Title:

What's new for trauma haemorrhage management?

Short Title:

Management of trauma haemorrhage

Authors:

Paul Vulliamy[1]

Anthony J Thaventhiran[1]

Ross A Davenport[1]

[1]Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London

Address for Correspondence:

Dr Ross A. Davenport

Blizard Institute, Whitechapel, London, United Kingdom, E1 2AT

Email: r.a.davenport@qmul.ac.uk

Abstract:

Uncontrolled haemorrhage is the leading cause of preventable death from injury and is a major contributor to the global burden of disease. The majority of deaths due to bleeding occur within the first three hours of hospital admission, and the window for meaningful intervention is therefore extremely small. Resuscitative efforts during active bleeding should focus on maintaining haemostatic function with blood product transfusion and early administration of tranexamic acid. Achieving control of haemorrhage is the overarching treatment priority and may require temporising measures prior to definitive surgical or radiological intervention. This review will summarise the contemporary approaches to resuscitation of bleeding trauma patients, options for achieving haemorrhage control, and current areas of active research including organ protective resuscitation and suspended animation.

MANUSCRIPT TEXT

Introduction

Physical injuries are a leading cause of death and disability worldwide. An estimated 1 billion injuries requiring healthcare occur each year, accounting for around 5 million deaths and 10% of the total global burden of disease (Global Burden of Disease Collaborators, 2017). Uncontrolled haemorrhage is the leading cause of preventable death from injury, the majority of which occur within the first three hours of hospital admission (Bardes et al, 2018). Modern trauma systems and resuscitation practices have therefore evolved to prioritise early definitive haemorrhage control whilst supporting haemostasis during active bleeding.

This review will summarise the current approaches to the management of traumatic haemorrhage, with reference to the National Institute for Clinical Excellence (NICE) guidelines for the management of major trauma (NICE, 2016). We will discuss the principles and practicalities of resuscitation during active bleeding, current strategies to achieve temporary and definitive haemorrhage control, and future directions for organ preservation during and after massive bleeding.

Resuscitation of the Bleeding Trauma Patient

Permissive Hypotension

Avoiding rapid normalisation of blood pressure during active bleeding is known as permissive hypotension. This strategy, first described during World War I, works on the principle that increases in blood pressure risk 'popping the clot' and therefore inducing further bleeding. The finding that early aggressive fluid resuscitation in patients with penetrating trauma results in increased mortality has led to the widespread incorporation of permissive hypotension into trauma resuscitation protocols (Bickell et al, 1994). Although there is solid pre-clinical evidence for this approach, clinical data is equivocal (Morrison et

al, 2011, Carrick et al, 2016). A restrictive volume replacement strategy is recommended in patients with haemorrhagic shock during active bleeding, but caution should be exercised in patients with a suspected concomitant brain injury in order to maintain adequate cerebral perfusion pressure.

Trauma-induced coagulopathy

Up to a quarter of all severely injured patients have impaired haemostatic function by the time of arrival in hospital (Brohi et al, 2003). This state, termed acute traumatic coagulopathy (ATC), develops within minutes of injury as an endogenous response to tissue damage and shock, and is characterised by a reduction in clot strength coupled with excessive clot breakdown (Davenport et al, 2011). It is associated with persistent uncontrolled bleeding, increased transfusion requirements and a four-fold higher mortality (Davenport et al, 2011). Efforts at resuscitation can add to this coagulopathy by causing dilution, acidaemia and hypothermia. Trauma-induced coagulopathy (TIC) is therefore a complex, multifactorial condition with both endogenous and iatrogenic elements. The pathophysiology and diagnosis of this state have been discussed in detail elsewhere (Davenport and Brohi, 2016). For the clinician managing major bleeding in the injured patient, awareness of ATC/TIC is essential to prioritise appropriate therapy during active haemorrhage.

Balanced Resuscitation

Balanced or haemostatic resuscitation is the principle of supporting haemostasis whilst bleeding is ongoing with the empiric provision of blood and blood products. A central component of this practice is administration of high volumes of fresh frozen plasma (FFP) and platelet concentrates alongside packed red blood cells (PRBCs). This practice is supported by a number of cohort studies and by the PROPPR randomised trial, which found reduced deaths due to haemorrhage in patients treated with a 1:1:1 ratio of FFP:Platelets:PRBCs as compared to a 1:1:2 ratio (Holcomb et al, 2015, Balvers et al, 2017) Early initiation of a fixed-ratio 1:1:1 resuscitation strategy is recommended by the NICE guidelines (**table 1**). Crystalloid infusion results in a dilutional coagulopathy and is associated

with worse outcomes when given during active haemorrhage (Neal et al, 2012). It should be avoided in the in-hospital setting, and only given in small volumes in the prehospital setting to patients *in extremis* to maintain a palpable central pulse.

It is essential that all hospitals manging trauma patients have an established major haemorrhage protocol (MHP;(NICE, 2016) Activation of this protocol should be based on the patient's injury profile and dynamic assessment of their haemodynamic status. This protocol should deliver packs containing a fixed ratio of PRBCs and other blood components. Blood product transfusion should be instituted empirically in trauma patients with evidence of bleeding and not deferred until blood results are available, although laboratory results can be used to guide ongoing resuscitation when they are available (Hunt et al, 2015).

Fibrinogen

Fibrinogen is the essential substrate for clot formation. Conversion of fibrinogen to cross-linked fibrin strands is the end point of the coagulation cascade and forms the basis of a stable clot. Depletion of fibrinogen is a characteristic feature of ATC, and hypofibrinogenaemia is strongly associated with mortality in trauma patients (Rourke et al, 2012). However, the evidence for appropriate fibrinogen replacement therapies in bleeding trauma patients is less clear compared to FFP and platelet transfusion. In the UK, cryoprecipitate is the standard therapy to replace fibrinogen in bleeding patients, but is typically not prioritised in MHP delivery and therefore not given until several hours after patients arrive at the major trauma centre (Stanworth et al, 2016). In the CRYOSTAT trial, a phase II randomised controlled trial at a single major trauma centre in the UK, early high-dose cryoprecipitate was effective in maintaining fibrinogen levels during active haemorrhage compared to standard care (Curry et al, 2015). The impact of early cryoprecipitate on survival is currently being evaluated in CRYOSTAT-2, a multicentre trial which is currently recruiting at all major trauma centres in England (Marsden et al, 2018). Until the evidence from this trial is available, current treatment regimens should include fibrinogen supplementation as part of the MHP.

Prehospital blood products

There is increasing interest in prehospital delivery of blood products in civilian trauma systems. In the UK, a number of prehospital services deliver PRBCs and, in some cases, FFP or lyophilised plasma at the roadside (Lyon et al, 2017, Oakeshott et al, 2018). The benefits of prehospital FFP have recently been demonstrated in the PAMPER trial, which found a 10% absolute reduction in mortality in severely injured patients receiving 2 units of FFP during prehospital transport compared to those receiving crystalloid (Sperry et al, 2018). The effect of pre-hospital PRBC and lyophilised plasma transfusion on survival is being evaluated in the RePhILL study, which is currently recruiting at a number of air ambulance services across the UK (Smith et al, 2018).

Whole blood

The use of whole blood rather than component therapy has received renewed attention in recent years, more than half a century after it was widely used in World War II and the Korean War. There are several theoretical advantages to whole blood in bleeding patients: it enables delivery of red cells and haemostatic components of blood in the ratios in which they are lost, and it avoids the need for freeze-thaw cycles which may result in loss of haemostatic potential (Spinella and Cap, 2016). Cold-stored, leukodepleted red cells and plasma is available through the NHS blood and transfusion service and is currently being evaluated by London's Air Ambulance in the pre-hospital phase as part of an feasibility study. It is important to note that this product does not contain platelets, which are lost during leukodepletion, and therefore is intended to supplement rather than replace a component-based approach. Work is in progress to develop a platelet-rich product with specialised filters (Remy et al, 2018).

Tranexamic Acid

In addition to blood products, early administration of the antifibrinolytic agent tranexamic acid (TXA) has become an important component of MHPs in much of the world since the publication of the landmark CRASH-2 trial (Shakur et al, 2010). The survival advantage conferred by TXA diminishes in a linear manner with increasing time from injury, and it

should therefore be administered in the prehospital phase where possible and ideally within one hour of injury (Gayet-Ageron et al, 2018). For reasons which remain unclear, TXA appears to increase mortality when given more than three hours after injury and should therefore be avoided when presentation is delayed.

Goal-directed resuscitation

Point-of-care viscoelastic tests such as TEG and ROTEM have been used extensively to profile post-traumatic alterations in haemostasis (Hagemo et al, 2015). These assays provide real-time quantification of different aspects of coagulation and yield meaningful results within five minutes of initiating the test. More recently, there has been growing interest in whether these assays can be used to direct blood product transfusion and TXA administration based on alterations in clot initiation, clot strength and clot breakdown (Baksaas-Aasen et al, 2018). Although this approach has been adopted in some centres, high quality evidence from randomized trials is still awaited – this knowledge gap will be addressed by the multicentre iTACTIC (implementation of Treatment Algorithms for the Management of Trauma Induced Coagulopathy) trial which has completed recruitment and will report in the next year (Baksaas-Aasen et al, 2017).

Table 1: Summary of 2016 NICE guidelines for the resuscitation of traumatic haemorrhage (NICE, 2016)

Use a trauma-specific **major haemorrhage protocol**
Use a **restrictive volume strategy** during active bleeding **unless major TBI present**
Do not give crystalloids or colloids during active haemorrhage in hospital
Start with a **fixed ratio** of blood products – aim for **1:1:1 FFP:Platelets:PRBCs**
Use **laboratory and/or point of care testing** to guide subsequent resuscitation
Give **TXA to bleeding patients** as early as possible but avoid if >3hrs post-injury
Prioritise **early definitive haemorrhage control**

Stopping the Bleeding

Definitive Haemorrhage Control

All interventions delivered while haemorrhage is ongoing are temporising measures, and normal physiology cannot be restored until definitive control of bleeding is achieved. The overarching priority in care of the bleeding patient is therefore early definitive haemorrhage control. In most patients, this will require surgical or radiological intervention.

Damage control surgery is an operative strategy which prioritises restoration of physiology over definitive anatomical reconstruction. In practice this means abbreviated procedures aimed at controlling bleeding and contamination. Examples are placement of temporary vascular shunts as opposed to definitive repairs, packing of major hepatic or pelvic injuries, and resection of injured bowel without restoring intestinal continuity. Temporary abdominal closure is routinely employed in patients with haemorrhagic shock requiring laparotomy, as it prevents abdominal compartment syndrome and enables early re-evaluation of injuries. Once transferred to critical care, the goals of treatment are restoration of homeostasis to enable the patient to tolerate a planned re-look procedure after 24-48 hours. In combination with balanced resuscitation, this strategy has led to major improvements in clinical outcomes among bleeding trauma patients (Cotton et al, 2011).

Increasingly, radiological procedures have replaced (or supplemented) conventional surgical management of many injuries. Angio-embolisation for bleeding in the pelvis, liver and spleen are mainstays of therapy and obviate the need for major surgery, which spares the critically injured patient a major additional physiological insult. Endovascular procedures for major vascular injuries, most notably traumatic aortic dissection, have also become the standard of treatment. A combination of surgical and radiological techniques may improve outcomes in patients with complex injuries (Matsumoto et al, 2018).

Temporary Haemorrhage Control

The time from injury to haemorrhage control is a critical determinant of outcome. Adjunctive measures to provide temporary control of bleeding and enable transfer to a facility capable of delivering definitive care therefore have great potential to improve care of bleeding patients.

REBOA

Among the most widely discussed and debated of these adjunctive therapies is resuscitative endovascular balloon occlusion of the aorta (REBOA). This procedure involves placement of an occlusive balloon in either the abdominal or thoracic aorta via a femoral access sheath. This essentially provides a minimally invasive alternative to thoracotomy and aortic cross clamping, achieving the same effect of interrupting blood flow to bleeding sites distal to the balloon and increasing central perfusion.

REBOA is reserved for patients with exsanguinating torso haemorrhage and can be deployed either in-hospital or pre-hospital (Sadek et al, 2016). The clearest indication for REBOA is major bleeding from pelvic fractures, in which scenario the balloon is inflated in the infra-renal aorta (zone 3). Balloon deployment in the thoracic aorta (zone 1) is also being increasingly used in traumatic cardiac arrest secondary to uncontrolled intra-abdominal haemorrhage. All patients undergoing REBOA need careful post-procedural care to mitigate the risks of limb ischaemia and the systemic complications of ischaemia-reperfusion syndrome.

Advocates of REBOA point to a number of retrospective cohort studies which suggest a survival benefit when compared to resuscitative thoracotomy (Moore et al, 2016). However, critics have voiced concerns regarding ischaemic complications of prolonged balloon occlusion times, local complications associated with femoral sheath placement, and the potential for inappropriate deployment in non-bleeding patients (Saito et al, 2015). There is currently a lack of level one evidence to support either perspective, a knowledge gap which is currently being addressed by the multicentre randomised UK-REBOA trial (Jansen et al, 2017).

Limb tourniquets

The use of tourniquets for control of extremity bleeding dates back at least to the 4th century BC. Although their use fell out of favour in modern civilian trauma care during the 20th century, the latest evidence suggests that tourniquets can reduce mortality from major limb bleeding without increasing the risk of amputation (Teixeira et al, 2018). In the UK, the NICE guidelines recommend that tourniquets should be reserved only for major limb bleeding which cannot be controlled by direct pressure alone. Judicious patient selection is important to minimise the risks of ischaemic complications associated with prolonged tourniquet use, the tourniquet time should be accurately recorded and the total duration of use kept to a minimum.

Pelvic Binders

Pelvic binders provide circumferential compression of the bony pelvis, providing emergency stabilisation of a pelvic fracture and theoretically reducing blood loss. Observational studies suggest a survival benefit associated with their use (Bakhshayesh et al, 2016). The risks associated with binder application for short periods are minimal, but prolonged use should be avoided to prevent pressure-related complications. Current NICE guidelines recommend applying a pelvic binder only in patients with haemodynamic instability and a suspected pelvic fracture.

Future directions

Despite major advances in the treatment of trauma-haemorrhage, it is important to recognise the limitations in contemporary resuscitation practices. Haemorrhage remains the dominant cause of preventable death from injury, and massive haemorrhage carries a mortality of around 50% (Stanworth et al, 2016, Bardes et al, 2018). Outcomes in patients requiring damage control surgery for intra-abdominal haemorrhage have not improved significantly in the last decade (Harvin et al, 2017, Marsden et al, 2018). The moniker of

haemostatic resuscitation may also be unfounded, as markers of shock and coagulopathy do not improve during active haemorrhage even if the core principles are adhered to (Khan et al, 2015). Because of this, there is increasing focus on novel strategies to improve survival after exsanguinating haemorrhage.

Emergency Preservation and Resuscitation

Induction of a period of 'suspended animation' has been proposed as a strategy to improve the dismal survival rates of traumatic cardiac arrest from haemorrhage. The most extensively investigated approach to achieving a period of metabolic arrest has been through the use of therapeutic hypothermia. This strategy, involving rapid cooling to a core temperature of 10°C by infusion of ice-cold saline into the thoracic aorta, can produce survival without neurological sequelae in otherwise fatal animal models of trauma haemorrhage (Alam et al, 2008). This approach is currently being evaluated in a prospective clinical trial of patients presenting with cardiac arrest from penetrating trauma (Tisherman et al, 2017).

Organ Protective Resuscitation

Multiple organ dysfunction is the major early sequela of trauma haemorrhage and contributes to much of the morbidity and mortality after the initial bleeding phase (Shepherd et al, 2017). Although there are currently no specific agents for the prevention and treatments of post-traumatic MODS, this is an area of active investigation. Perhaps the most promising potential therapy is artesunate, a widely used antimalarial drug which has potent cytoprotective effects and attenuates organ dysfunction in a rodent model of haemorrhagic shock (Sordi et al, 2017). This is currently being evaluated in a phase II clinical trial of bleeding patients in which artesunate or placebo is given as a bolus within four hours of injury.

Novel strategies for haemorrhage control

In recognition of the fact that many bleeding patients currently exsanguinate before intervention, there are a number of novel strategies for temporary haemorrhage control currently being investigated. These include a self-expanding haemostatic foam which can be injected into the abdominal cavity to tamponade bleeding. This has shown promise in large animal models of trauma haemorrhage and is currently being evaluated in a human trial (Rago et al, 2014, Chang et al, 2015). Abdominal and junctional tourniquets are another recent development with the aim of controlling proximal limb and abdominal injuries, which have received particular attention from military trauma services (Smith et al, 2018). Further studies of the efficacy and safety of this approach are ongoing.

Summary

Haemorrhage after major injury remains a highly lethal condition and is a significant contributor to global morbidity and mortality. Rapid identification and definitive control of bleeding is the over-arching principle of management. Temporary measures to achieve haemorrhage control can be employed to 'buy time' during transfer to definitive care. Resuscitation during active bleeding aims to maintain haemostatic competence and prevent dilutional coagulopathy by delivering high doses of blood components and pro-haemostatic agents such as tranexamic acid. Organ protection during resuscitation is an area of active investigation and is likely to play an increasing role in future treatment strategies.

Competing Interests

None declared.

References

Alam HB, Duggan M, Li Y, et al. Putting life on hold-for how long? Profound hypothermic cardiopulmonary bypass in a Swine model of complex vascular injuries. J Trauma. 2008; 64(4): 912-22. https://doi.org/10.1097/TA.0b013e3181659e7f

Bakhshayesh P, Boutefnouchet T & Totterman A Effectiveness of non invasive external pelvic compression: a systematic review of the literature. Scand J Trauma Resusc Emerg Med. 2016; 2473. https://doi.org/10.1186/s13049-016-0259-7

Baksaas-Aasen K, Gall L, Eaglestone S, et al. iTACTIC - implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy: study protocol for a multicentre, randomised controlled trial. Trials. 2017; 18(1): 486. https://doi.org/10.1186/s13063-017-2224-9

Baksaas-Aasen K, Van Dieren S, Balvers K, et al. Data-driven Development of ROTEM and TEG Algorithms for the Management of Trauma Hemorrhage: A Prospective Observational Multicenter Study. Ann Surg. 2018. https://doi.org/10.1097/sla.0000000000002825

Balvers K, van Dieren S, Baksaas-Aasen K, et al. Combined effect of therapeutic strategies for bleeding injury on early survival, transfusion needs and correction of coagulopathy. Br J Surg. 2017; 104(3): 222-229. https://doi.org/10.1002/bjs.10330

Bardes JM, Inaba K, Schellenberg M, et al. The contemporary timing of trauma deaths. J Trauma Acute Care Surg. 2018; 84(6): 893-899. https://doi.org/10.1097/ta.0000000000001882

Bickell WH, Wall MJ, Jr., Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994; 331(17): 1105-9. https://doi.org/10.1056/nejm199410273311701

Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma. 2003; 54(6): 1127-30. https://doi.org/10.1097/01.TA.0000069184.82147.06

Carrick MM, Morrison CA, Tapia NM, et al. Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: Early termination of a randomized prospective clinical trial. J Trauma Acute Care Surg. 2016; 80(6): 886-96. https://doi.org/10.1097/TA.0000000000001044

Chang JC, Holloway BC, Zamisch M, et al. ResQFoam for the Treatment of Non-Compressible Hemorrhage on the Front Line. Mil Med. 2015; 180(9): 932-3. https://doi.org/10.7205/milmed-d-15-00049

Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg. 2011; 254(4): 598-605. https://doi.org/10.1097/SLA.0b013e318230089e

Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. Br J Anaesth. 2015; 115(1): 76-83. https://doi.org/10.1093/bja/aev134

Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med. 2011; 39(12): 2652-8. https://doi.org/10.1097/CCM.0b013e3182281af5

Davenport RA & Brohi K Cause of trauma-induced coagulopathy. Curr Opin Anaesthesiol. 2016; 29(2): 212-9. https://doi.org/10.1097/aco.0000000000000295

Gayet-Ageron A, Prieto-Merino D, Ker K, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet. 2018; 391(10116): 125-132. https://doi.org/10.1016/s0140-6736(17)32455-8

Global Burden of Disease Collaborators Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017; 390(10100): 1151-1210. https://doi.org/10.1016/s0140-6736(17)32152-9

Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Crit Care. 2015; 1997. https://doi.org/10.1186/s13054-015-0823-y

Harvin JA, Maxim T, Inaba K, et al. Mortality after emergent trauma laparotomy: A multicenter, retrospective study. J Trauma Acute Care Surg. 2017; 83(3): 464-468. https://doi.org/10.1097/ta.0000000000001619

Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015; 313(5): 471-82. https://doi.org/10.1001/jama.2015.12

Hunt BJ, Allard S, Keeling D, et al. A practical guideline for the haematological management of major haemorrhage. Br J Haematol. 2015; 170(6): 788-803. https://doi.org/10.1111/bjh.13580

Jansen JO, Pallmann P, MacLennan G, et al. Bayesian clinical trial designs: Another option for trauma trials? J Trauma Acute Care Surg. 2017; 83(4): 736-741. https://doi.org/10.1097/ta.0000000000001638

Khan S, Davenport R, Raza I, et al. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. Intensive Care Med. 2015; 41(2): 239-47. https://doi.org/10.1007/s00134-014-3584-1

Lyon RM, de Sausmarez E, McWhirter E, et al. Pre-hospital transfusion of packed red blood cells in 147 patients from a UK helicopter emergency medical service. Scand J Trauma Resusc Emerg Med. 2017; 25(1): 12. https://doi.org/10.1186/s13049-017-0356-2

Marsden M, Benger J, Brohi K, et al. Coagulopathy, cryoprecipitate and CRYOSTAT-2: realising the potential of a nationwide trauma system for a national clinical trial. British Journal of Anaesthesia. 2018. https://doi.org/10.1016/j.bja.2018.10.055

Marsden M, Carden R, Navaratne L, et al. Outcomes following trauma laparotomy for hypotensive trauma patients: a UK military and civilian perspective. J Trauma Acute Care Surg. 2018. https://doi.org/10.1097/ta.0000000000001988

Matsumoto S, Cantrell E, Jung K, et al. Influence of postoperative hepatic angiography on mortality after laparotomy in Grade IV/V hepatic injuries. J Trauma Acute Care Surg. 2018; 85(2): 290-297. https://doi.org/10.1097/ta.0000000000001906

Moore LJ, Martin CD, Harvin JA, et al. Resuscitative endovascular balloon occlusion of the aorta for control of noncompressible truncal hemorrhage in the abdomen and pelvis. Am J Surg. 2016; 212(6): 1222-1230. https://doi.org/10.1016/j.amjsurg.2016.09.027

Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients

with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011; 70(3): 652-63. https://doi.org/10.1097/TA.0b013e31820e77ea
Neal MD, Hoffman MK, Cuschieri J, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. J Trauma Acute Care Surg. 2012; 72(4): 892-8. https://doi.org/10.1097/TA.0b013e31823d84a7
NICE National Institute for Health and Care Excellence. Major Trauma: assessment and initial management. NICE guideline [NG39]. 2016.
Oakeshott JE, Griggs JE, Wareham GM, et al. Feasibility of prehospital freeze-dried plasma administration in a UK Helicopter Emergency Medical Service. Eur J Emerg Med. 2018. https://doi.org/10.1097/mej.0000000000000585
Rago A, Duggan MJ, Marini J, et al. Self-expanding foam improves survival following a lethal, exsanguinating iliac artery injury. J Trauma Acute Care Surg. 2014; 77(1): 73-7. https://doi.org/10.1097/ta.0000000000000263
Remy KE, Yazer MH, Saini A, et al. Effects of platelet-sparing leukocyte reduction and agitation methods on in vitro measures of hemostatic function in cold-stored whole blood. J Trauma Acute Care Surg. 2018; 84(6S Suppl 1): S104-s114. https://doi.org/10.1097/ta.0000000000001870
Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost. 2012; 10(7): 1342-51. https://doi.org/10.1111/j.1538-7836.2012.04752.x
Sadek S, Lockey DJ, Lendrum RA, et al. Resuscitative endovascular balloon occlusion of the aorta (REBOA) in the pre-hospital setting: An additional resuscitation option for uncontrolled catastrophic haemorrhage. Resuscitation. 2016; 107135-8. https://doi.org/10.1016/j.resuscitation.2016.06.029
Saito N, Matsumoto H, Yagi T, et al. Evaluation of the safety and feasibility of resuscitative endovascular balloon occlusion of the aorta. J Trauma Acute Care Surg. 2015; 78(5): 897-903; discussion 904. https://doi.org/10.1097/ta.0000000000000614
Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010; 376(9734): 23-32. https://doi.org/10.1016/s0140-6736(10)60835-5
Shepherd JM, Cole E & Brohi K Contemporary Patterns of Multiple Organ Dysfunction in Trauma. Shock. 2017; 47(4): 429-435. 10.1097/shk.0000000000000779
Smith IM, Crombie N, Bishop JR, et al. RePHILL: protocol for a randomised controlled trial of pre-hospital blood product resuscitation for trauma. Transfus Med. 2018; 28(5): 346-356. https://doi.org/10.1111/tme.12486
Smith S, White J, Wanis KN, et al. The effectiveness of junctional tourniquets: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2018. https://doi.org/10.1097/ta.0000000000002159
Sordi R, Nandra KK, Chiazza F, et al. Artesunate Protects Against the Organ Injury and Dysfunction Induced by Severe Hemorrhage and Resuscitation. Ann Surg. 2017; 265(2): 408-417. https://doi.org/10.1097/SLA.0000000000001664
Sperry JL, Guyette FX, Brown JB, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. N Engl J Med. 2018; 379(4): 315-326. https://doi.org/10.1056/NEJMoa1802345
Spinella PC & Cap AP Whole blood: back to the future. Curr Opin Hematol. 2016; 23(6): 536-542. https://doi.org/10.1097/moh.0000000000000284

Stanworth SJ, Davenport R, Curry N, et al. Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. Br J Surg. 2016; 103(4): 357-65. https://doi.org/10.1002/bjs.10052

Teixeira PGR, Brown CVR, Emigh B, et al. Civilian Prehospital Tourniquet Use Is Associated with Improved Survival in Patients with Peripheral Vascular Injury. J Am Coll Surg. 2018; 226(5): 769-776.e1. https://doi.org/10.1016/j.jamcollsurg.2018.01.047

Tisherman SA, Alam HB, Rhee PM, et al. Development of the emergency preservation and resuscitation for cardiac arrest from trauma clinical trial. J Trauma Acute Care Surg. 2017; 83(5): 803-809. https://doi.org/10.1097/ta.0000000000001585

Table 1: Summary of 2016 NICE guidelines for the resuscitation of traumatic haemorrhage[3]

Use a trauma-specific **major haemorrhage protocol**
Use a **restrictive volume strategy** during active bleeding **unless major TBI present**
Do not give crystalloids or colloids during active haemorrhage in hospital
Start with a **fixed ratio** of blood products – aim for **1:1:1 FFP:Platelets:PRBCs**
Use **laboratory and/or point of care testing** to guide subsequent resuscitation
Give **TXA to bleeding patients** as early as possible but avoid if >3hrs post-injury
Prioritise **early definitive haemorrhage control**