\textsuperscript{66} However, treatment algorithms for management of trauma patients within a specific hospital will be dictated by its structure, equipment and personnel situation. Findings on the chest and pelvic X-ray may indicate significant blood loss within the chest (hemothorax) and pelvic compartment (significant pelvic fracture). As time is a crucial factor in the treatment of exsanguination, all diagnostic procedures have to be minimized in duration and, ideally, performed simultaneously or in a rapid sequential order. Therefore, thorough organization of the trauma team with dedicated tasks for its members is essential. Hemostatic procedures have to be performed
immediately after the localization of the bleeding site. Procedures for temporary control of external blood loss and blood loss from fractures may be applied: direct pressure, pressure bandages, (traction) splinting and pelvic wrapping. Also, rapid posterior and anterior nasal packing may be performed using two Foley-catheters and ribbon gauze. Rapid external fixation of the posterior pelvic ring with the C-clamp can be performed as a hemostatic procedure in the emergency department. Emergency Department (ED) thoracotomy or resuscitative thoracotomy can be performed in selective cases of (imminent) circulatory arrest in penetrating as well as blunt trauma. Exsanguinating bleeding from thoracic organs may be stopped by clamping bleeding vessels or by inserting Foley catheters in cardiac wounds. Aortic cross clamping may limit subdiaphragmatic hemorrhage and increases proximal arterial pressure in order to preserve perfusion of brain and heart. ED thoracotomy has also been described to be successful in few cases of non-torso injury (i.e. patients exsanguinating from penetrating neck or extremity injury). However, the salvage rate of ED thoracotomy in trauma is still around 10% for all causes (not only exsanguinating injuries) in trauma and extremely low in blunt trauma. Further operative procedures are often needed to stop bleeding from internal injuries, pelvic fractures and penetrating extremity injury.
**Damage control surgery**

The concept of damage control surgery, the staged approach in treatment of severe trauma, has proven to be of vital importance in the treatment of exsanguinating trauma patients and is widely adopted. Worldwide, courses are held for (trauma) surgeons who are not frequently exposed to patients with exsanguinating injuries to be taught about the concept and learn operative damage control techniques in live, anesthetized animals. The patient that has entered (or is about to enter) the bloody vicious circle of shock, hypothermia and coagulopathy must be recognized immediately and decision-making is aimed at restoring the patient’s physiology.

In the first phase of damage control, abbreviated surgical techniques to control bleeding and contamination are performed within a limited time frame. Regarding hemorrhage control, numerous techniques as ligation of bleeding vessels, application of temporary shunts, temporary occlusion of wounds or major blood vessels with balloon catheters, abdominal packing, splenectomy or nephrectomy, lobectomy and subsequent rapid, temporary closure of the abdomen or chest may control surgical bleeding.\(^{71,72}\) The use of fibrin sealants in surgical and traumatic hemorrhage may be rising but not extensively reported.\(^{73}\) Possibly, there is a role for the intraoperative use of fibrin sealants in trauma cases with moderate bleeding.\(^{74}\) In an experimental model of Grade V renal injury in hypothermic swine, simulating a damage control scenario, application of Floseal\textsuperscript{®} gelatin matrix hemostatic sealant followed by compression reduced blood loss significantly.\(^{75}\) There is no clinical evidence for topical hemostatic sealants in damage control surgery. Also, there have been no clinical reports yet on the use of high intensity focused ultrasound application for bleeding from liver and spleen injury.\(^{76}\) The concept of damage control surgery, initially described for massive abdominal trauma is nowadays also well established in chest trauma and peripheral vascular injuries.\(^{77}\) However, in polytrauma, pelvic fracture may still remain as the major cause of preventable hemorrhagic death. Moreover, Tien et al. recently found that 86% of all preventable hemorrhagic deaths in a Level I trauma center occurred because of delay in treating massive pelvic bleeding in blunt trauma.\(^{78}\) The delay varied from 1.5 up to 8 hours and was mainly caused by obtaining a CT-scan and waiting time for pelvic angiography after laparotomy and pelvic external fixation. There has been a long-lasting debate about the best approach of patients with exsanguinating hemorrhage from pelvic fractures. There is no discussion about the application initial measurement of emergency pelvic binding or wrapping in exsanguinating patients with pelvic fracture. Also, when co-existent, abdominal hemorrhage should be addressed first by damage control laparotomy. In a recent review Gansslen et al. describe treatment options in patients with pelvic and
hemodynamic instability. Angiography with embolization of isolated arterial bleeding can be possibly effective as only in 10-20% arterial bleeding in the source of bleeding and is the common approach in North America. Introduction of institutional practice guidelines using this approach as the primary hemostatic intervention (within 90 min after admission) after initial resuscitation in the emergency room has shown to decrease mortality rate significantly in a single institution. However, angioembolization only addresses arterial bleeding and is time consuming. So, angioembolization may not be suitable for 'damage control' but for the more stable patient. As the source of pelvic bleeding may be predominantly of venous origin, pelvic packing (tamponade through an operative extraperitoneal approach i.e. peripelvic packing or preperitoneal packing) controls diffuse venous bleeding rapidly. Stabilization of the (posterior) pelvic ring is necessary for effective packing. This approach, combining peripelvic packing with rapid internal/external pelvic ring fixation has been advocated in exsanguinating patients in recent publications. Angioembolization is advised in more stable patients or as an adjunct in case of ongoing pelvic hemorrhage (indicative of arterial bleeding) after peripelvic packing and pelvic ring stabilization. There are no studies available comparing both approaches for blood loss and outcome but Cothren et al. have pointed out that there may be a 'paradigm shift' moving away from angioembolization towards the approach of peripelvic packing in hemodynamically unstable patients with pelvic fracture. Exsanguination from internal carotid injury caused by basal skull fractures through the petrous bone causing may cause rapid exsanguinations at the scene or in the emergency room. There are no clinical reports on emergency treatment of these devastating injuries. After surgery, during phase two, further treatment of hypothermia, shock and coagulopathy will take place in ICU. After 24 to 48 hours and improved patient conditions, definitive surgical procedures and closure of for example the abdomen can be performed (phase three of damage control) ongoing bleeding must be addressed. Angio-embolization of bleeding vessels in various types of injuries as well as stenting of larger vessels have become common procedures in trauma patients. However, those techniques may not be indicated in patients who do not respond to fluid suppletion indicating ongoing bleeding and imminent exsanguination. Emergency interventional radiology may not be available in some hospitals and when available, the procedure itself as well as the response time of the radiologist will be too lengthy. In transient responders, angioembolization may be safe to stop bleeding in various injuries. The approach of patients with traumatic aortic rupture may be changing as well. In patients with a traumatic aortic rupture who reach the hospital alive, the lesion is tamponaded by the adventitial tissues that thereby have prevented rapid exsanguination directly after the impact. Emergent operative repair is
the standard of care as the risk of rupture and subsequent exsanguination increases in time when left untreated. However, the impact of operative repair on mortality and morbidity is high. Although endovascular stent grafting has emerged as a new treatment modality of this injury its role is not clear. It seems safe and feasible in a case series of 11 patients with short term follow up (18 months) in a single center study. After a systemic literature review of 284 patients, Lettinga-van der Poll et al. conclude that endovascular stenting of traumatic aortic ruptures seems to reduce morbidity and mortality in trauma patients. There are, however, no reports yet on possible long-term complications such as stent migration, erosion and infection after stent grafting. In relatively stable patients, delayed repair of traumatic aortic rupture has been advocated since it might result in better outcome than emergent repair. However, early treatment with for example stent grafting may allow the trauma team to more effectively manage concomitant injuries as head injury. Nevertheless, the approach has to be tailored to condition of the patient and the availability of expertise and resources within the specific center. The hemodynamically unstable patient (not responding to fluid therapy) may definitely need a thoracotomy.
Resuscitation and coagulation management

In exsanguinating trauma, aggressive resuscitation with blood products increases survival rates to around 45%. The patients in need of massive blood transfusion have to be identified rapidly and transfusion should be started immediately. Therefore the issue of 'blind' transfusion or 'damage control resuscitation' has received a lot of attention in the past two years.

In patients with exsanguinating injuries, urgent transfusion of blood products is needed to restore oxygen transport, perfusion and coagulation. In contrast to the clinical situation of massive blood loss during elective operations, massive transfusion in exsanguinating trauma is performed 'blindly' i.e. not guided by laboratory tests. During these hectic circumstances, massive transfusions protocols are vital to assure proper treatment. If not, coagulation factors and platelets will not be administered timely and/or in enough quantities and coagulopathy is further promoted. Blood component therapy itself as well as sound logistic procedures regarding automatic delivery of products in packages (containing packed red blood cells: PRBC, fresh frozen plasma: FFP and platelets: PLTs) to the shock room or operating theaters has to be well defined in those protocols.

Massive transfusion protocols exist at a relatively small number of large and well-organized trauma centers. However, even some of those protocols are based on time-consuming laboratory tests (PT, aPTT, fibrinogen level, platelet count) and can be considered as 'reactive' protocols. The fixed ratio between the amounts of PRBC, FFP and PLTs within a transfusion package is subject to debate. Nevertheless, the composition of a transfusion package must be comparable to the composition of whole blood regarding total volume and the total amount of coagulation factors and platelets. Malone et al. have suggested that the use of a simple ratio of 1:1:1 for PRBC:FFP:PLTs may result in the administration of higher plasma and platelets doses and may improve outcome. Also, institution of such a protocol will facilitate multi-center research on hemorrhage control and resuscitation. For instance, interventional studies with new procoagulants, such as rFVIIa can be done more accurately.

In the military and austere environment with limited resources regarding the availability of blood products, fresh whole blood donated by a 'walking blood bank' can be used. An equivalent of fresh whole blood is far more superior to component therapy regarding clotting factor activity, hematocrit and platelet count and function. However, safety concerns and demanding logistics may render whole blood transfusion unsuitable for use in the civilian situation. Nevertheless, as an evitable consequence of blood component therapy, massive transfusion with blood components by itself will lead to coagulopathy by hemodilution. The interest for the use of procoagulants and/or
pharmacotherapeutic intervention with coagulation factors has been raised by the introduction of rFVIIa in exsanguinating trauma patients.\textsuperscript{104} Its beneficial effect as a ‘rescue’-drug has been described in several case series reviewed by Dutton.\textsuperscript{105} In a retrospective review of 117 combat trauma patients who received rFVIIa, early administration (before the transfusion of 8 PRBC units) of rFVIIa reduced red blood cell use by 20%.\textsuperscript{106} A prospective randomized clinical trial showed decrease in transfusion requirements when rFVIIa was used early as an adjunct to massive transfusion.\textsuperscript{107} The exact timing and role of rFVIIa in the treatment of bleeding in trauma is currently under investigation in a large, multi-center, randomized trial. Individual trauma centers may already have incorporated rFVIIa within their (ICU) protocols in order to prevent off-label administration of this relatively expensive drug in futile cases.\textsuperscript{96,106} Standard coagulation tests in exsanguinating trauma, such as PTT, PT and platelets do not reflect the actual coagulation status in the patient. The tests are time-consuming and do not test coagulation function. However, the role of thromboelastography (TEG) (or thromboelastometry TEM) as a point-of-care test for the coagulation status in massive blood loss is emerging, providing information about actual clot formation and stability, shortly (10 min) after the blood sample is taken.\textsuperscript{106,110} Thus, therapy can be directed by the test results allowing for administration of specific coagulation factors e.g. fibrinogen and/or prothrombin complex concentrate (PCC) that may be depleted despite administration with FFP during massive transfusion of blood components. Also, coagulopathy caused by hyperfibrinolysis or by decreased platelet function and/or platelet numbers or heparin can be rapidly detected and countered.\textsuperscript{109} The possible benefit of antifibrinolytics in hemorrhaging trauma has not been elucidated yet by randomized controlled trials.\textsuperscript{111} However, a large international, randomized placebo-controlled trial of the effects of the early administration of tranexamic acid in traumatic hemorrhage showed beneficial effects on post-traumatic hemorrhage.\textsuperscript{112} Treatment of traumatic coagulopathy however remains a challenge. Dilution and consumption of coagulation factors, acidosis, hypothermia, the use of HES in resuscitation may all contribute to coagulopathy. Measures should be taken to limit these causes and an early point-of-care test to screen for coagulopathy is warranted.\textsuperscript{113} However, there is some evidence now that coagulopathy in major traumatic injury develops early, for example before dilution and consumption of coagulation factors as a direct result of tissue hypoperfusion.\textsuperscript{114} Rewarming and prevention of further hypothermia is an essential part of therapy in the bleeding patient. Hypothermia is known to be an independent predictor of mortality. It affects adhesion, aggregation and function of platelets and the enzymatic activity of the clotting cascade. Laboratory coagulation test do not reflect these effects as samples from a hypothermic patient are rewarmed to 37 °C.\textsuperscript{115-117} Despite the
fact that hypothermia may be protective by decreasing oxygen consumption, aggressive rewarming with fluid resuscitation may still be the best practice in hemorrhagic shock.\textsuperscript{118} Rewarming can be achieved through various passive (increased room temperature, blanket coverage) and active (heating blankets, radiant warmers, body cavity lavage, warmed intravenous fluids, cardiopulmonary bypass) methods. In 1991 Gentilello \textit{et al.} introduced rapid rewarming by continuous arteriovenous extracorporeal rewarming.\textsuperscript{119} Rapid rewarming with this device, improved survival and decreased blood and fluid requirements, organ failures and length of ICU stay when compared to standard (slow) rewarming.\textsuperscript{120} No recent clinical studies are available regarding rapid versus slow rewarming of hypothermic trauma patients.
Conclusion

Recognition of traumatic hemorrhage as a treatable ‘disease’ has been well established. The treatment of the patient with exsanguinating injuries has many aspects. Progress has been made in many fields regarding early hemorrhage control, resuscitation and coagulation management throughout the last decade and has great potential to improve outcomes in trauma patients. However, as the treatment of these patients (and the interpretation of outcome studies) will always depend on local, regional and international differences regarding trauma mechanism, geography, (pre-) hospital trauma system organization, patient population and resources, a differentiated, but protocol-driven approach tailored to the local situation is advocated.

Future directions

As a differentiated approach is warranted, future directions in the treatment of patients with exsanguinating injuries may point in the direction of efforts to improve pre-hospital care by having experts at the scene for critical decision-making. Also, regarding resuscitation, pre-hospital blood transfusion in cases of stay and play and/or long transport times may be feasible, while awaiting results from oxygen carriers trials. Research has to clarify optimal pre-hospital fluid resuscitation and possibilities for early coagulation management. The concept of operating room resuscitation may be further developed. Advanced trauma resuscitation protocols incorporating sliding-gantry based CT may reduce time to definitive hemorrhage control. Surgeons taking care of these patients are warranted to be familiar with the concept of damage control and operative techniques for rapid hemorrhage control. This necessitates frequent hands-on training at the animal laboratory for surgeons in low-volume trauma centers. Further research towards evidence-based ‘blind’ transfusion protocols and coagulation management using point-of care tests is mandatory. It is of great importance that politicians and care providers realize that treatment of these patients requires an expensive but worthy team effort throughout the trauma chain of survival.
References


82. Contostavlos DL. Exsanguination from impact head trauma; the explanation for the "empty heart" sign. Forensic Sci Int 1998;95: 201-12.


