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Donat R Spahn (donat.spahn@usz.ch)
Vladimir Cerny (cernyvla@fnhk.cz)
Timothy J Coats (tc61@le.ac.uk)
Jacques Duranteau (Jacques.Duranteau@bct.ap-hop-paris.fr)
Enrique Fernandez-Mondejar (enrique.fernandez.mondejar.sspa@juntadeandalucia.es)
Giovanni Gordini (g.gordini@118er.it)
Philip F Stahel (pfstahel@aol.com)
Beverley J Hunt (Beverley.Hunt@gstt.nhs.uk)
Radko Komadina (sbcrdi@guest.arnes.si)
Edmund Neugebauer (sekretariat-neugebauer@ifom-uni-wh.de)
Yves Ozier (yves.ozier@cch.ap-hop-paris.fr)
Louis Riddez (louis.riddez@karolinska.se)
Arthur Schultz (arthur.schultz@lbitrauma.org)
Jean-Louis Vincent (jlvincen@ulb.ac.be)
Rolf Rossaint (rossaint@post.rwth-aachen.de)

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Management of bleeding following major trauma: a European guideline

Donat R. Spahn[1], Vladimir Cerny[2], Timothy J. Coats[3], Jacques Duranteau[4], Enrique Fernández-Mondéjar[5], Giovanni Gordini[6], Philip F. Stahel[7], Beverley J. Hunt[8], Radko Komadina[9], Edmund Neugebauer[10], Yves Ozier[11], Louis Riddez[12], Arthur Schultz[13], Jean-Louis Vincent[14], Rolf Rossaint[15 *]

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Author affiliations:

[1] Donat R. Spahn

Professor and Chairman

Department of Anesthesiology

University Hospital Zurich

8091 Zurich

Switzerland

[2] Vladimir Cerny

Charles University in Prague

Faculty of Medicine in Hradec Králové

Department of Anaesthesiology and Intensive Care Medicine

University Hospital Hradec Králové

50005 Hradec Králové

Czech Republic

[3] Timothy J. Coats

Professor of Emergency Medicine

Leicester Royal Infirmary

Accident and Emergency Department

Infirmary Square

Leicester LE1 5WW

United Kingdom

[4] Jacques Duranteau

Department of Anaesthesia and Intensive Care

University of Paris XI

Faculté de Médecine Paris-Sud

63 rue Gabriel Péri

94276 Le Kremlin-Bicêtre

France

[5] Enrique Fernández-Mondéjar

Department of Emergency and Critical Care Medicine

University Hospital Virgen de las Nieves

ctra de Jaén s/n

18013 Granada

Spain

[6] Giovanni Gordini

Department of Anaesthesia and Intensive Care

Ospedale Maggiore

Largo Nigrisoli 2

40100 Bologna

Italy

[7] Philip F. Stahel

Associate Professor

Department of Orthopaedic Surgery

Denver Health Medical Center

University of Colorado Medical School

777 Bannock Street

Denver, CO 80204

USA

[8] Beverley J. Hunt

Consultant, Departments of Haematology, Pathology and Rheumatology

Guy's & St Thomas' Foundation Trust

London SE1 7EH

United Kingdom

[9] Radko Komadina

Department of Traumatology

General and Teaching Hospital Celje

3000 Celje

Slovenia

[10] Edmund Neugebauer

Institute for Research in Operative Medicine

University of Witten/Herdecke

Ostmerheimerstrasse 200

51109 Köln (Merheim)

Germany

[11] Yves Ozier

Department of Anaesthesia and Intensive Care

Université René Descartes Paris 5

AP-HP

Hopital Cochin

Paris, France

[12] Louis Riddez

Department of Surgery and Trauma

Karolinska University Hospital

171 76 Solna

Sweden

[13] Arthur Schultz

Ludwig-Boltzmann-Institute for Experimental and Clinical Traumatology

Donaueschingenstrasse 13

1200 Vienna

Austria

[14] Jean-Louis Vincent

Professor and Head

Department of Intensive Care

Erasme Hospital

University of Brussels, Belgium

CP537 route de Lennik 808

1070 Brussels

Belgium

[15] Rolf Rossaint (*corresponding author)

Professor and Chair

Department of Anaesthesiology

University Hospital Aachen

Pauwelsstraße 30

52074 Aachen

Germany

Email: rossaint@post.rwth-aachen.de

ABSTRACT

Introduction: Evidence-based recommendations can be made with respect to many aspects of the acute management of the bleeding trauma patient, which when implemented may lead to improved patient outcomes.

Methods: The multidisciplinary Task Force for Advanced Bleeding Care in Trauma, was formed in 2005 with the aim of developing guidelines for the management of bleeding following severe injury. Recommendations were formulated using a nominal group process and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence and based on a systematic review of published literature.

Results: Key recommendations include the following: The time elapsed between injury and operation should be minimised for patients in need of urgent surgical bleeding control, and patients presenting in haemorrhagic shock and an identified source of bleeding should undergo immediate surgical bleeding control unless initial resuscitation measures are successful. A damage control surgical approach is essential in the severely injured patient. Pelvic ring disruptions should be closed and stabilised, followed by appropriate angiographic embolisation or surgical bleeding control, including packing. Patients presenting with haemorrhagic shock and an unidentified source of bleeding should undergo immediate further assessment as appropriate using focused sonography, computed tomography, serum lactate and/or base deficit measurements. This guideline also reviews appropriate physiological targets and suggested use and dosing of blood products, pharmacological agents and coagulation factor replacement in the bleeding trauma patient.

Conclusion: A multidisciplinary approach to management of the bleeding trauma patient will assist in creating circumstances in which optimal care can be provided. By their very nature, these guidelines reflect the current state-of-the-art and will need to be updated and revised as important new evidence becomes available.

INTRODUCTION

Traumatic injury is the leading cause of death worldwide among persons between 5–44 years of age [1] and accounts for 10% of all deaths [2]. In 2002, 800,000 injury-related deaths in Europe accounted for 8.3% of total deaths [3]. Because trauma affects a disproportionate number of young people, the burden to society in terms of lost productivity, premature death and disability is considerable. Despite improvements in trauma care, uncontrolled bleeding contributes to 30–40% of trauma-related deaths and is the leading cause of potentially preventable early in-hospital deaths [4-6].

Resuscitation of the trauma patient with uncontrolled bleeding requires the early identification of potential bleeding sources followed by prompt action to minimise blood loss, to restore tissue perfusion and to achieve haemodynamic stability. Massive bleeding in trauma patients, defined here as the loss of one blood volume within 24 h or the loss of 0.5 blood volumes within 3 h, is often caused by a combination of vascular injury and coagulopathy. Contributing factors to traumatic haemorrhage include both surgical and non-surgical bleeding, prior medication, co-morbidities and acquired coagulopathy [7].

Here we describe early diagnostic measures to identify haemorrhage that should trigger surgical or radiological interventions in most cases. Specific interventions to manage bleeding associated with pelvic ring injuries and hypothermia are discussed, as well as recommendations for the optimal application of fluid, pharmacological, blood product and coagulation factor therapy in trauma patients.

These guidelines for the management of the bleeding trauma patient were developed by a multidisciplinary group of European experts and designated representatives from relevant professional societies to guide the clinician in the early phases of treatment. The recommendations presented here are based on a critical survey of the published literature and formulated according to a consensus reached by the author group. Many of the critical issues faced by the treating physician have not been, and for ethical or practical reasons may never be, addressed by prospective randomised clinical studies, therefore the formulation and grading of the recommendations presented here are weighted to reflect both this reality and the current state-of-the-art.

METHODS

These recommendations were formulated and graded according the Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence outlined by Guyatt GH et al. [8] and summarised in Table 1. Comprehensive computer database literature searches were performed using the indexed online databases MEDLINE/PubMed and the Cochrane Library. Lists of cited literature within relevant articles were also screened. The primary intention of the review was to identify prospective randomised and nonrandomised controlled trials, existing systematic reviews and guidelines. In the absence of such evidence, case control studies, observational studies and case reports were considered.

Boolean operators and MeSH-thesaurus keywords were applied as a standardised use of language to unify differences in terminology into single concepts. Appropriate MeSH-headings and subheadings for each question were selected and modified based on search results. The scientific questions posed that lead to each recommendation and the MeSH headings applied to each search are listed in additional data file 1 (supplementary material). Searches were limited to English language abstracts and human studies; gender and age were not limited. No time period limits were imposed on searches unless the search result exceeded 300 hits. Original publications were evaluated for abstracts that were deemed relevant. In the case of a guideline updates, searches were limited to the time period following the publication of the last version of the guideline. If an acceptable systematic review or meta-analysis was identified, searches to update the data were typically limited to the time period following the search cut-off date reported in the review. Original publications were evaluated according to the levels of evidence developed by the Oxford Centre for Evidence-based Medicine [9].

The selection of the scientific inquiries to be addressed in the guideline, screening and grading of the literature to be included, and formulation of specific recommendations was performed by members of the Task Force for Advanced Bleeding Care in Trauma, a multidisciplinary, pan-European group of experts with specialties in Surgery, Anaesthesia, Emergency Medicine, Intensive Care Medicine and Haematology. The core group formed in 2004 to produce educational material on care of the bleeding trauma patient [10], on which a subsequent review article was based [11]. The Task Force consisted of the core group, additional experts in haematology and guideline development, and representatives of relevant European professional societies, including the European Shock Society (ESS), the European Society for Anaesthesia (ESA), the European Society for Emergency Medicine (EuSEM), the European Society for Intensive Care Medicine (ESICM) and the European Trauma Society (ETS). The European Hematology Association (EHA) declined the invitation to send a representative to join the Task Force. Task Force members participated in a workshop on the critical appraisal of medical literature. The nominal group process included four face-to-face meetings, supplemented by several Delphi rounds [12]. The guideline development group met in June 2005 to define the scientific questions to be addressed in the guideline and again in October 2005 to finalise the scientific scope of the guidelines. Selection, screening and grading of the literature and formulation of recommendations was accomplished in sub-committee groups consisting of at least three members via electronic or telephone communication. Following distribution of the recommendations to the entire group, a further meeting of the Task Force was held in April 2006 with the aim of reaching a consensus on the draft recommendations from each sub-committee. Following final refinement of specific recommendations among committee members, a subset of the Task Force met in July 2006 to finalise the manuscript document. The document was approved by the endorsing organisations in September and October 2006. An updated version of the guideline is anticipated in due time.

Using the GRADE system for assessing each recommendation, the letter attached to the grade of recommendation reflects the degree of literature support for the recommendation, while the number indicates the level of support for the recommendation assigned by the committee of experts. Recommendations are grouped by category and somewhat chronologically in the treatment decision-making process, but not by priority or hierarchy.

RESULTS

I. Initial resuscitation and prevention of further bleeding

Evidence to support the initial phase of resuscitation and prevention of further bleeding is lacking, and there have been few studies on the effect of coagulopathy on outcome. Patients with a coagulopathic condition have worse outcomes than patients of the same injury severity without a clotting disturbance [13, 14], and patients with head injury also have worse outcomes in association with a coagulopathy [15], however contrary to popular belief, there is no evidence that head injured patients are more likely to develop a coagulopathy than other severely injured patients [16].

There is no evidence as to whether the degree of initial bleeding affects coagulopathy. Coagulopathy is predicted by a systolic blood pressure below 70 mmHg [17], however this could be either a direct effect of bleeding or an associated effect of injury severity. There is no high-level scientific evidence that the initial amount of bleeding affects the patient's outcome; however the experience of treating physicians is that uncontrolled haemorrhage is associated with poor outcome. Common experience is that wound compression prevents bleeding, although it is not known whether or not this reduces the incidence of coagulopathy. There is also no evidence that tells us whether or not control of acid-base balance during initial resuscitation affects outcome.

Evidence does exist to support expedient care for patients following traumatic injury; however there have been no studies that compare outcomes in patients transported to different types of hospital facilities on the basis of the amount of bleeding. Pre-hospital bleeding uncontrolled by compression and splintage requires rapid surgical or radiological intervention.

R1

We recommend that the time elapsed between injury and operation be minimised for patients in need of urgent surgical bleeding control. (Grade 1A)

Rationale:

Trauma patients in need of emergency surgery for ongoing haemorrhage demonstrate better survival if the elapsed time between the traumatic injury and admission to the operating theatre is minimised [18-21]. Although there are no randomised control studies to verify this statement, there are retrospective studies that provide enough evidence for early surgical intervention in these patients. This is particularly true for patients who present in an exsanguinated state or in severe haemorrhagic shock due to penetrating vascular injuries [18, 19]. In accordance with these observations Blocksom et al. concluded that rapid resuscitation and surgical control of haemorrhage is of utmost importance and one of the prognostic determinants in a retrospective study on duodenal injuries [20]. Another retrospective study by Ertel et al. that included 80 polytrauma patients in extremis or with persistent haemodynamic instability also favoured early surgical intervention to stabilise a pelvic fracture or to surgically control bleeding [21].

In addition, studies of different trauma systems indirectly emphasise the importance of minimising the time between initial care and surgery for those with signs of exsanguination or ongoing severe haemorrhage. Hill et al. observed a significant decrease in mortality from shock by introducing an educational program on trauma and by establishing a 60 min emergency department time limit for patients in a state of haemorrhagic shock [22]. Others also stress the importance of a well functioning system capable of timely control of haemorrhage in the exsanguinating or the severely bleeding patient [23, 24]. In a retrospective review of 537 deaths in the operation room, Hoyt et al. drew the conclusion that delayed transfer to the operating room was a cause of death that could be avoided by shortening the time required for diagnosis and resuscitation prior to surgery [25].

II. Diagnosis and monitoring of bleeding

Upon arrival in the emergency room, an initial clinical assessment of the extent of bleeding should be employed to identify patients at risk of coagulopathy.

R2

We recommend that the extent of traumatic haemorrhage be clinically assessed using a grading system such as that established by the American College of Surgeons. (Grade 1C)

Rationale:

An evaluation of the mechanism of injury (e.g. blunt vs. penetrating trauma) is a useful tool for determining which patients are candidates for surgical bleeding control. Table 2 summarises the four classes of physiological response and clinical signs of bleeding as defined by the American College of Surgeons [26]. This type of grading system may be useful in the initial assessment of bleeding. The initial assessment can also assist in determining the next patient management goal to minimise blood loss and achieve haemodynamic stability.

R3

We do not suggest hyperventilation or the use of excessive positive end-expiratory pressure (PEEP) when ventilating severely hypovolemic trauma patients. (Grade 2C)

Rationale:

There is a tendency for rescue personnel to hyperventilate patients during resuscitation [27, 28], and hyperventilated trauma patients appear to have increased mortality when compared with non-hyperventilated patients [28]. The experimental correlate may be an increased cardiac output in hypoventilated pigs in haemorrhagic shock [29] and a decrease in cardiac output due to 5 cm positive end-expiratory pressure (PEEP) in rats in haemorrhagic shock [30]. In contrast, the elimination of PEEP and, to an even greater extent, negative expiratory pressure ventilation increases cardiac output and survival of rats in haemorrhagic shock [30].

R4

We recommend that patients presenting with haemorrhagic shock and an identified source of bleeding undergo an immediate bleeding control procedure unless initial resuscitation measures are successful. (Grade 1B)

<u>Rationale:</u>

The source of bleeding may be immediately obvious, with penetrating injuries being more likely to require surgical bleeding control. In a retrospective study of 106 abdominal vascular injuries, all 41 patients arriving in shock following gun shot wounds were candidates for rapid transfer to the operating theatre for surgical bleeding control [19]. A similar observation in a study of 271 patients undergoing immediate laparotomy for gun shot wounds indicate that these wounds combined with signs of severe hypovolaemic shock specifically require early surgical bleeding control. This observation is true to a lesser extent for abdominal stab wounds [31]. Data on injuries from the Vietnam War caused by penetrating metal fragments from explosives or gun shot wounds confirm the need for early surgical control when patients present in shock [18].

In blunt trauma the mechanism of injury can to a certain extent determine whether the patient in haemorrhagic shock will be a candidate for surgical bleeding control. Only a few studies addressing the relationship between the mechanism of injury and the risk of bleeding exist, however, and none of these publications is a randomised prospective trial of high evidence. No objective data exists describing the risk of bleeding depending on the mechanism of injury of skeletal fractures, particularly long bone fractures.

Road traffic accidents are the leading cause of pelvic injury. Motor vehicle crashes cause approximately 60% of pelvic fractures followed by falls from great height (23%). Most of the remainder result from motorbike collisions and vehicle-pedestrian accidents [32, 33]. There is a correlation between “unstable” pelvic fractures and intra-abdominal injuries [32, 34]. An association between major pelvic fractures and severe head injuries, concomitant thoracic, abdominal, urological and skeletal injuries is also well described [32]. High-energy injuries produce greater damage to both the pelvis and organs. Patients with high-energy injuries require more transfusion units and more than 75% have associated head, thorax, abdominal or genitourinary injuries [35]. It is well documented that “unstable” pelvic fractures are associated with massive haemorrhage [34], and haemorrhage is the leading cause of death in patients with major pelvic fractures. Pelvic fractures account for 1-3% of all skeletal injuries. In patients with multiple trauma, the incidence of pelvic fracture increases up to 25% [33].

R5

We recommend that patients presenting with haemorrhagic shock and an unidentified source of bleeding undergo immediate further assessment. (Grade 1B)

A patient in haemorrhagic shock with an unidentified source of bleeding should undergo urgent clinical assessment of chest, abdominal cavity and pelvic ring stability using focused abdominal sonography in trauma (FAST) assessment of thorax and abdomen and/or computerised tomographic (CT) examination in the shock room.

Sonography

R6

We recommend early focused sonography (FAST) for the detection of free fluid in patients with suspected torso trauma. (Grade 1B)

R7

We recommend that patients with significant free intraabdominal fluid according to sonography (FAST) and haemodynamic instability undergo urgent surgery. (Grade 1C)

<u>Rationale:</u>

Blunt abdominal trauma represents a major diagnostic challenge and an important source of internal bleeding. FAST has been established as a rapid and non-invasive diagnostic approach for detection of intraabdominal free fluid in the emergency room [36, 37]. Large prospective observational studies determined a high specificity (range 0.97–1.0) and a high accuracy (range 0.92–0.99) but low sensitivity (range 0.56–0.71) of initial FAST examination for detecting intraabdominal injuries in adults and children [38-45]. Shackford et al. assessed the accuracy of FAST performed by non-radiologist clinicians (i.e. surgeons and emergency physicians who were certified for FAST by defined standards) for detecting a haemoperitoneum in 241 prospectively investigated adult patients with blunt abdominal trauma (except for n=2 with penetrating injuries) during a 4-year period [38]. These findings were confirmed by Richards and co-workers in another 4-year prospective study of 3264 adult patients with blunt abdominal trauma [39]. Similar conclusions were drawn by the same group of investigators in a paediatric population, based on a prospective study on 744 consecutive children ≤16 years of age who underwent emergency FAST for blunt abdominal trauma [40]. Liu and colleagues conducted a 1-year prospective comparison on the diagnostic accuracy of CT scan, diagnostic peritoneal lavage (DPL), and sonography in 55 adult patients with blunt abdominal trauma [41]. The authors found a high sensitivity (0.92), specificity (0.95) and accuracy (0.93) of initial FAST examination for the detection of haemoperitoneum. While CT scan and DPL were shown to be more sensitive (1.0 for DPL, 0.97 for CT) than sonography for detection of haemoperitoneum, however, these diagnostic modalities are more time-consuming (CT and DPL) and invasive (DPL) [41].

The hypotensive patient (systolic blood pressure <90 mmHg) presenting free intraabdominal fluid according to FAST is a potential candidate for early surgery if he or she cannot be stabilised by initiated fluid resuscitation, according to a retrospective study of 138 patients by Farahmand et al. [46]. A similar conclusion can be drawn from a prospective blinded study of 400 hypotensive blunt trauma victims (<90 mmHg systolic) showing that specific levels of intraabdominal fluid detected by FAST in these patients was an accurate indicator of the need for urgent surgery [47]. In addition, a retrospective study by Rozycki et al. of 1540 patients (1227 blunt, 313 penetrating trauma) using FAST as an early diagnostic tool, showed that the ultrasound examination had a sensitivity and specificity close to 100 percent when the patients were hypotensive [48].

A number of patients who present free intraabdominal fluid according to FAST can safely undergo further investigation with multi-slice spiral computed tomography (MSCT). Under normal circumstances, adult patients need to be haemodynamically stable when MSCT is performed outside of the emergency room. In a retrospective study of 1540 patients (1227 blunt, 313 penetrating trauma) who were assessed early using FAST, a successful non-operative management was achieved in 24 (48%) of the 50 patients who were normotensive on admission and had true positive sonographic examinations. These results justified undergoing a MSCT scan of the abdomen rather than performing an exploratory laparotomy immediately [48]. In a review article, Lindner et al. also concluded that the haemodynamically stable patient should undergo MSCT scanning regardless of the findings from ultrasound or clinical examination [49].

Computer tomography

R8

We recommend that haemodynamically stable patients with suspected head, chest and/or abdominal bleeding following high-energy injuries undergo further assessment using computed tomography (CT). (Grade 1C)

Rationale:

The increasing role of multi-slice spiral computed tomography in the imaging concept of acute trauma patients is well documented [50-55]. The integration of modern MSCT scanners in the emergency room area allows the immediate examination of trauma victims following admission [52, 53].

Using modern 16-slice CT scanners, total whole-body scanning time amounts to approximately 120 seconds. 64-slice CT scanners may reduce scanning time to less than 30 seconds. In a retrospective study comparing 370 patients in 2 groups, Weninger [53] showed that the full extent of injury was definitively diagnosed 12±9 min following application of the MSCT protocol. In the group of conventionally diagnosed patients, definitive diagnosis was possible after 41±27 min. Faster diagnosis led to shorter ER and OR time and shorter ICU stay [53]. Compared to MSCT, all traditional techniques of diagnostic and imaging evaluation have some limitations. The diagnostic accuracy, safety and effectiveness of immediate MSCT is dependent on sophisticated prehospital treatment by trained and experienced emergency personnel and short transportation times [56, 57].

If a MSCT is not available in the emergency room, the realisation of CT scanning implies transportation of the patient to the CT room, therefore the clinician must evaluate the implications and potential risks and benefits of the procedure. According to established standards, such as those developed by the American College of Surgeons, only the haemodynamically stable patient should be considered for CT scanning. During transport to the MSCT and imaging all vital signs should be closely monitored and resuscitation measures continued.

For those patients in whom haemodynamic stability is questionable, other imaging techniques such as ultrasound and chest and pelvic radiography may be useful. Peritoneal lavage is rarely indicated if ultrasound or CT is available [58]. Transfer time to and from all forms of diagnostic imaging needs to be carefully considered in any patient who is haemodynamically unstable. In addition to the initial clinical assessment, near patient testing results, including full blood count, haematocrit, blood gases and lactate, should be readily available under ideal circumstances.

Haematocrit

R9

We do not recommend the use of single haematocrit measurements as an isolated laboratory marker for bleeding. (Grade 1B)

<u>Rationale:</u>

Haematocrit (Hct) measurements are part of the basic diagnostic work-up for trauma patients. The diagnostic value of the Hct for detecting trauma patients with severe injury and occult bleeding sources has been a topic of debate in the past decade [59-61]. A major limit of the diagnostic value is the confounding influence of resuscitative measures on the Hct due to administration of intravenous fluids and red cell concentrates [61-64]. A retrospective study of 524 trauma patients determined a low sensitivity (0.5) of the initial Hct on admission for detecting those patients with an extent of traumatic haemorrhage requiring surgical intervention [61].

Two prospective observational diagnostic studies determined the sensitivity of serial Hct measurements for detecting patients with severe injury [59, 60]. Paradis et al. found that the mean change in Hct between arrival and 15 minutes and between 15–30 minutes was not significantly different between patients with serious injuries (n=21) compared to trauma patients without serious injuries (n=39) [59]. While a decrease in Hct of ≥6.5% at 15 and 30 min had a high specificity (0.93–1.0) for a serious injury, the sensitivity for detecting severely injured patients was very low (0.13 – 0.16) [59]. The authors also found that a normal Hct on admission did not preclude a significant injury [59]. Zehtabchi and colleagues expanded the time window of serial Hct assessments to 4 h after arrival [60]. All trauma patients requiring a blood transfusion within the first 4 h were excluded from the study. In the remaining 494 patients, a drop in Hct of >10% between admission and four hours was highly specific (0.92–0.96) for severe injury, but associated with a very low sensitivity (0.09–0.27) for detecting patients with significant injuries [60]. The limitation of the high specificity of the decrease in Hct after 4 h in this study is that it included only trauma patients who did not receive any blood transfusions during the first 4 h [60]. In summary, decreasing serial haematocrit measurements may reflect continued bleeding, however the patient with significant bleeding may maintain their serial haematocrit.

Serum lactate

R10

We recommend serum lactate measurement as a sensitive test to estimate and monitor the extent of bleeding and shock. (Grade 1B)

Rationale:

Serum lactate has been used as a diagnostic parameter and prognostic marker of haemorrhagic shock since the 1960s [65]. The amount of lactate produced by anaerobic glycolysis is an indirect marker of oxygen debt, tissue hypoperfusion, and the severity of haemorrhagic shock [66-69]. Vincent et al. reported on the value of serial lactate measurements in predicting survival in a prospective study on a heterogenic group of 27 patients with circulatory shock [70]. The authors concluded that changes in lactate concentrations provide an early and objective evaluation of a patient's response to therapy and suggested that repeated lactate determinations represent a reliable prognostic index for patients with circulatory shock [70]. Abramson and colleagues performed a prospective observational study on multiple trauma patients for evaluating the correlation between lactate clearance and survival [71]. Patients who died within the first 48 hours (n=25) were excluded from the study. The remaining 76 patients were analyzed with respect to the time of serum lactate normalisation, compared between survivors and non-survivors who died after 48 h [71]. Survival was 100% in those patients where lactate levels returned to the normal range (≤ 2 mmol/l) within 24 h. Survival decreased to 77.8 % if normalisation occurred within 48 hours, and to 13.6% in those patients where lactate levels were elevated above 2 mmol/l for more than 48 h [71]. These findings were confirmed in a study on 129 trauma patients by Manikis et al. [72]. The authors found that the initial lactate levels were higher in non-survivors than in survivors, and the prolonged time for normalisation of lactate levels >24 h was associated with the development of posttraumatic organ failure [72]. Together, both the initial serum lactate and serial lactate levels are reliable indicators of morbidity and mortality following trauma [71, 72].

Base deficit

R11

We recommend base deficit as a sensitive test to estimate and monitor the extent of bleeding and shock. (Grade 1C)

Rationale:

Base deficit values derived from arterial blood gas analysis provide an indirect estimation of global tissue acidosis due to impaired perfusion [66, 68]. Siegel and colleagues demonstrated that the initial base deficit represented an independent single predictor of posttraumatic mortality in 185 patients with blunt liver trauma [73]. Two large retrospective studies on 3791 [74] and 2954 trauma patients [75] have strengthened the utility of the initial base deficit as a sensitive diagnostic marker of the degree and the duration of inadequate perfusion and as a prognostic parameter for posttraumatic complications and death. Davis et al. stratified the extent of base deficit into three categories: mild (-3 to -5 mEq/l) moderate (-6 to -9 mEq/l) and severe (<-10 mEq/l) [75]. Based on this stratification, they established a significant correlation between the admission base deficit and transfusion requirements within the first 24 h and with the risk of posttraumatic organ failure or death [75]. In a different retrospective study, the same group of authors showed that the base deficit is a better prognostic marker of death than the pH in arterial blood gas analyses [76]. Furthermore, the base deficit was shown to represent a highly sensitive marker for the severity of injury and the incidence of posttraumatic death, particularly in trauma patients older than 55 years of age [77]. In paediatric patients, admission base deficit was also shown to correlate significantly with the extent of posttraumatic shock and mortality, as determined in a retrospective study of 65 critically injured children using a cut-off value of <-5 mEq/l [78]. However, in contrast to the data on lactate levels in haemorrhagic shock, reliable large-scale prospective studies on the correlation between base deficit and outcome are still lacking.

Although both the base deficit and serum lactate levels are well correlated with shock and resuscitation, these two parameters do not strictly correlate with each other in severely injured patients [79]. Therefore, the independent assessment of both parameters is recommended for the evaluation of shock in trauma patients [66, 68, 79, 80]. Composite scores to assess the likelihood of massive transfusion that include base deficit and other clinical parameters have been developed, but require further validation [80, 81].

III. Rapid control of bleeding

R12

We recommend that patients with pelvic ring disruption in haemorrhagic shock undergo immediate pelvic ring closure and stabilisation. (Grade 1B)

R13

We recommend that patients with ongoing haemodynamic instability despite adequate pelvic ring stabilisation receive early angiographic embolisation or surgical bleeding control, including packing. (Grade 1B)

<u>Rationale:</u>

Markers of pelvic haemorrhage include anterior-posterior and vertical shear deformations, CT “blush” (active arterial extravasation), bladder compression pressure, pelvic haematoma volumes greater than 500 ml evident by CT, and ongoing haemodynamic instability despite adequate fracture stabilisation [82-85]. Initial therapy of pelvic fractures includes control of venous and/or canellous bone bleeding by pelvic closure [86]. Some institutions use primarily external fixators to control haemorrhage from pelvic fractures [82], however pelvic closure may also be achieved using a bed sheet, pelvic binder or a pelvic C-clamp [86-90]. Although arterial haemorrhage from pelvic fractures may be lethal, venous bleeding may be equally devastating. Arterial embolisation appears to achieve its effect by controlling the arterial bleeding and allowing the tamponade effect of the haematoma to control venous bleeding [91, 92].

Results of surgery to control pelvic haemorrhage via laparotomy have remained poor due to the existence of an extensive collateral circulation. However, in suboptimal situations, e.g. when embolisation is not possible, extraperitoneal packing of the pelvis may reduce the loss of blood. Extraperitoneal haemorrhage in patients with haemorrhagic shock and pelvic ring disruption may be attributed to ruptured veins, fracture surfaces and/or arterial sources. The overall mortality rate of patients with severe pelvic ring disruptions and haemodynamic instability remains as high as 30–45% [93]. Angioembolisation is often applied in patients with ongoing haemodynamic instability despite adequate fracture stabilisation and the exclusion of extra-pelvic sources of haemorrhage. Repeat angiography may be of value in those selected patients [86]. Patients who require embolisation tend to be older, have a higher injury severity score and are more likely to be coagulopathic and haemodynamically unstable than patients who not require embolisation [94].

R14

We recommend that early bleeding control be achieved by packing, direct surgical bleeding control and the use of local haemostatic procedures. In the exsanguinating patient, aortic cross clamping may be employed as an adjunct to achieve bleeding control. (Grade 1C)

<u>Rationale:</u>

The choice of thoracic or abdominal aortic clamping should be determined according to the site of bleeding, available surgical skill and speed. The patient in haemorrhagic shock in whom immediate aortic cross clamping is warranted is characterised by an injury to the torso and the severity of the blood loss and shock. The hypotensive state will not respond to the intravenous resuscitation and may lead to cardiac arrest. The cause of injury is predominantly penetrating e.g. a gunshot wound or a stab wound. Depending on the cause of injury, the mortality rate in these situations is extremely high [18, 19, 95]. However, when the source of bleeding is intraabdominal, thoracic aortic clamping combined with other measures for haemorrhage control can be life salvaging in nearly one third of patients according to Millikan and Moore [96, 97]. It is unclear whether the thoracic aortic-clamping should be performed before or after the abdominal incision [98]. No studies exist that compare thoracic aortic clamping above the diaphragm with abdominal aortic clamping just below the diaphragm, although the latter method is favoured by some surgeons [98].

The cross clamping of the aorta should be considered as an adjunct to other initial haemorrhage control measures such as the evacuation of blood, direct surgical bleeding control or packing of bleeding sources [99]. When aortic clamping is deemed necessary due to continuous bleeding or low blood pressure, the prognosis is generally poor [100]

R15

We recommend that damage control surgery be employed in the severely injured patient presenting with deep hemorrhagic shock, signs of ongoing bleeding and coagulopathy. Additional factors that should trigger a damage control approach are hypothermia, acidosis, inaccessible major anatomic injury, a need for time-consuming procedures or concomitant major injury outside the abdomen. (Grade 1C)

Rationale:

The severely injured patient arriving to hospital with continuous bleeding or in deep haemorrhagic shock generally has a poor chance of survival unless early control of bleeding, proper resuscitation and blood transfusion is achieved. This is particularly true for patients who present with uncontrolled bleeding due to multiple penetrating injuries as well as patients with multiple injuries and unstable pelvic fractures with ongoing bleeding from fracture sites and retroperitoneal vessels. The common denominator in these patients is the exhaustion of physiological reserves with resulting profound acidosis, hypothermia and coagulopathy. In the trauma community this is also called the “bloody vicious cycle” or the “lethal triad”. In 1983, Stone et al. described the technique of abbreviated laparotomy, packing to control haemorrhage and of deferred definitive surgical repair until coagulation had been established. In the meantime, a number of authors have described the beneficial results of this concept, which is now called “damage control” [31, 33, 87, 90, 101-104]. Damage control consists of three components. The first component is an abbreviated resuscitative laparotomy for control of bleeding, the restitution of blood flow where necessary and the control of contamination. This should be achieved as quickly as possible without spending unnecessary time on traditional organ repairs that can be deferred to a later phase. The abdomen is packed and temporary abdominal closure is performed. The second component is intensive care treatment, focused on core rewarming, correction of the acid-base imbalance and coagulopathy as well as optimising the ventilation and the haemodynamic status. Further diagnostic investigations are also frequently performed during this phase. The third component is the definitive surgical repair that is performed only when target parameters have been achieved [99, 105-107].

Despite the lack of controlled randomised studies comparing damage control to traditional surgical management, a retrospective review by Stone et al. presents data in favour of damage control for the severely injured presenting signs of coagulopathy during surgery [101]. In accordance, Rotondo et al. found similar results in a subgroup of patients with major vascular injury and two or more visceral injuries, and Carrillo et al. demonstrated the benefit of damage control in patients with iliac vessel injury [102, 103]. In addition, the cumulative review of 961 patients treated with damage control report an overall mortality and morbidity rate of 52% and 40% respectively [106].

IV. Tissue oxygenation, type of fluid and hypothermia

R16

We suggest a target systolic blood pressure of 80–100 mmHg until major bleeding has been stopped in the initial phase following trauma without brain injury. (Grade 2C)

<u>Rationale:</u>

In order to maintain tissue oxygenation, traditional treatment of trauma patients uses early and aggressive fluid administration to restore blood volume. This approach may, however, increase the hydrostatic pressure on the wound, cause a dislodgement of blood clots, a dilution of coagulation factors and undesirable cooling of the patient. The concept of low volume fluid resuscitation, so-called “permissive hypotension”, avoids the adverse effects of early aggressive resuscitation while maintaining a level of tissue perfusion that, although lower than normal, is adequate for short periods [108]. Its general effectiveness remains to be confirmed in randomised clinical trials, however studies have demonstrated increased survival when a low volume fluid resuscitation concept was used in penetrating trauma [109, 110]. In contrast, no significant difference was found in patients with blunt trauma [111]. One study concluded that mortality was higher after on-site resuscitation compared with in-hospital resuscitation [112]. It seems that greater increases in blood pressure are tolerated without exacerbating haemorrhage when they are achieved gradually and with a significant delay following the initial injury [113]. All the same, a recent Cochrane systematic review concluded that there is no evidence from randomised clinical trials for or against early or larger volume of intravenous fluids in uncontrolled haemorrhage [114]. The low volume approach is contraindicated in traumatic brain injury and spinal injuries, because an adequate perfusion pressure is crucial to ensure tissue oxygenation of the injured central nervous system. In addition, the concept of permissive hypotension should be carefully considered in the elderly patient and may be contraindicated if the patient suffers from chronic arterial hypertension.

Red blood cell (RBC) transfusion enables the maintenance of oxygen transport in some patients. Early signs of inadequate circulation are relative tachycardia, relative hypotension, oxygen extraction greater than 50% and PvO_2 <32 mmHg [115-117]. The depth of shock, hemdoynamic response to resuscitation and the rate of actual blood loss in the acutely bleeding and hemodynamically unstable patient may also be integrated into the indication for RBC transfusion. In general, RBC transfusion is recommended to maintain Hb between 7–9 g/dl [118].

R17

We suggest that crystalloids be applied initially to treat the bleeding trauma patient. Colloids may be added within the prescribed limits for each solution. (Grade 2C)

<u>Rationale:</u>

It is still unclear which type of fluid should be employed in the initial treatment of the bleeding trauma patient. Although several meta-analyses have shown an increased risk of death in patients treated with colloids compared with patients treated with crystalloids [119-123] and three of these studies showed that the effect was particularly significant in a trauma subgroup [119, 122, 123], a more recent meta-analysis showed no difference in mortality between colloids and crystalloids [124]. Problems in evaluating and comparing the use of different resuscitation fluids include the heterogeneity of populations and therapy strategies, limited quality of analysed studies, mortality not always being the primary outcome, and different, often short, observation periods. It is therefore difficult to reach a definitive conclusion as to the advantage of one type of resuscitation fluid over the other. The SAFE study compared 4% albumin with 0.9 % sodium chloride in 6997 ICU patients and showed that albumin administration was not associated with worse outcomes, however, there was a trend towards higher mortality in the trauma subgroup that received albumin (p=0.06) [125]. Promising results have been obtained with hypertonic solutions. One study showed that use of hypertonic saline was associated with lower intracranial pressure than with normal saline in brain-injured patients [126] and a meta-analysis comparing hypertonic saline dextran with normal saline for resuscitation in hypotension from penetrating torso injuries showed improved survival in the hypertonic saline dextran group when surgery was required [127]. A clinical trial with brain injury patients found that hypertonic saline reduces intracranial pressure more effectively than dextran solution with 20% mannitol [128]. However, Cooper et al. found almost no difference in neurological function 6 months after traumatic brain injury in patients who had received pre-hospital hypertonic saline resuscitation compared to conventional fluid [129].

R18

We recommend early application of measures to reduce heat loss and warm the hypothermic patient in order to achieve and maintain normothermia. (Grade 1C)

Rationale:

Hypothermia, defined as a core body temperature less than 35ºC, is associated with acidosis, hypotension and coagulopathy in severely injured patients. In a retrospective study with 122 patients, hypothermia was an ominous clinical sign, accompanied by high mortality and blood loss [130]. The profound clinical effects of hypothermia ultimately lead to higher morbidity and mortality, and hypothermic patients require more blood products [131].

Hypothermia is associated with an increased risk of severe bleeding, and hypothermia in trauma patients represents an independent risk factor for bleeding and death [132]. The effects of hypothermia include altered platelet function, impaired coagulation factor function (a 1ºC drop in temperature is associated with a 10% drop in function), enzyme inhibition and fibrinolysis. [133, 134] Body temperatures below 34ºC compromise blood coagulation, but this has only been observed when coagulation tests (PT and activated partial thromboplastin time) are carried out at the low temperatures seen in patients with hypothermia, and not when assessed at 37ºC, as is routine practice for such tests. Steps to prevent hypothermia and the risk of hypothermia-induced coagulopathy include removing wet clothing, covering the patient to avoid additional heat loss, increasing the ambient temperature, forced air warming, warm fluid therapy, and, in extreme cases, extracorporeal re-warming devices [135, 136].

Animal and human studies of controlled hypothermia in haemorrhage have shown some positive results compared with normothermia [137, 138]. In 2003 McIntyre [139] published a meta-analysis showing a beneficial effect on mortality rates and neurological outcome when using mild hypothermia in traumatic brain injury. In contrast, in 2004 one meta-analysis analyzed the effect of hypothermia in traumatic brain injury using the results of 8 studies with predefined criteria for randomised controlled trials; no reduction in mortality rates and only a slight benefit in neurological outcome could be demonstrated [140]. These contradictory results may be due to the different exclusion and inclusion criteria for the studies used for the analysis. Hendersen et al. included two studies in which patients without increased intracranial pressure were enrolled. Had these two studies been excluded from the meta-analysis, a benefit with respect to improved neurological outcome might have been demonstrated [141]. Moreover, the studies included differed with respect to the speed of induction and duration of hypothermia, which may be very important factors influencing the benefit of this treatment.

If mild hypothermia is applied in traumatic brain injury, cooling should take place within the first 3 h following injury, be maintained for ~48 h, rewarming should last 24 h, and the cerebral perfusion pressure should be maintained >50 mmHg (70 mmHg). Patients most likely to benefit from hypothermia are those with a GCS at admission between 4 and 7 [142]. Possible side effects are hypotension, hypovolaemia, electrolyte disorders, insulin resistance and reduced insulin secretion, and increased risk of infection [143]. Further studies are warranted to investigate the postulated benefit of hypothermia in traumatic brain injury taking these important factors into account.

V. Management of bleeding and coagulation

RBCs, FFP and platelets

R19

We recommend a target Hb of 7–9 g/dl. (Grade 1C)

<u>Rationale:</u>

Experimental evidence exists that erythrocytes are involved in the biochemical and functional responsiveness of activated platelets, suggesting that erythrocytes contribute to haemostasis. In addition to the rheological effect on the margination of platelets, red cells support thrombin generation [144]. However, the optimal haematocrit or haemoglobin concentration required to sustain haemostasis in massively bleeding patients is unclear. Further investigations into the role of the haemoglobin concentration on haemostasis in massively transfused patients are therefore warranted.

The specific effect of the Hct on blood coagulation is largely unknown [145]. An acute reduction of the Hct may result in an increase in the bleeding time [146, 147] with restoration upon re-transfusion [146]. This may be related to the presence of the enzyme elastase on the surface of RBC membranes, which may activate coagulation factor IX, thereby triggering blood coagulation [148, 149]. However, a moderate reduction of the Hct does not increase blood loss from a standard spleen injury [147], and an isolated in vitro reduction of the Hct did not compromise blood coagulation as assessed by thromboelastography [150].

No prospective randomised trial comparing restrictive and liberal transfusion regimens in trauma exists, however 203 trauma patients from the Transfusion Requirements in Critical Care (TRICC) trial [151] were re-analysed [118]. A restrictive transfusion regimen (Hb transfusion trigger <7.0 g/dl) resulted in fewer transfusions as compared with the liberal transfusion regimen (Hb transfusion trigger <10 g/dl) and appeared to be safe. However, no statistically significant benefit in terms of multiple organ failure or post-traumatic infections was observed. It should be emphasised that this study was neither designed nor powered to answer these questions with precision. In addition, it cannot be excluded that the number of RBC units transfused merely reflects the severity of injury. Therefore, the observed correlation between numbers of RBC units transfused and multiple organ failure [152] may reflect a correlation between the severity of injury and multiple organ failure. Adequately powered studies similar to the TRICC trial are therefore urgently needed in post-traumatic patients.

Despite the lack high level scientific evidence for a specific haemoglobin transfusion trigger in patients with traumatic brain injury, these patients are currently transfused in many centres to achieve a haemoglobin of around 10 g/dl [153]. This may be justified by the recent finding that increasing the haemoglobin from 8.7–10.2 g/dl improved local cerebral oxygenation [154]. It remains unclear, however, whether this practice will result in an improved neurologic outcome. Although the lowest haematocrit was correlated with adverse neurological outcome, in a recent retrospective study, RBC transfusions were equally found to be an independent factor for adverse neurological outcome [155]. Interestingly, the number of days with a haematocrit below 30% was found to be correlated with an improved neurological outcome. Therefore the authors suggest that patients with severe traumatic brain injury should not have a different haemoglobin transfusion threshold than other critically ill patients [155].

R20

We recommend treatment with thawed FFP in patients with massive bleeding or significant bleeding complicated by coagulopathy (PT or aPTT >1.5 times control). The initial recommended dose is 10–15 ml/kg, but further doses may be required. (Grade 1C)

<u>Rationale:</u>

The clinical efficacy of fresh frozen plasma (FFP) is largely unproven [156]. Nevertheless most guidelines recommend the use of FFP either in massive bleeding or in significant bleeding complicated by coagulopathy (PT, aPTT >1.5 times control) [7, 157, 158]. Patients treated with oral anticoagulants (vitamin K antagonists) present a particular challenge, and thawed FFP is recommended [158] only when prothrombin complex concentrate (PCC) is not available [157]. The most frequently recommended dose is 10–15 ml/kg [157, 158] however further doses may be required [159].

As with all products derived from human blood, the risks associated with FFP treatment include circulatory overload, ABO incompatibility, transmission of infectious diseases including the prion diseases, mild allergic reactions and particularly transfusion-related acute lung injury (TRALI) [157, 160, 161]. FFP and platelet concentrates appear to be the most frequently implicated blood products in TRALI [160-163]. Although the formal link between the administration of FFP, control of bleeding and an eventual improvement in the outcome of bleeding patients is lacking, most experts would agree that FFP treatment is beneficial in patients with massive bleeding or significant bleeding complicated by coagulopathy.

R21

We recommend that platelets be administered to maintain a platelet count above 50×10^9/l (Grade 1C). We suggest maintenance of a platelet count above 100×10^9/l in patients with multiple trauma who are severely bleeding or have traumatic brain injury. (Grade 2C). We suggest an initial dose of 4–8 platelet concentrates or one apheresis pack. (Grade 2C)

<u>Rationale:</u>

In medical conditions leading to thrombocytopenia, haemorrhage does not often occur until the platelet count falls to less than 50×10^9/l, and platelet function decreases exponentially below this point. [164-167]. There is no direct evidence to support a particular platelet transfusion threshold in the trauma patient. An NIH-sponsored consensus development conference held in 1986 determined that bleeding is unlikely to be caused by thrombocytopenia at platelet counts of 50×10^9/l or greater, and agreed that platelet transfusion is appropriate to prevent or control bleeding associated with deficiencies in platelet number or function [168, 169]. The NIH consensus did not consider trauma, however it seems reasonable to recommend that a platelet count of at least 50×10^9/l should be maintained following injury.

An argument can be made for maintaining a higher level of platelets, perhaps up to 100×10^9/l, following injury. If a patient has increased fibrin degradation products, for example in patients with massive bleeding, disseminated intravascular coagulation or hyperfibrinolysis, this will interfere with platelet function and a higher threshold of 75×10^9/l has been suggested by consensus groups [170, 171]. Transfusion threshold levels of up to a 100×10^9/l threshold have been suggested for treatment of severe brain injury and massive haemorrhage, however the evidence for the higher threshold is weak [170, 171].

When platelet transfusion was introduced in the 1950s, no clinical trials were employed to assess the utility of platelet therapy compared to placebo, and such trials today might be considered unethical. The appropriate dose of platelets is therefore uncertain. Platelet concentrate produced from a unit of whole blood contains on average, 7.5×10^{10} platelets and should increase the platelet count by $5–10\times10^{9}$/l in a 70 kg recipient. Apheresis platelet concentrates generally contain approximately $3–6\times10^{11}$ platelets, depending on local collection practice, and physicians should be cognisant of the doses provided locally. A pool of 4–8 platelet concentrates or a single donor apheresis unit is usually sufficient to provide haemostasis in a thrombocytopenic, bleeding patient.

If required, the dose of platelets ($\times10^{9}$) can be calculated in more detail from the desired platelet increment, the patient's blood volume in litres (estimated by multiplying the patient's body surface area by 2.5, or 70 ml/kg in an adult) and a correction factor of 0.67 to allow for pooling of approximately 33% of transfused platelets in the spleen.

R22

We recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by a plasma fibrinogen level less than 1 g/l. We suggest an initial fibrinogen concentrate dose of 3–4 g or 50 mg/kg of cryoprecipitate approximately equivalent to 15–20 units in a 70 kg adult. Repeat doses should be guided by laboratory assessment of fibrinogen levels. (Grade 1C)

Rationale:

Cryoprecipitate or fibrinogen are used for the correction of both inherited and acquired hypofibrinogenaemia. Their use is based on the assumption that low fibrinogen levels are associated with a risk of bleeding, and that the achievement of higher levels of fibrinogen decreases that risk. The evidence for the clinical efficacy of cryoprecipitate and fibrinogen in trauma patients is limited; no clinical randomised studies have been performed to determine whether the administration of cryoprecipitate or fibrinogen improves clinical outcome in severely bleeding trauma patients. Only indirect observational studies are available, however this evidence suggests that clinically significant bleeding decreases in variety of clinical scenarios following treatment with both agents. Hypofibrinogenaemia responds well to treatment with cryoprecipitate concentrate [172]. Administration of fibrinogen was associated with bleeding control in patients with generalised, mostly traumatic, bleeding [173]. Administration of 4 g of fibrinogen raised fibrinogen levels from 0.1–1 g/l and bleeding control was achieved in patients with bleeding associated with uterine rupture and abortion [174]. A few observational studies report the successful use of fibrinogen in patients with congenital afibrinogenaemia [175-177]. The optimal initial dose has not been defined, and regional differences in cryoprecipitate and fibrinogen preparations exist, however available evidence suggests that an initial dose of cryoprecipitate or fibrinogen should raise fibrinogen plasma level above 1 g/l in order to provide sufficient haemostasis [174, 176, 178].

There are no specific risks related to administration of fibrinogen or cryoprecipitate other than the risks associated with other blood components and the increased risk associated with pooled vs. single-donor blood products. Fibrinogen or cryoprecipitate can have unpredictable adverse effects. Of particular concern are allergic reactions and anaphylaxis. There are no reported specific adverse events related to administration of fibrinogen or cryoprecipitate in patients with hypofibrinogenaemia.

Pharmacological agents

A large body of evidence for the use of antifibrinolytic agents for the management of bleeding in elective surgery and cardiac surgery patients exists. For the purpose of these guidelines, we have assumed that these effects are transferable to trauma patients, and our recommendation is based upon this unproven assumption.

R23

We suggest that antifibrinolytic agents be considered in the treatment of the bleeding trauma patient. Suggested dosages are tranexamic acid 10–15 mg/kg followed by an infusion of 1–5 mg/kg/h; ε-aminocaproic acid 100–150 mg/kg followed by 15 mg/kg/h; or, after a test dose, aprotinin 2 million KIU immediately followed by 500,000 KIU/h in an intravenous infusion. Antifibrinolytic therapy should be stopped once bleeding has been adequately controlled. (Grade 2C)

<u>Rationale:</u>

Tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid) is a synthetic lysine analogue that is a competitive inhibitor of plasmin and plasminogen. Tranexamic acid is distributed throughout all tissues and the plasma half-life is 120 min. There is large variation in the dose employed. In vitro studies have suggested that a dose of 10 μg/ml is required to inhibit fibrininolysis [179]. Studies of plasma levels [180] confirmed that the Horrow regime (10 mg/kg followed by 1 mg/kg/h) [181], shown to reduce blood loss in cardiac surgery, attained these levels. Other studies have used boluses of up to 5 g per patient [182] with no ill effect.

ε-aminocaproic acid is also a synthetic lysine analogue that has a potency 10-fold weaker than tranexamic acid. It is therefore administered in a loading dose of 150 mg/kg followed by a continuous infusion of 15 mg/h. The initial elimination half-life is 60–75 min and must therefore be administered by continuous infusion in order to maintain therapeutic drug levels until the bleeding risk has diminished.

Aprotinin is a broad spectrum serine protease inhibitor isolated from bovine lung, which forms irreversible inhibitory complexes with a number of serine proteases. In particular, it is a powerful antiplasmin agent, and the initial elimination of aprotinin is 1.5–2 h [183]. The “high-dose” regime [184] (2 M KIU to patient and cardiopulmonary bypass prime and an infusion of 500,000 KIU/h) has been shown to reduce perioperative bleeding in open cardiac surgery. Lower doses do produce adequate antiplasmin effects, however. A dose of 2 M units is approved for the treatment of hyperfibrinolysis.

The clear efficacy of antifibrinolytic agents in elective surgery and especially in cardiac surgery has been shown in numerous clinical trials [184, 185]. A larger number of trials to evaluate the efficacy aprotinin have been published than assessments of lysine analogue efficacy. It may be possible to extrapolate the benefits of antifibrinolytic agents to bleeding secondary to trauma, however this assumption is not backed by any published data suggesting that the haemostatic response to trauma is similar to the haemostatic response to elective surgery. Insufficient evidence from randomised, controlled trials of antifibrinolytic agents in trauma patients to either support or refute a clinically important treatment effect exists. Further randomised controlled trials of antifibrinolytic agents in trauma patients are required [186]. The efficacy of tranexamic acid in trauma will be assessed by the ongoing the CRASH II study (www.CRASH2.LSHTM.ac.uk), in which 20,000 trauma patients worldwide are being randomised to 1 g tranexamic acid over 10 min followed by 1 g infused over 8 h.

The risk of precipitated thrombosis with the use of antifibrinolytic agents has been of major theoretical concern, however the Cochrane review of antifibrinolytics cites studies that included over 8000 patients and demonstrated no increased risk of either arterial or venous thrombotic events [187]. All antifibrinolytics are renally excreted and accumulate in individuals with renal failure, therefore dosage should be reduced in patients with renal failure. In practice, mild degrees of renal failure do not seem to affect outcome.

Because aprotinin is a bovine protein with an associated risk of anaphylaxis, a test dose must be given. After high-dose aprotinin as many as 50% of patients develop specific IgG antibodies within 3 months of exposure. The manufacturer estimates a 0.5% overall risk of anaphylactic reactions following aprotinin treatment, which may increase to 6–9% following re-exposure [183].

An open study by Mangano et al. suggested that aprotinin usage in cardiac surgery was associated with an increased risk of myocardial infarction, stroke and renal failure [188]. A further publication cited an increased risk of renal problems in patients receiving aprotinin compared to tranexamic acid [189]. Because the Mangano et al. study was open, it remains unclear whether sicker patients in the study may have preferentially received aprotinin. The results of a blinded comparative study of aprotinin vs. tranexamic acid vs. ε-aminocaproic acid [190] which aims to recruit 3,000 patients will assess safety and efficacy issues in cardiac surgery. At present, in light of the current US Food and Drug Administration warning against the use of aprotinin [191], the greater cost associated with aprotinin use and the need to give a test dose, often impractical in an emergency situation, we favour the use of tranexamic acid or ε-aminocaproic acid in trauma patients.

Factor replacement

R24

We suggest that the use of rFVIIa be considered if major bleeding in blunt trauma persists despite standard attempts to control bleeding and best practice use of blood components. We suggest an initial dose of 200 μg/kg followed by two 100 μg/kg doses administered at 1 and 3 h following the first dose. (Grade 2C)

<u>Rationale:</u>

Recombinant activated coagulation factor VII (rFVIIa) is not a first-line treatment for bleeding, and rFVIIa will only be effective once sources of major bleeding have been controlled. Once major bleeding from damaged vessels has been stopped, rFVIIa may be helpful to induce coagulation in areas of diffuse small vessel coagulopathic bleeding. rFVIIa should only be considered if first-line treatment with a combination of surgical approaches and best practice use of blood products (RBCs, platelets, FFP, and cryoprecipitate/fibrinogen resulting in Hct >24%, platelets >50,000x10^9/l and fibrinogen >0.5–1.0 g/l), correction of severe acidosis, severe hypothermia and hypocalcaemia (resulting in pH >7.20, temperature >32ºC, and ionised Ca++ >0.8 mmol/l) fail to control bleeding. Since rFVIIa acts on the patient's own clotting system, a sufficient number of platelets are needed to allow a thrombin burst to be induced by the pharmacological, supraphysiological doses of rFVIIa through direct binding to activated platelets [192, 193]. Reduction in platelet count may lead to impaired thrombin generation [194]. Moreover, fibrinogen is required in order to ensure formation of a stable clot [158, 195]. A recent study showed that a pH below 7.20 will substantially reduce rFVIIa activity, whereas the same study demonstrated that temperature >32ºC only slightly improved rFVIIa activity [196]. Independent of rFVIIa activity, however, pH and body temperature should be restored to as near physiological levels as possible, since even small reductions in pH and temperature may result in slower coagulation enzyme kinetics [133, 134, 197]. Moreover, hypocalcaemia is frequently present in severely injured patients [198] and may require the administration of i.v. calcium with frequent ionised serum calcium measurement [199].

A number of case studies and case series have reported that treatment with rFVIIa can be beneficial in the treatment of coagulopathic bleeding following trauma [200-203]. A recently published multicentre, randomised, double-blind, placebo-controlled study examined the efficacy of rFVIIa in patients with blunt or penetrating trauma [204]. Patients were randomised to receive either three doses of rFVIIa (200, 100 and 100 µg/kg) or placebo after they had received 6 units of RBC, and received the first dose of their assigned medication following transfusion of a further 2 units of RBC (8 in total), followed by a second and third dose, 1 and 3 h after the initial dose. Treatment with rFVIIa in blunt trauma produced a significant reduction in RBC transfusion requirements and the need for massive transfusions (>20 units RBC) in patients with blunt trauma surviving for more than 48 h, and also significantly reduced the incidence of acute respiratory distress syndrome in all patients with blunt trauma. In contrast, no significant effects were seen on RBC transfusion requirements in the penetrating trauma patients in this study, although trends towards reduced RBC requirements and fewer massive transfusions were observed. Therefore, no recommendation can be made to use the drug in this group.

The required dose(s) of rFVIIa is still under debate. Whereas the above dosing recommendation is based on the only published RCT available in trauma patients, and is also recommended by a group of European experts [205], Israeli guidelines based on findings from a case series of 36 patients who received rFVIIa on a compassionate-use basis in Israel [200] propose an initial dose of 120 μg/kg (between 100 and 140 μg/kg), with a second and third dose if required. Further support for the dose regimen recommended here, comes from pharmacokinetic modelling techniques, which have shown that the dose regimen for rFVIIa treatment used in the above cited RCT is capable of providing adequate plasma levels of drug to support haemostasis [206]. If rFVIIa is administered, the patient's next of kin should be informed that rFVIIa is being used outside the currently approved indications (off-label use), especially since the use of rFVIIa may increase the risk of thromboembolic complications [207].

R25

We recommend the use of prothrombin complex concentrate according to the manufacturer's instructions only for the emergency reversal of vitamin K-dependent oral anticoagulants. (Grade 1C)

<u>Rationale:</u>

Despite its common use, there is no clear indication for prothrombin complex concentrate (PCC) use in bleeding non-haemophilia patients. The evidence of clinical efficacy of PCC in patients without haemophilia is limited, and no clinical randomised studies have been performed to determine whether administration of PCC improves clinical outcome in severely bleeding trauma patients. PCC has been used to control bleeding in haemophilia patients [208-210] or to reverse effect of oral anticoagulant agents [211, 212]. The American Society of Anesthesiology recommends the use of prothrombin complex concentrate in patients with clinical coagulopathy and prolonged prothrombin time >1.5 times normal [158]. Because there are variations in the production of PCC, the dosage should be determined according to the instructions of the individual manufacturer [213].

Administration of prothrombin complex concentrate may carry the risk of venous and arterial thrombosis or disseminated intravascular coagulation [214, 215], however the type of surgery has no influence on the type and severity of these complications [216]. Decreased clearance of activated clotting factor complexes increase the likelihood of these complications in patients with liver disease [217].

R26

We do not recommend the use of antithrombin III in the treatment of the bleeding trauma patient. (Grade 1C)

Antithrombin concentrates are indicated in inherited and acquired antithrombin deficiency. Although antithrombin deficiency does occur in consumptive coagulopathy, this is not an isolated condition; all coagulation factors and physiological anticoagulants undergo consumption under these circumstances. The best replacement therapy is fresh frozen plasma. Clinical studies of antithrombin concentrate in severe blunt trauma and in critical care have shown no benefit [218, 219].

DISCUSSION

These guidelines for the management of the bleeding trauma patient are based on a critical appraisal of the published literature and formulated according to a consensus reached by the author group and the professional societies involved. We have attempted to address a number of critical issues faced by the treating physician confronted with a critically bleeding patient in an evidence-based manner. Figure 1 graphically summarises the recommendations included in this guideline. Unfortunately in emergency medicine, a number of pivotal issues have not, and may never be, addressed in randomised clinical trials due to ethical and practical considerations. This reality renders the need for best-practice guidelines even more acute.

Although the emphasis in these guidelines has been on the management of critical bleeding in the trauma patient, the high risk of venous thromboembolism in trauma patients should always be kept in mind, and thromboprophylactic treatment considered once bleeding has been controlled [220]. In addition, a conscious decision was made to exclude animal studies from the literature reviewed for the development of these guidelines. Because no animal model that accurately mimics the human coagulation system exists, randomised controlled trials in humans provide the strongest evidence for the management of bleeding in humans.

We have made an effort to consider a number of specific patient subgroups which may require treatment that has been adapted to their physiological condition. Very little evidence exists, however, to support specific recommendations for these special patient groups. The physiology of elderly patients with respect to coagulopathy is probably not different than younger adults, however the bleeding patient who has been treated with an anticoagulant or an antiplatelet agent may present with a greater risk of coagulopathic bleeding. We have also considered the management of bleeding following injury in children. There is generally a more conservative approach to the surgical management of bleeding in children, and some evidence that commonly-quoted age-related physiological norms are not applicable to the injured child exists. There is, however, little evidence for specific differences in bleeding and coagulation management in children, therefore, we suggest that these guidelines should be applied to both adults and children until more specific research data becomes available.

The apparent weakness of much of the published evidence cited in this work highlights the need for further clinical studies, and underlines the importance of future research that may lead to more clear-cut evidence-based clinical guidelines. The GRADE system employed in developing these guidelines [8] is appropriate in that it allows strong recommendations to be supported by weak clinical evidence in a field where many of the ideal randomised controlled clinical trials may never be performed. Other systems, such as the grades of recommendation developed by the Oxford Centre for Evidence-based Medicine [9], may be less dependent on the weight of expert opinion, therefore the process employed between the published evidence and guideline recommendation must be transparent in order to ensure acceptance and implementation of the guideline. To minimise the bias introduced by individual experts, this guideline employed a nominal group process to develop each recommendation, several Delphi rounds to reach an agreement on the questions to be considered and to reach a final consensus on each recommendation, and the composition of the group consisted of a multidisciplinary pan-European group of experts, including the active involvement of representatives from five of the most relevant European professional societies.

CONCLUSION

We have made every effort to make these guidelines applicable in daily practice in a variety of clinical settings. We wish to emphasise our conviction that a multidisciplinary approach to management of the bleeding trauma patient will assist in creating circumstances in which optimal care can be provided. By their very nature, these guidelines reflect the current state-of-the-art and will need to be updated and revised regularly as important new evidence becomes available.

KEY MESSAGES

- This guideline to clinical practice provides evidence-based recommendations developed by a multidisciplinary task force with respect to many aspects of the acute management of the bleeding trauma patient, which when implemented may lead to improved patient outcomes.
- The time elapsed between injury and operation should be minimised for patients in need of urgent surgical bleeding control, and patients presenting in haemorrhagic shock and an identified source of bleeding should undergo immediate surgical bleeding control unless initial resuscitation measures are successful.
- Patients presenting with haemorrhagic shock and an unidentified source of bleeding should undergo immediate further assessment as appropriate using focused sonography, computed tomography, serum lactate and/or base deficit measurements.
- A damage control surgical approach is essential in the severely injured patient, which may include the closure and stabilization of pelvic ring disruptions, followed by appropriate angiographic embolisation or surgical bleeding control, including packing.
- This guideline also reviews appropriate physiological targets and suggested use and dosing of blood products, pharmacological agents and coagulation factor replacement in the bleeding trauma patient.

ABBREVIATIONS

ACS	American College of Surgeons
aPTT	Activated partial thromboplastin time
ATLS	Advanced Trauma Life Support
CT	Computerised tomography
DPL	Diagnostic peritoneal lavage
ESA	European Society for Anaesthesia
ESICM	European Society for Intensive Care Medicine
ESS	European Shock Society
ETS	European Trauma Society
EuSEM	European Society for Emergency Medicine
FAST	Focused abdominal sonography in trauma
FFP	Fresh frozen plasma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hct	Haematocrit
LoE	Level of evidence
MeSH	Medical Subject Heading
MSCT	Multi-slice spiral computed tomography
PCC	Prothrombin complex concentrate
PEEP	positive end-expiratory pressure
PT	Prothrombin time
RBC	Red blood cell
rFVIIa	Recombinant activated coagulation factor VII
TRALI	Transfusion-related acute lung injury
TRICC	Transfusion Requirements in Critical Care

COMPETING INTERESTS

- In the past 5 years, **DRS** has received honoraria for consulting or lecturing from the following companies: Abbott, Alliance Pharmaceutical, Astra-Zeneca, B. Braun, Fresenius, GlaxoSmithKline, Janssen-Cilag, Kabi, Novo Nordisk, Organon, Roche and ZLB Behring. He serves as chair of the Advanced Bleeding Care (ABC) European medical education initiative and as co-chair of the ABC-Trauma (ABC-T) European medical education initiative, both of which are managed by Thomson Physicians World GmbH and supported by educational grants from Novo Nordisk; he represented the European Society of Anaesthesiologists on the ABC-T Task Force.
- **VC** is a member of the ABC and ABC-T European medical education initiative faculties.
- **TJC** has has received honoraria for consulting and lecturing for Novo Nordisk and is a member of the ABC-T European medical education initiative faculty. In the past 5 years his research group has received research grant funding from Pfizer, the Moulton Foundation, Novo Nodisk, Barts and the London Special Trustees, Boehringer Ingelheim and the Anthony Hopkins Memorial fund.
- **JD** is a member of the ABC-T European medical education initiative faculty.
- **EF-M** has received honoraria for consulting from Pulsion Mecial Systems and is a member of the ABC-T European medical education initiative faculty.
- **GG** is a member of the ABC-T European medical education initiative faculty.
- **PS** has received honoraria for lecturing for Novo Nordisk and is a member of the ABC-T European medical education initiative faculty.
- **BJH** has received educational grants or honoraria for lecturing from the following companies: Astra Zeneca, GlaxoSmithKlein, Novo Nordisk and Sanofi Aventis.
- **RK** represented the European Trauma Society on the ABC-T Task Force.
- **EN** has received honoraria for consulting or lecturing from the following companies in the past 5 years: Biotest, Bristol-Myers-Squibb, Cook, Novo Nordisk, Pfizer and

Sanofi-Aventis. He has received study grants from Bristol Myers Squibb, Choice Medical Communications, Mundipharma and Novo Nordisk.

- In the past 5 years, **YO** has received institutional support from Bayer Pharma, Novo Nordisk and LFB for consulting or lecturing; he represented the European Society of Intensive Care Medicine on the ABC-T Task Force.
- **LR** represented the European Society for Emergency Medicine on the ABC-T Task Force.
- **AS** represented the European Shock Society on the ABC-T Task Force.
- **J-LV** has received honoraria from the following companies: Abbott, AM Pharma, Asahi, AstraZeneca, Baxter, Biomerieux, Biosite, Edwards, Eli Lilly, Esai, Ferring, Novo Nordisk, Pfizer, Pulsion, Takeda, Theravance and Wyeth.
- **RR** has received honoraria for consulting or lecturing from the following companies: Air Liquide, Bayer, the German Working Group for Arthroscopy (Deutsche Arbeitsgemeinschaft für Arthroskopie) (AGA), Lilly, Messer Griesheim (Messer Group GmbH), Novo Nordisk and ZLB Behring; he serves as the chair of the ABC-T European medical education initiative.

AUTHORS' CONTRIBUTIONS

All of the authors participated in the formulation of questions to be addressed in the guideline, screening of abstracts and literature, face-to-face and remote consensus-finding processes, drafting, review, revision and approval of the manuscript.

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FIGURES

Figure 1. Flow chart of treatment aspects for the bleeding trauma patient discussed in this guideline.

TABLES

Table 1. Grading of recommendations after Guyatt et al.

Grade of Recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendations, can apply to most patients in most circumstances without reservation
1B Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendations, can apply to most patients in most circumstances without reservation
1C Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C Weak recommendation, Low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

Table 2. American College of Surgeons Advanced Trauma Life Support classification of haemorrhage severity.

*Haemorrhage severity according to ACS/ATLS classification**	**Class I**	**Class II**	**Class III**	**Class IV**
Blood loss (ml)	<750	750–1500	1500–2000	>2000
Pulse rate (/min)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal	Decreased	Decreased	Decreased
Respiratory rate (/min)	14–20	20–30	30–40	>40
Urine output (ml/h)	>30	20–30	5–15	Negligible
CNS (mental status)	Slightly anxious	Mildly anxious	Anxious, confused	Lethargic

* estimated numbers are for a 70 kg adult

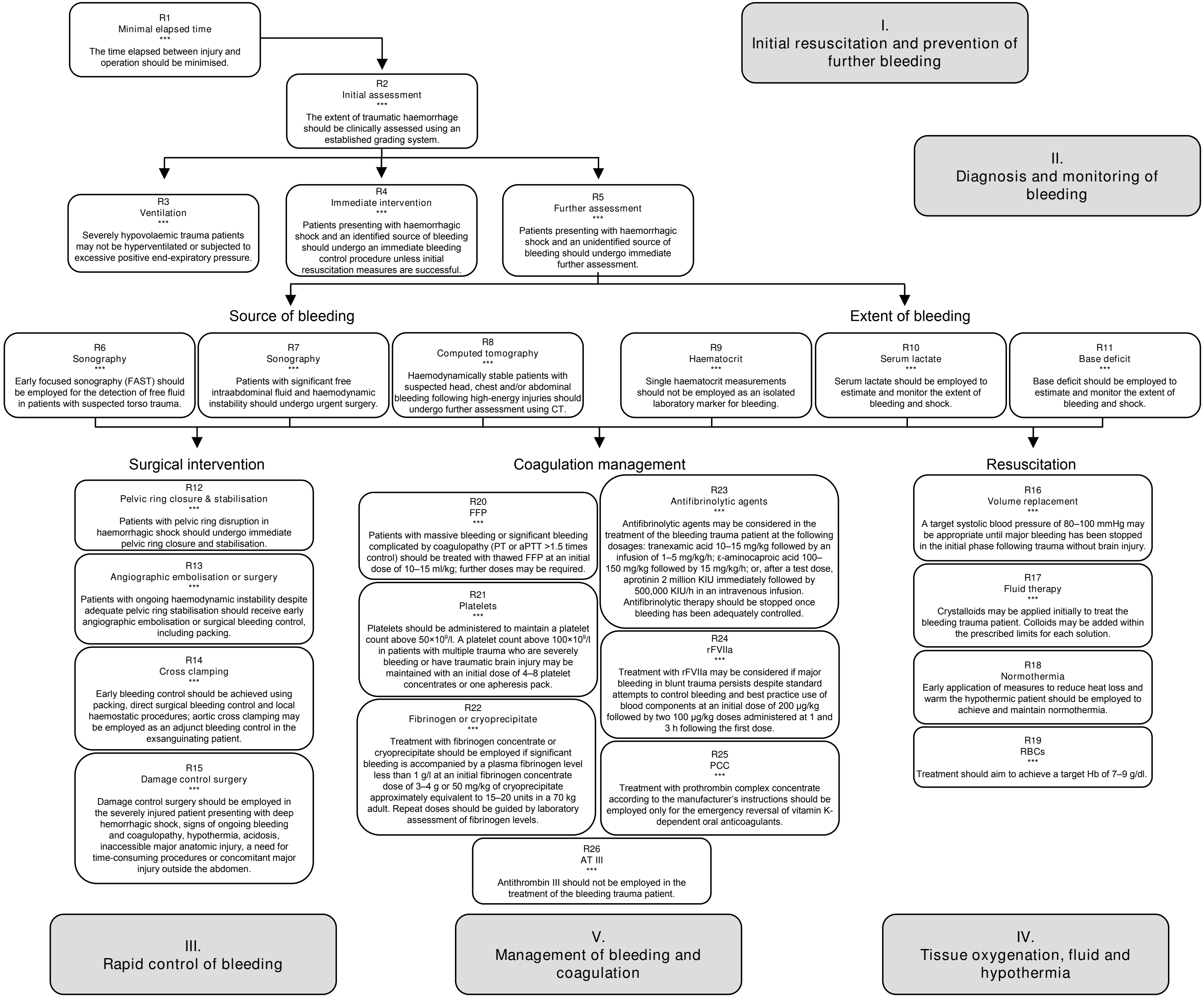
Table reprinted with permission from the American College of Surgeons [26]

ACS; American College of Surgeons

ATLS; Advanced Trauma Life Support

CNS; central nervous system

Figure 1


I.
Initial resuscitation and prevention of further bleeding
R1
Minimal elapsed time
***
The time elapsed between injury and operation should be minimised.
R2
Initial assessment
***
The extent of traumatic haemorrhage should be clinically assessed using an established grading system.
R3
Ventilation
***
Severely hypovolaemic trauma patients may not be hyperventilated or subjected to excessive positive end-expiratory pressure.
R4
Immediate intervention
***
Patients presenting with haemorrhagic shock and an identified source of bleeding should undergo an immediate bleeding control procedure unless initial resuscitation measures are successful.
R5
Further assessment
***
Patients presenting with haemorrhagic shock and an unidentified source of bleeding should undergo immediate further assessment.
II.
Diagnosis and monitoring of bleeding
Source of bleeding
Extent of bleeding
R6
Sonography
***
Early focused sonography (FAST) should be employed for the detection of free fluid in patients with suspected torso trauma.
R7
Sonography
***
Patients with significant free intraabdominal fluid and haemodynamic instability should undergo urgent surgery.
R8
Computed tomography
***
Haemodynamically stable patients with suspected head, chest and/or abdominal bleeding following high-energy injuries should undergo further assessment using CT.
R9
Haematocrit
***
Single haematocrit measurements should not be employed as an isolated laboratory marker for bleeding.
R10
Serum lactate
***
Serum lactate should be employed to estimate and monitor the extent of bleeding and shock.
R11
Base deficit
***
Base deficit should be employed to estimate and monitor the extent of bleeding and shock.
Surgical intervention
Coagulation management
Resuscitation
R12
Pelvic ring closure & stabilisation
***
Patients with pelvic ring disruption in haemorrhagic shock should undergo immediate pelvic ring closure and stabilisation.
R13
Angiographic embolisation or surgery
***
Patients with ongoing haemodynamic instability despite adequate pelvic ring stabilisation should receive early angiographic embolisation or surgical bleeding control, including packing.
R14
Cross clamping
***
Early bleeding control should be achieved using packing, direct surgical bleeding control and local haemostatic procedures; aortic cross clamping may be employed as an adjunct bleeding control in the exsanguinating patient.
R15
Damage control surgery
***
Damage control surgery should be employed in the severely injured patient presenting with deep hemorrhagic shock, signs of ongoing bleeding and coagulopathy, hypothermia, acidosis, inaccessible major anatomic injury, a need for time-consuming procedures or concomitant major injury outside the abdomen.
R20
FFP
***
Patients with massive bleeding or significant bleeding complicated by coagulopathy (PT or aPTT >1.5 times control) should be treated with thawed FFP at an initial dose of 10–15 ml/kg; further doses may be required.
R21
Platelets
***
Platelets should be administered to maintain a platelet count above 50×10⁹/l. A platelet count above 100×10⁹/l in patients with multiple trauma who are severely bleeding or have traumatic brain injury may be maintained with an initial dose of 4–8 platelet concentrates or one apheresis pack.
R22
Fibrinogen or cryoprecipitate
***
Treatment with fibrinogen concentrate or cryoprecipitate should be employed if significant bleeding is accompanied by a plasma fibrinogen level less than 1 g/l at an initial fibrinogen concentrate dose of 3–4 g or 50 mg/kg of cryoprecipitate approximately equivalent to 15–20 units in a 70 kg adult. Repeat doses should be guided by laboratory assessment of fibrinogen levels.
R23
Antifibrinolytic agents
***
Antifibrinolytic agents may be considered in the treatment of the bleeding trauma patient at the following dosages: tranexamic acid 10–15 mg/kg followed by an infusion of 1–5 mg/kg/h; ε-aminocaproic acid 100–150 mg/kg followed by 15 mg/kg/h; or, after a test dose, aprotinin 2 million KIU immediately followed by 500,000 KIU/h in an intravenous infusion. Antifibrinolytic therapy should be stopped once bleeding has been adequately controlled.
R24
rFVIIa
***
Treatment with rFVIIa may be considered if major bleeding in blunt trauma persists despite standard attempts to control bleeding and best practice use of blood components at an initial dose of 200 µg/kg followed by two 100 µg/kg doses administered at 1 and 3 h following the first dose.
R25
PCC
***
Treatment with prothrombin complex concentrate according to the manufacturer's instructions should be employed only for the emergency reversal of vitamin K-dependent oral anticoagulants.
R26
AT III
***
Antithrombin III should not be employed in the treatment of the bleeding trauma patient.
R16
Volume replacement
***
A target systolic blood pressure of 80–100 mmHg may be appropriate until major bleeding has been stopped in the initial phase following trauma without brain injury.
R17
Fluid therapy
***
Crystalloids may be applied initially to treat the bleeding trauma patient. Colloids may be added within the prescribed limits for each solution.
R18
Normothermia
Early application of measures to reduce heat loss and warm the hypothermic patient should be employed to achieve and maintain normothermia.
R19
RBCs
***
Treatment should aim to achieve a target Hb of 7–9 g/dl.
III.
Rapid control of bleeding
V.
Management of bleeding and coagulation
IV.
Tissue oxygenation, fluid and hypothermia

Additional files provided with this submission:

Additional file 1: additional data file 1.doc, 130K
http://ccforum.com/imedia/1746053240121454/supp1.doc