Recent developments in the assessment of the multiply injured trauma patient

Eric M. Campion and Robert C. Mackersie

Purpose of review
To provide an update on the recent developments and controversies in the assessment of the traumatically injured patient.

Recent findings
Recent literature suggests that: whole-body computed tomography (CT) is an effective strategy in more severely injured blunt trauma patients; 64-slice CT scanning now provides an effective noninvasive screening method for blunt cerebrovascular injury; the need for MRI imaging, in addition to CT, for the diagnosis of occult ligamentous injury of the cervical spine remains an unresolved controversy; point-of-care testing has made significant improvements in our ability to predict which patients will need a massive transfusion; and thromboelastography has enhanced our ability to tailor a hemostatic resuscitation more accurately.

Summary
The recent advances in the assessment of the multiply injured patient allow clinicians to more efficiently diagnose a patient's injuries and implement treatment in a more timely manner.

Keywords
blunt cerebrovascular injury, cervical spine injury, massive transfusion triggers, trauma assessment, whole-body computed tomography

INTRODUCTION

Traumatic injury is the leading cause of death and disability for young adults and accounts for one in every eight male deaths and one in every 14 female deaths worldwide [1]. Road injuries alone are the eighth leading cause of years of life lost globally [2].

Rapid identification and management of a patient's injuries is felt to be a key factor in improving the morbidity and mortality of injured patients. The initial evaluation of the multiply injured patient is outlined by the Advanced Trauma Life Support guidelines [3]. This approach emphasizes the rapid and prioritized evaluation of patients in a matter sufficient to identify life-threatening injuries first. The following discussion will not reiterate the more basic principles of initial resuscitation and evaluation, but will focus on several topics related to the assessment of the multiply injured patient that are subjects of recent controversy and research.

WHOLE-BODY COMPUTED TOMOGRAPHY IMAGING

Computed tomography (CT) imaging has given clinicians a fast and accurate method to noninvasively identify injuries. As CT technology has improved, increased image-acquisition speed and resolution has improved diagnostic accuracy and expanded its use to include vascular imaging. Many trauma centers are now advocating whole-body CT (WBCT) as part of the early assessment of multiply injured patients. WBCT typically includes a CT scan of the head, complete spine, chest, abdomen, and pelvis. The purported advantages of this method include more rapid identification and treatment of critical injuries, and potentially reduced morbidity and mortality. However, this strategy has raised concerns about the risks of excessive radiation exposure and increased cost as compared to more selective imaging strategies.

Multiple studies have been performed in an attempt to determine whether or not routine WBCT

University of California, San Francisco and San Francisco General Hospital, San Francisco, California, USA

Correspondence to Eric M. Campion, MD, 1001 Potrero Ave Ward 3A, San Francisco, CA 94110, USA. Tel: +1 415 206 4627; e-mail: eric.campion@ucsfmedctr.org

Curr Opin Crit Care 2014, 20:620–625
DOI:10.1097/MCC.0000000000000151

KEY POINTS

- Protocolized whole-body CT for diagnosis of traumatic injuries has recognized value, but the exact indications remain controversial.
- CT angiography, with at least 64-slice capacity, is adequate to replace conventional angiography for BCVI screening.
- High-resolution CT imaging alone is probably sufficient to clear the cervical spine of major injury in obtunded patients.
- Point-of-care testing, including TEG, allows hemostatic resuscitation to be tailored to individual patient needs.

imaging confers any survival benefit. Huber-Wagner *et al.* [4] published a German retrospective multicenter study of WBCT versus non-WBCT and found a survival benefit associated with WBCT after risk adjustment for trauma injury severity score (TRISS) and revised injury severity classification (RISC) scores. The relative risk reduction was between 13 and 25% depending on the risk score used [4]. The same authors also demonstrated a survival advantage in hemodynamically unstable patients undergoing WBCT [5▪]. Other studies have shown somewhat mixed results, with some supporting a survival benefit to WBCT, whereas others were unable to demonstrate such an advantage [6–10]. All of the referenced studies on mortality with WBCT are retrospective in nature and suffer from potential bias and confounding. There has not been a randomized trial utilizing WBCT, published to date.

Whole-body CT has the potential benefit of shortening the time to definitive diagnosis of injuries by streamlining the diagnostic process. Several studies have shown a decreased time in the emergency room [8,9,11], and two studies demonstrated a decreased time to operative intervention [7,9]. Wurmb *et al.* [8] demonstrated in a retrospective study that the complete work-up of the patient was completed in 23 min after arrival in the WBCT group as compared to 70 min in the selective imaging group. This led to a decrease in the time to final management plan from 82 to 47 min [8]. A study by Tillou *et al.* [12] demonstrated that had physicians ordered selective imaging, they would have missed injuries in 17% of patients. However, the clinical impact of these potential missed injuries is not clear.

The principal deterrent to the more widespread use of CT is the risk of radiation exposure, approximately 10–20 mSv with WBCT. It is estimated that for every 10 mSv of radiation exposure, the risk of cancer increases by one in 1000 [13]. This effect, however, is highly age-dependent, with children and adolescents being the most susceptible. Estimates of age-adjusted radiation risk suggest a greatly diminished effect after age 35 [14]. Clinical studies examining the radiation exposure of trauma patients during their initial work-up found that the use of WBCT led to at least twice the relative risk of being exposed to above 20 mSv [15]. This is consistent with other studies showing an increased risk of radiation exposure attributable to CT imaging in trauma patients [16–18].

As healthcare costs continue to increase, it is important to consider the financial implications of diagnostic imaging. None of the studies on WBCT specifically looked at the costs associated with this strategy. While CT imaging is clearly associated with increased costs, these may be offset by a decrease in missed injuries and decreased hospitalization requirements.

Whole-body CT is a promising strategy for managing patients with multiple blunt traumatic injuries. It likely decreases the time required to complete the work-up of patients and may lead to faster treatment decisions. It logically follows that decreasing time to treatment has the potential to save lives; however, this must be balanced against cost and a potential radiation risk to those with negative images. WBCT is currently used liberally in our practice for patients that are obtunded with a mechanism of injury concordant with multisystem trauma, and for patients with physiologic alterations suggestive of early shock that remain stable enough for CT imaging. We have a much lower threshold for WBCT in the elderly given a higher incidence of serious, clinically occult injuries and the minimal consequences of radiation exposure in that population.

DIAGNOSIS OF BLUNT CEREBROVASCULAR INJURY

Blunt cerebrovascular injury (BCVI) had been previously thought to be a rare event, but several studies over the past few decades have shown it to be much more common than was previously thought. BCVI is diagnosed in 1–2% of patients sustaining significant blunt trauma [19–21]. These injuries can lead to devastating neurologic complications such as stroke and death. The associated mortality for stroke resulting from BCVI has been reported at up to 50% in a recent study [20]. The early identification and treatment of BCVI may significantly reduce the stroke rate and mortality [22,23], and has led to efforts to identify the 'at-risk' population and the optimal method for BCVI screening.

The original studies of BCVI were performed using digital subtraction angiography (DSA) which had been considered the gold standard for diagnosis. However, this technique is invasive and is associated with a number of serious complications, including stroke, making it unattractive as a screening method for BCVI. Due to both resource issues and complications, clinicians have been searching for a less invasive screening method that would prove as effective as DSA in diagnosing BCVI. Improvements in CT technology with more helical 'slices' and faster speeds have allowed it to replace conventional DSA for a number of injuries, including BCVI.

Using computed tomographic angiography (CTA) as a screening tool for BCVI was described in a study by Rogers *et al.* [24] in 1999. Subsequent to this, a number of further studies were published evaluating the use of CTA in screening for BCVI. Sensitivity in published series has been wide ranging from 29 to 100%. Specificity has been much more consistent with most modern studies showing rates above 90% [25]. The sensitivity for detection of BCVI is likely a direct effect of speed and the capacity of the more modern scanners (number of slices). Many centers have changed their primary screening modality to CTA based on these early results. The group out of Memphis has published extensively on BCVI and had continued to utilize conventional DSA based on unconvincing results using CTA [26]. However, using a 64-slice CT scanner, they published a recent study demonstrating a sensitivity of 68% on a per-vessel basis and 84% on a per-patient basis [27▪]. This was significantly improved from their previous experience with 32-slice CTA where a sensitivity of 51% was found [26]. When they analyzed their rate of significant complications (0.5%), they found it to be similar to the morbidity associated with potential missed injuries at 0.4%, leading them to conclude that CTA with a 64-slice multidetector CT scan was well tolerated and effective as a primary screening modality for BCVI. This is consistent with conclusions from multiple other authors regarding multislice CTA [23,28,29]. Multidetector CT arteriography using 64 or more channels appears to be adequate for screening for BCVI, and is a reasonable replacement for DSA.

The Eastern Association for Surgery of Trauma (EAST) has published guidelines on screening for BCVI (listed below) [30].

(1) Unexplained neurological abnormality
(2) Massive epistaxis from arterial source
(3) Glasgow coma score below 8
(4) Petrous bone fracture
(5) Cervical spine fractures:
    (a) of C1–C3
    (b) through the foramen transversarium
    (c) with subluxation or rotational component
(6) Lefort II or III facial fractures

These and similar guidelines are widely used in trauma centers across the world. Some recent articles suggest that it may be time to expand the indications for screening in order to decrease the approximately 20% of patients with BCVI that do not have one of the screening criteria [31]. Additional indicators that may increase the screening sensitivity for BCVI include mandibular fractures, any basilar skull fracture, complex frontal skull fractures with orbital involvement, and combined traumatic brain injury with thoracic injuries [32,33▪]. Overall, as the noninvasive diagnosis of BCVI continues to expand with CTA, so will the indications for screening. Some institutions have begun to include routine CTA of the neck with WBCT in order to increase the diagnostic rate of BCVI, but this technique will need continued study to ensure that the sensitivity and specificity is similar to a dedicated CTA [33▪].

The main goal of screening for BCVI is to allow early treatment and reduce the morbidity and mortality associated with BCVI. In addition to its diagnostic efficacy, CTA is far more accessible in many centers than conventional DSA, potentially reducing both the time from injury to diagnosis and the ultimate stroke rate. In a study by Eastman *et al.* [23], the use of a screening protocol for BCVI was associated with a decrease in time to diagnosis from 31.2 to 2.65 h, and a decrease in the stroke rate from 15.2 to 3.8%. These data suggest that the replacement of DSA with CTA may lead to faster diagnosis which would allow earlier treatment and thereby decrease the rate of stroke.

CTA with a 64-slice or greater multidetector CT scan to screen for BCVI is now widely accepted as a diagnostic alternative to DSA. The speed and accessibility of CTA provide additional advantages that should ultimately reduce the morbidity and mortality from BCVI-related strokes. Defining the precise risk factors that will accurately identify patients in need of BCVI screening and determining the cost, benefits, and outcomes for this screening warrant further study.

DIAGNOSIS OF CERVICAL SPINE INJURY

The consequences of missed cervical spine injuries, both in terms of cost and associated morbidity, have pushed tolerances for diagnostic error to almost zero. Plain films of the cervical spine had previously been the gold standard for the diagnosis of cervical spine injury, but they have been supplanted by CT

imaging [34]. Controversy still remains in determining which patients require diagnostic imaging at all, and the extent of imaging needed to reliably exclude occult ligamentous injury.

The ability to reliably 'clear' the cervical spine on the sole basis of the physical examination can reduce costs and expedite care while avoiding serious missed injuries. Groups such as the National Emergency X-Radiography Utilization Study (NEXUS) study group and the investigators for the Canadian C-spine rule evaluated clinical criteria to rule out cervical spine injury [35,36]. The decision rules based on the NEXUS and Canadian studies are easily adapted to the clinical environment and have gained wide acceptance. The Canadian C-spine rule, although considerably more sensitive, lacks specificity, making it less advantageous for practitioners dealing with major trauma. A major critique of these clinical clearance rules is that the studies that they were based on utilized plain films, an inferior modality to determine fractures as compared to CT imaging. The use of NEXUS criteria has been questioned in recent studies in the literature, reporting a significant number of missed injuries among major mechanism trauma patients [37]. The physical exam is particularly unreliable in the elderly. This population has a higher incidence of fracture, but a lower sensitivity (65.9%) using the NEXUS criteria, than a younger population in a recent study [38]. Clinical clearance criteria should be used with caution in patients with a significant mechanism of injury, particularly in the elderly.

Another area of controversy pertains to the optimal method for reliably excluding cervical spine injuries in patients who cannot be cleared on a clinical basis. Plain films, and more recently CT, are being utilized to diagnose fractures, with further imaging with flexion/extension fluoroscopy, or MRI used to evaluate potential ligamentous injuries. These ligamentous injuries may result in significant cervical instability and may lead to devastating neurologic consequences if missed. This leaves clinicians with the unfortunate choices of leaving cervical collars in place for extended periods of time, relying on CT findings to screen for major ligamentous injury, or routinely transporting critically ill patients to MRI scanners. Cervical collars have significant complications on their own and have been shown to contribute to increased intracranial pressure and significant wound problems [39–42].

With the advent of multidetector CT imaging of the cervical spine, many investigators are questioning the need for prolonged c-spine immobilization. A number of studies have been performed looking at the rate of missed injuries with modern multidetector CT technology. A meta-analysis performed in 2011 demonstrated sensitivity and specificity of above 99% for CT imaging of the spine to rule out unstable skeletal or ligamentous injury, and concluded CT alone to be sufficient for this purpose [43]. Conversely, another recent meta-analysis of CT imaging in the obtunded patient showed a negative predictive value for clinically significant injury of 92.9% with a negative predictive value for surgical intervention of 99.6% [44]. Using similar data, the authors arrived at a disparate conclusion that MRI was still an essential modality to evaluate for ligamentous injury in patients unable to undergo an adequate physical examination. This is despite the fact that they did not include a single study that was published after the 2011 meta-analysis. The reasons for the disparities seem to be due to a different interpretation of what constitutes an unstable injury and what amount of risk is considered acceptable. However, given the rarity of unstable ligamentous injury, it will be important for large surgical societies to provide consensus on what rate of missed injury would be acceptable, given the potentially devastating consequences. Our current practice is to accept a radiographically normal 64-slice CT scan of the cervical spine as an acceptable imaging modality to clear the cervical spine in the absence of any demonstrable neurologic abnormality.

MASSIVE TRANSFUSION TRIGGERS AND TRAUMA-RELATED COAGULOPATHY

In 2007, Holcomb *et al.* introduced data from the conflicts in Iraq and Afghanistan showing that a balanced resuscitation of packed red blood cells and fresh frozen plasma in a ratio nearing 1 : 1 was associated with improved mortality in military casualties [45,46]. This strategy, referred to as damage control resuscitation (DCR), has subsequently been associated with reduced mortality in the civilian population as well [47]. Over the next several years, this concept has been widely adopted throughout trauma centers all over the world.

An important tenet of DCR is the early provision of blood product support. The early identification of patients who will ultimately require massive transfusion has remained a challenge. Multiple scoring systems have been developed to address this, but many are overly complex and rely on data that are not readily available in the trauma bay. Recent advances in point-of-care testing have made it possible to gain important laboratory information within minutes of the patient arriving. These data have been utilized in the PROMMTT (PRospective, Observational, Multi-center Major Trauma Transfusion) trial to validate various transfusion triggers in a prospective manner. In this study, international

normalized ratio (INR) greater than 1.5, SBP below 90 mmHg, hemoglobin below 11 g/dl and base deficit at least 6, and penetrating mechanism and heart rate above 120 were associated with an increased risk of massive transfusion [48▪]. As identified in a previous retrospective study, INR was the most predictive single factor [49]. Adding these factors in an equally weighted fashion gives a stepwise increase in massive transfusion risk in which two factors showed an approximate 30% chance of massive transfusion and up to 80% if all six met their targets. This index gives clinicians a simplified manner with which to assess the risk of requiring massive transfusion.

In addition to point-of-care standard laboratory testing, thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have come into more widespread use in trauma resuscitation. These devices measure the viscoelastic properties of blood utilizing a moving pin or cup, and provide measures of clotting time, clot firmness, and clot lysis. A number of studies suggest that rapid TEG may supplant more conventional coagulation factor testing in the coagulopathic trauma patient [50,51]. A prospective evaluation of the rapid TEG on 1974 patients found rapid TEG values to be more predictive for massive transfusion than INR [50]. In another study, TEG-guided resuscitation was compared to a standard massive transfusion protocol. The results suggested that TEG-guided resuscitation outperformed the massive transfusion protocol in penetrating trauma patients [52▪]. Utilization of TEG as a replacement for traditional coagulation studies will need to be validated in studies at other centers, but shows great promise.

The rapid bedside determination of laboratory studies is likely to continue to proliferate and offers significant opportunity to improve care in extremely dynamic clinical scenarios such as the massively bleeding patient. TEG and ROTEM allow rapid evaluation of a patient's ability to properly form and breakdown clot in a real-time manner. This allows clinicians to rapidly tailor their resuscitation to the specifics of a given patient and should be integrated into massive transfusion protocols in the future.

CONCLUSION

The assessment of multiply injured trauma patients is an area of active research. New imaging and laboratory technologies have provided significant advances in our ability to rapidly diagnose injuries in the most critically ill. It is essential that physicians managing the care of the critically injured stay abreast of the latest developments in trauma assessment.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Mathers CD, Boerma T, Ma Fat D. Global and regional causes of death. Br Med Bull 2009; 92:7–32.
2. Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2095–2128.
3. American College of Surgeons. Advanced trauma life support. 9th ed. Chicago: American College of Surgeons Committee on Trauma; 2012.
4. Huber-Wagner S, Lefering R, Qvick LM, *et al.* Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. Lancet 2009; 373:1455–1461.
5. ▪ Huber-Wagner S, Biberthaler P, Haberle S, *et al.* Whole-body CT in haemodynamically unstable severely injured patients: a retrospective, multicentre study. PLoS One 2013; 8:e68880.

This study demonstrated that WBCT could be safely utilized in hemodynamically unstable trauma patients in the confines of a well structured environment.

6. Yeguiayan JM, Yap A, Freysz M, *et al.* Impact of whole-body computed tomography on mortality and surgical management of severe blunt trauma. Crit Care 2012; 16:R101.
7. Wurmb TE, Quaisser C, Balling H, *et al.* Whole-body multislice computed tomography (MSCT) improves trauma care in patients requiring surgery after multiple trauma. Emerg Med J 2011; 28:300–304.
8. Wurmb TE, Fruhwald P, Hopfner W, *et al.* Whole-body multislice computed tomography as the first line diagnostic tool in patients with multiple injuries: the focus on time. J Trauma 2009; 66:658–665.
9. Weninger P, Mauritz W, Fridrich P, *et al.* Emergency room management of patients with blunt major trauma: evaluation of the multislice computed tomography protocol exemplified by an urban trauma center. J Trauma 2007; 62:584–591.
10. Kimura A, Tanaka N. Whole-body computed tomography is associated with decreased mortality in blunt trauma patients with moderate-to-severe consciousness disturbance: a multicenter, retrospective study. J Trauma Acute Care Surg 2013; 75:202–206.
11. Hutter M, Woltmann A, Hierholzer C, *et al.* Association between a single-pass whole-body computed tomography policy and survival after blunt major trauma: a retrospective cohort study. Scand J Trauma Resusc Emerg Med 2011; 19:73–7241.
12. Tillou A, Gupta M, Baraff LJ, *et al.* Is the use of pan-computed tomography for blunt trauma justified? A prospective evaluation. J Trauma 2009; 67:779–787.
13. Costello JE, Cecava ND, Tucker JE, Bau JL. CT radiation dose: current controversies and dose reduction strategies. AJR Am J Roentgenol 2013; 201:1283–1290.
14. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. N Engl J Med 2007; 357:2277–2284.
15. Asha S, Curtis KA, Grant N, *et al.* Comparison of radiation exposure of trauma patients from diagnostic radiology procedures before and after the introduction of a panscan protocol. Emerg Med Australas 2012; 24:43–51.
16. Rodriguez RM, Baumann BM, Raja AS, *et al.* Diagnostic yields, charges, and radiation dose of chest imaging in blunt trauma evaluations. Acad Emerg Med 2014; 21:644–650.
17. Ahmadinia K, Smucker JB, Nash CL, Vallier HA. Radiation exposure has increased in trauma patients over time. J Trauma Acute Care Surg 2012; 72:410–415.
18. Inaba K, Branco BC, Lim G, *et al.* The increasing burden of radiation exposure in the management of trauma patients. J Trauma 2011; 70:1366–1370.
19. Goodwin RB, Beery PR 2nd, Dorbish RJ, *et al.* Computed tomographic angiography versus conventional angiography for the diagnosis of blunt cerebrovascular injury in trauma patients. J Trauma 2009; 67:1046–1050.
20. Stein DM, Boswell S, Sliker CW, *et al.* Blunt cerebrovascular injuries: does treatment always matter? J Trauma 2009; 66:132–143.
21. Berne JD, Cook A, Rowe SA, Norwood SH. A multivariate logistic regression analysis of risk factors for blunt cerebrovascular injury. J Vasc Surg 2010; 51:57–64.

22. Miller PR, Fabian TC, Bee TK, *et al.* Blunt cerebrovascular injuries: diagnosis and treatment. J Trauma 2001; 51:279–285.

23. Eastman AL, Muraliraj V, Sperry JL, Minei JP. CTA-based screening reduces time to diagnosis and stroke rate in blunt cervical vascular injury. J Trauma 2009; 67:551–556.

24. Rogers FB, Baker EF, Osler TM, *et al.* Computed tomographic angiography as a screening modality for blunt cervical arterial injuries: preliminary results. J Trauma 1999; 46:380–385.

25. Roberts DJ, Chaubey VP, Zygun DA, *et al.* Diagnostic accuracy of computed tomographic angiography for blunt cerebrovascular injury detection in trauma patients: a systematic review and meta-analysis. Ann Surg 2013; 257:621–632.

26. DiCocco JM, Emmett KP, Fabian TC, *et al.* Blunt cerebrovascular injury screening with 32-channel multidetector computed tomography: more slices still don't cut it. Ann Surg 2011; 253:444–450.

27. ■ Paulus EM, Fabian TC, Savage SA, *et al.* Blunt cerebrovascular injury screening with 64-channel multidetector computed tomography: more slices finally cut it. J Trauma Acute Care Surg 2014; 76:279–283.

This study compares 64-slice CTA with conventional angiography and demonstrates that CTA with modern CT scanners is sufficient to replace conventional angiography for screening purposes.

28. Liang T, Tso DK, Chiu RY, Nicolaou S. Imaging of blunt vascular neck injuries: a review of screening and imaging modalities. AJR Am J Roentgenol 2013; 201:884–892.

29. Burlew CC, Biffl WL. Imaging for blunt carotid and vertebral artery injuries. Surg Clin North Am 2011; 91:217–231.

30. Bromberg WJ, Collier BC, Diebel LN, *et al.* Blunt cerebrovascular injury practice management guidelines: the Eastern Association for the Surgery of Trauma. J Trauma 2010; 68:471–477.

31. Emmett KP, Fabian TC, DiCocco JM, *et al.* Improving the screening criteria for blunt cerebrovascular injury: the appropriate role for computed tomography angiography. J Trauma 2011; 70:1058–1063; discussion 1063-5.

32. Burlew CC, Biffl WL, Moore EE, *et al.* Blunt cerebrovascular injuries: redefining screening criteria in the era of noninvasive diagnosis. J Trauma Acute Care Surg 2012; 72:330–335.

33. ■ Bruns BR, Tesoriero R, Kufera J, *et al.* Blunt cerebrovascular injury screening guidelines: what are we willing to miss? J Trauma Acute Care Surg 2014; 76:691–695.

Evaluates a protocol of obtaining CTA of the head and neck with every WBCT and looks at BCVI that would have been missed by conventional indications for screening.

34. Como JJ, Diaz JJ, Dunham CM, *et al.* Practice management guidelines for identification of cervical spine injuries following trauma: update from the eastern association for the surgery of trauma practice management guidelines committee. J Trauma 2009; 67:651–659.

35. Hoffman JR, Mower WR, Wolfson AB, *et al.* Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. N Engl J Med 2000; 343:94–99.

36. Stiell IG, Wells GA, Vandemheen KL, *et al.* The Canadian C-spine rule for radiography in alert and stable trauma patients. J Am Med Assoc 2001; 286:1841–1848.

37. Duane TM, Mayglothling J, Wilson SP, *et al.* National Emergency X-Radiography Utilization Study criteria is inadequate to rule out fracture after significant blunt trauma compared with computed tomography. J Trauma 2011; 70:829–831.

38. Goode T, Young A, Wilson SP, *et al.* Evaluation of cervical spine fracture in the elderly: can we trust our physical examination? Am Surg 2014; 80:182–184.

39. Hunt K, Hallworth S, Smith M. The effects of rigid collar placement on intracranial and cerebral perfusion pressures. Anaesthesia 2001; 56:511–513.

40. Ackland HM, Cooper DJ, Malham GM, Kossmann T. Factors predicting cervical collar-related decubitus ulceration in major trauma patients. Spine (PhilaPa 1976) 2007; 32:423–428.

41. Mobbs RJ, Stoodley MA, Fuller J. Effect of cervical hard collar on intracranial pressure after head injury. ANZ J Surg 2002; 72:389–391.

42. Ho AM, Fung KY, Joynt GM, *et al.* Rigid cervical collar and intracranial pressure of patients with severe head injury. J Trauma 2002; 53:1185–1188.

43. Panczykowski DM, Tomycz ND, Okonkwo DO. Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: meta-analysis of 14,327 patients with blunt trauma. J Neurosurg 2011; 115:541–549.

44. Russin JJ, Attenello FJ, Amar AP, *et al.* Computed tomography for clearance of cervical spine injury in the unevaluable patient. World Neurosurg 2013; 80:405–413.

45. Holcomb JB, Jenkins D, Rhee P, *et al.* Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007; 62:307–310.

46. Borgman MA, Spinella PC, Perkins JG, *et al.* The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007; 63:805–813.

47. Holcomb JB, Wade CE, Michalek JE, *et al.* Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248:447–458.

48. ■ Callcut RA, Cotton BA, Muskat P, *et al.* Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. J Trauma Acute Care Surg 2013; 74:59–65.

Utilizing the prospective PROMMTT database to demonstrate the utility of individual massive transfusion triggers.

49. Callcut RA, Johannigman JA, Kadon KS, *et al.* All massive transfusion criteria are not created equal: defining the predictive value of individual transfusion triggers to better determine who benefits from blood. J Trauma 2011; 70:794–801.

50. Holcomb JB, Minei KM, Scerbo ML, *et al.* Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg 2012; 256:476–486.

51. Cotton BA, Faz G, Hatch QM, *et al.* Rapid thrombelastography delivers real-time results that predict transfusion within 1 h of admission. J Trauma 2011; 71:407–414.

52. ■ Tapia NM, Chang A, Norman M, *et al.* TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg 2013; 74:378–385.

Utilizes a TEG-guided resuscitation as opposed to defined ratios in massive transfusion and demonstrates an improvement in penetrating trauma.

Transfusion strategy in multiple trauma patients

Oliver M. Theusinger, Philipp Stein, and Donat R. Spahn

Purpose of review
To point out the tolerance of anemia, the possible use of alternatives to allogeneic blood products as well as the pathophysiological effects of transfusions in the context of multiple trauma patients.

Recent findings
Restrictive transfusion triggers are beneficial for patient outcome in trauma.
The actual European Trauma Treatment Guidelines suggest the use of point-of-care devices, the use of transfusion algorithms and factor concentrates to control coagulopathy. The use of high ratios of plasma to red blood cells to improve survival has been shown to suffer from a time-dependent survival bias. In massive bleeding, factor-based treatment of coagulopathy is feasible and preferable to plasma transfusion, if available. In nonmassive bleeding, allogeneic transfusion of blood products increases the appearance of serious adverse events and mortality and should be avoided unless clearly indicated.

Summary
Transfusion in trauma has to be an individual decision for a specific patient, not for a specific laboratory value. Transfusion management must aim at reducing or even avoiding the use of allogeneic blood products. This may lead to a new gold standard with cost reduction and amelioration of outcome of major trauma patients.

Keywords
allogeneic blood products, assessment of anemia, pathophysiology of transfusions, transfusion triggers, trauma

INTRODUCTION

Mortality related to trauma may be up to 40% in the civilian sector [1▪▪,2,3]. Of those 40%, one quarter of the deaths are related to coagulopathy and uncontrolled blood loss that may be preventable [4▪▪,5]. For this reason, treatment of coagulopathy and hemostatic control are key to reduce mortality due to exsanguination, to save blood products and to improve outcome [1▪▪,6–11].

Using restrictive transfusion triggers and patient-specific physiological reserve of anemia are the two aspects that can also be applied in multiple trauma patients to reduce the use of blood products [12▪,13▪,14▪▪,15,16▪▪].

Point-of-care (POC) devices, such as rotational thromboelastometry (ROTEM, TEM Innovations GmbH, Munich, Germany) or thromboelastography (TEG, Haemoscope Corporation, Niles, Illinois, USA) are becoming more popular to treat bleeding in trauma and are highly recommended to guide hemostatic therapy during coagulopathy [1▪▪,17,18].

The purpose of this review is to enlighten patient tolerance to anemia, the use of transfusion algorithms and alternatives to allogeneic blood products, the outcome of transfused patients, complications and pathophysiological effects of blood products as well as transfusion triggers and thresholds to use blood products in a restrictive manner.

PATHOPHYSIOLOGICAL EFFECTS OF TRANSFUSION

Although blood transfusions are considered to be well tolerated in first world countries with regard to the direct transmission of infectious agents, there are still some serious adverse events that need to be mentioned. Although their frequency is low, hemolytic and delayed hemolytic reactions are severe adverse events [19]. They may be due to the transfusion of AB0 incompatible blood product. Delayed

Institute of Anesthesiology, University Hospital of Zurich, University of Zurich, Zurich, Switzerland

Correspondence to Oliver M. Theusinger, MD, PrivatDozent, Institute of Anesthesiology, University Hospital of Zurich and University of Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland. Tel: +41 44 255 27 10; fax: +41 44 255 44 09; e-mail: oliver.theusinger@usz.ch

Curr Opin Crit Care 2014, 20:646–655
DOI:10.1097/MCC.0000000000000152

KEY POINTS

- Also, in trauma, restrictive transfusion triggers are beneficial for patient outcome.
- Goal-directed transfusion algorithms and the use of POC devices in trauma reduce the need of allogeneic blood products.
- There is no clear evidence for high FFP : RBC ratios as this concept suffers from a time-dependent survival bias in patients receiving high FFP : RBC ratios.

hemolytic reactions occur in patients who have developed antibodies from previous (AB0 compatible) transfusions or pregnancy. These antibodies in question sometimes present in low concentrations and are too weak to be detected by standard procedures at the time of antibody screening before the intended transfusion. Subsequent transfusion with red blood cells (RBCs) having the corresponding antigen results in an anamnestic antibody response and consecutive hemolysis of transfused RBCs. Febrile reactions (a rise of 1.0 °C from baseline) due to cytokines and antibodies to leukocyte antigens reacting with leukocytes or leukocyte fragments are common with a frequency of about 10% [19]. Foreign plasma proteins are able to cause allergic reactions causing urticaria and may be associated with laryngeal edema and bronchospasm; their frequency is about 1%. Anaphylactic reactions are rare and may be due to an anti-immunoglobulin A reaction, leading to cardiovascular instability, dyspnea, stridor, shock and possible cardiac arrest. Transfusion-related acute lung injury (TRALI) is underrecognized, and thus its frequency is rare [20▪]. The pathomechanism is supposed to be linked to the presence of antibodies in the donor plasma, which react with the recipient's leukocyte antigens or induce the production of inflammatory mediators resulting in a noncardiogenic pulmonary edema with a 10% fatality [21,22▪]. Bacterial contamination occurs when a small number of bacteria enter a blood component during collection or processing. During storage, bacteria may proliferate, resulting in a large number of organisms and endotoxins being given with the transfusion. This complication is rare in first world countries but leads to major complications including fatalities [23▪].

In addition to the above-mentioned distinctive side-effects, RBC transfusions in trauma patients increase the risk of multiorgan failure, infections, renal dysfunction, length of stay (LOS) and mortality [24,25] .

Trauma patients are at greater risk for massive transfusion. In addition, longer storage time of RBCs [26–28] leads to even longer LOS [29,30], additional occurrence of deep vein thrombosis [31] and even higher mortality [26,30–33] with a possible dose effect regarding older blood products [27,31,33].

ASSESSMENT OF ANEMIA IN TRAUMA

The initial hemoglobin or hematocrit measurement is not a precise measure of the actual blood loss of a trauma victim, particularly after a limited initial fluid therapy. Therefore, a near normal hematocrit value in the emergency department does not rule out significant blood loss (low sensitivity) [34]. But, a primarily low hematocrit has a high specificity in identifying major injury and blood loss requiring operative intervention [34,35]. Moreover, a low hematocrit is associated with higher injury severity scores, hypotension and acidosis [36]. Preexisting anemia or severe hemodilution cannot be ruled out as other reasons for a low hematocrit, but a drop in the hematocrit value over time (serial measurement) is sensitive and specific for bleeding, even in the context of fluid resuscitation [37].

In 2002, Kinoshita *et al.* [38] were the first to describe an apparatus to measure hemoglobin concentrations noninvasively using three different wavelengths. The development of multiwavelength pulse oximeters showed promising results and a relatively acceptable accuracy in perioperative patients when peripheral perfusion, indexed as signal quality by the machine, was good (in 70% of cases) [39]. However, for trauma patients, this method is inadequate as shock, hypothermia and vasoconstriction influence the results [40,41▪]. In a study comprising 525 trauma patients, detection of a hemoglobin value was impossible only in 34% of the readouts [42].

Although noninvasive hemoglobin measurement shows promising results in patients with an adequate peripheral perfusion, it is not yet useful in the setting of trauma and hemorrhagic shock to guide transfusion decision making.

TRANSFUSION TRIGGERS AND THRESHOLDS (THE EMPIRICAL APPROACH)

Blood transfusion historically is thought to save the life of bleeding patients, but no high evidence data are available to date to support this axiom [43].

In the perioperative setting, not referring specifically to trauma victims, anemic patients have a significantly higher perioperative 30-day mortality after major noncardiac surgery, compared to controls with normal hemoglobin levels [44,45].

However, allogeneic blood transfusion is not the 'cure' for the anemic patient. Specific risks, such as (viral) infection, TRALI, transfusion-related circulatory overload and immunomodulation, account for the transfusion-associated worsened outcome [46,47].

Formerly accepted hemoglobin transfusion triggers of about 100 g/l were abandoned [48].

A Cochrane review concerning transfusion triggers states that blood transfusion probably can be withheld to hemoglobin levels of as low as 70 g/l. The threshold for patients with coronary artery disease remains to be exactly determined but is likely at or below 80 g/l. Further research is needed to evaluate the role of even lower hemoglobin levels [9]. A randomized controlled multicenter study showed a lower mortality, fewer complications and a shorter length of hospital stay in patients with acute upper gastrointestinal bleeding when transfused restrictively (Hb <70 g/l) as compared with a more liberal transfusion regimen (Hb <90 g/l) [49▪▪]. In hip fracture surgery patients with a history of, or risk factors for, cardiovascular disease, liberal transfusion strategy (threshold 100 g/l) did not reduce rates of death on 60-day follow-up or reduce in-hospital morbidity in elderly patients [50].

In 203 trauma patients, analyzed as a subgroup of the prospective randomized controlled 'transfusion requirements in critical care' trial [51], a restrictive transfusion trigger (<70 g/l) to maintain hemoglobin between 70 and 90 g/l was not inferior to a liberal (>100 g/l) regimen with hemoglobin concentrations between 100 and 120 g/l. Patients in the restrictive group received significantly fewer allogeneic RBC transfusions. Reported 30-day all-cause mortality, rate of multiorgan dysfunction, LOS in the hospital and in the ICU were comparable and not significantly different between the two groups [51].

In patients with traumatic brain injury (TBI), RBC transfusion increased local brain tissue oxygen partial pressure in 74% of the patients [52]. However, this effect was not seen with 'old' blood stored more than 19 days [53]. Despite increased oxygen partial pressure, no positive effect on cerebral metabolism was seen [54]. More days with a hematocrit below 30% were associated with improved neurologic outcomes in a retrospective analysis of 169 patients [55]. Transfusion, but not anemia, significantly led to higher mortality and more complications among 1150 TBI patients [56]. Increasing the hematocrit above 28% in the initial operation phase following severe TBI was not associated with an increased or decreased morbidity or mortality [57]. Initial anemia (Hb <100 g/l) in the emergency department following TBI was not a mortality risk factor [58].

The current knowledge gives no compelling evidence to treat patients with severe TBI differently in contrast to other critically ill patients concerning RBC transfusion [1▪▪].

Clinical indicators such as injury severity score above 25, the need for procedural bleeding control [59▪] and multiple scoring systems consisting of international normalized ratio (INR), mechanism of injury, positive results for focused assessment with sonography for trauma, blood pressure, initial hemoglobin and heart rate can help identify trauma patients at risk for massive transfusion, but also patients highly unlikely to need a massive transfusion [60▪,61]. These variables and scores may be used as an adjunct to guide resuscitation, but they do not reflect the specific needs of an individual trauma victim.

Emphasis must be put on the fact that transfusion has to be an individual decision for a specific patient at a specific moment in time, not for a specific hemoglobin value, and RBC transfusion must be avoided whenever possible.

ACUTE ANEMIA, HEMODILUTION AND ANEMIA TOLERANCE (THE INDIVIDUAL PHYSIOLOGICAL APPROACH)

Only 0.3 ml of oxygen is dissolved physically in 100 ml of blood at room air breathing (FiO2 0.21 and atmospheric pressure 1013 mbar), but it can play a vital role in severe acute anemia states. With a FiO2 of 1.0 and a hemoglobin value of 10 g/l, the physically dissolved amount of oxygen equals the amount of oxygen bound to hemoglobin [62]. Survival of transient acute anemia (hemoglobin 7 g/l) was reported [63]. Even without allogeneic blood transfusion, a nadir hemoglobin of 14 g/l was survived by a patient refusing blood products [64].

Cellular and circulatory physiological compensatory mechanisms facilitate vital oxygen delivery to the tissues (DO2) during anemia [65▪]. DO2 is the product of cardiac output and arterial oxygen content of the blood. The body's demand for oxygen is five-fold exceeded by DO2 in physiological conditions. Moreover, a rise in cardiac output and an increase in O_2 extraction can compensate for a decline in the oxygen content of the blood in states of acute anemia [66].

A critical hemoglobin value [Hb(crit)] is reached when whole body oxygen consumption (VO2) starts to decline because of insufficient DO2 (=global body hypoxia). In an animal model, all of the study pigs consecutively died within 3 h after reaching the

Hb(crit) with a FiO2 of 0.21 [67]. Increasing the FiO2 leads to more physically dissolved oxygen, resulting in a lower Hb(crit) and a higher level of possible hemodilution [68▪].

In addition, Lauscher *et al.* [69▪▪] demonstrated that there are organ-specific thresholds of anemic hypoxia in anesthetized pigs. Kidney and skeletal muscle showed tissue hypoxia before reaching Hb(crit) and significantly earlier than cardiac ventricle and brain. On the contrary, the liver showed even fewer cellular signs of hypoxia at a hemoglobin level of 40 g/l compared with the control group (normal hemoglobin values) [69▪▪]. The impact of this animal model data is unclear for the time being. Further investigations need to be performed to elucidate the clinical relevance in the human body. Moreover, current transfusion thresholds (70 g/l) are high above the critical individual organ margin described in the animal study.

Other clinically susceptible factors to increase anemia tolerance are deep neuromuscular blockade [70], hypothermia, by reducing (cerebral) oxygen consumption by 6% per degree Celsius [71] and administration of norepinephrine to overcome arterial hypotension during hemodilution [72].

This growing knowledge may lead to a better understanding of the role of transfusion in the context of severe traumatic bleeding. Measures to increase anemia tolerance, further insights into organ-specific oxygen demand and assessment of organ ischemia thresholds may reveal new physiologic triggers to guide red cell transfusion therapy in the future.

ALTERNATIVES TO ALLOGENEIC BLOOD PRODUCTS

Actual studies clearly show that a high amount of RBCs, fresh frozen plasmas (FFPs) and platelets can be reduced without additional risks for patients by using transfusion algorithms in trauma on the basis of coagulation factor concentrates [73,74]. Data from four European countries (United Kingdom, Germany, Italy and Switzerland) were used to calculate blood substitution and costs of blood products needed. The results showed that these products account for approximately one third of all costs associated with trauma care [75]. The reduction of septic complications and organ failure tends to reduce days on ventilator, whilst on ICU and shorten overall in-hospital LOS which clearly contribute to cost reduction in trauma care without increasing the risk of patients [76].

The use of POC devices as well as goal-directed algorithms is getting essential (Fig. 1) [77▪▪]. Because of their use, coagulopathy in trauma can be treated early and effectively and blood loss and the use of blood products can be reduced [1▪▪,78▪▪,79▪▪].

Thromboelastometry (ROTEM) measures and graphically displays the viscoelasticity of the developing blood clot. The first usable results are provided within 5–10 min, whereas the classical laboratory results may take from 30 to 90 min and thereby delay effective therapy for patients [77▪▪]. Details on the ROTEM method and technology are to be found in the literature [80]. Another device to be used is the thromboelastography (TEG, Haemoscope Corporation, Niles, Illinois, USA) working similarly to the ROTEM, details are described in the literature [81]. The use of POC devices is acutely clearly recommended by the European Trauma Guidelines [1▪▪].

The use of FFP leads to adverse effects that are similar to those of RBCs (increased mortality, multiple organ failure, infections, lung injury, immunomodulation) [82▪]. The use of FFP is getting more and more questionable as concentrations of factors are variable and large volumes are necessary to achieve an effect. Actually, the use of fibrinogen concentrates is favorable compared with FFPs [83]. According to the European Trauma Guidelines, the use of FFP or fibrinogen is indicated in patients with massive transfusions. A ratio of 1 : 2 (FFP : RBC) is suggested if FFP is being used. However, in non-massive bleeding, plasma transfusion should be avoided [1▪▪]. Fibrinogen has been shown to be the coagulation factor which drops critically first during bleeding; for this reason, its concentration needs to be monitored closely [1▪▪,73,84]. The actual recommended fibrinogen target levels of 1.5–2.0 g/l have been defined by the European Trauma Treatment Guidelines [1▪▪]. As the concentration of fibrinogen in FFP does not exceed 2 g/l, the use of fibrinogen concentrates has the advantage of reaching fibrinogen levels above 2.0 g/l without volume overload [85]. The second coagulation factor to be monitored closely is factor XIII which, in combination with fibrinogen, is essential for a stable clot; its level should be maintained above 60% by administration of factor concentrate in case of active bleeding [86–89]. In addition to those single-factor concentrates, prothrombin complex concentrates may be taken into consideration [73,89–93]. There are different types of prothrombin complex concentrates regarding factors contained (three vs. four), their relative composition and their thrombotic potential. Their use in trauma is recommended since 2013, but only under strict surveillance by rotational thromboelastometry and in the context of algorithms, which suggest small and repeated

Diagnogstic	Intervention
Preoperative history 1. Drugs affecting coagulation - Antiplatelet drugs - Heparin - Oral anticoagulation (Vit. K antagonists, Xa antagonists, IIa antagonists) 2. Coagulation status? 3. HIT II?	**ROTEM after anesthesia induction** - Transplant surgery - Cardiac and vascular surgery - Difficult cancer surgery - Liver insufficiency - Intra-abdominal sepsis - Emergency room entry
Blood loss > 50% with diffuse bleeding	
ROTEM analysis - EXTEM, INTEM, FIBTEM, APTEM - HEPTEM in heart and vascular surgery	**Target values** - Normothermia (temp. > 35°C) - Normocalcemia (Ca >1.15 mmol/l) - No acidosis (pH > 7.2) - Hematocrit > 0.21 - Hypotension (MAP 55–60 mmHg) **Crystalloid and/or colloid volume substitution**
FIBTEM < 7 mm	Fibrinogen 2–4 g i.v. (maximal 3x2g), after a total of 6 g give FXIII
INTEM (CT and CFT prolonged) and **HEPTEM** normal OR ACT pathological and heparinase ACT normal	Protamine sulfate 1:1 to heparin **crystalloid and colloid volume substitution**
EXTEM / INTEM Decrease of MCF after maximum was reached **APTEM:** normal ⇨ Hyperfibrinolysis	Tranexamic acid - 15 mg/kg BW as bolus i.v. - 1–2 mg/kg/h during surgery i.v. as perfusion
On-going diffuse bleeding	
EXTEM /INTEM MCF<40 mm CT EXTEM /INTEM normal MCF FIBTEM <7 mm Hct > 0.21 MCF FIBTEM > 7mm Platelets < 50 000/ µl (< 100 000/ µl in cardiac surgery or in patients suffering from traumatic brain injury) **Coagulation test incl. F XIII, F V, INR, PT, aPTT**	Fibrinogen up to 6 g, followed by **Factor XIII** 15 U/kg BW **crystalloid and colloid volume substitution** **Platelet concentrates** **Target of Factor XIII: > 60% (Factor XIII 15 U/kg BW)** **Target of Factor V: >20% (in particular in liver insufficiency /trauma or intra-abdominal sepsis: 2–4 U FFP)**
On-going diffuse bleeding	
Quick's value < 30% and Factor V > 20 % OR EXTEM/INTEM: CT, CFT prolonged	**4 factor prothrombin complex concentrate** 1000–2000 IU - Factor II, VII, IX and X Depending on the patient's bodyweight
In case of massive transfusion	**Target hematocrit: 0.21 –0.24**
If massive diffuse bleeding continues and	
Treated acidosis Treated hypothermia Excluded hypocalcemia Hematocrit: 0.21–0.24 Excluded DIC Fibrinogen was substituted Platelets >50 000/µl (>100 000/µl in cardiac surgery or in patients suffering from traumatic brain injury)	Recombinant Factor VIIa 60 µg/kg bodyweight i.v. A second dose of 60 µg/kg bodyweight i.v. can be given again after 2–4 hours, if bleeding has not completely stopped.

FIGURE 1. Third version of the transfusion algorithm of the University Hospital of Zürich 2013, Switzerland. BW, body weight; CFT, clot formation time; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; i.v., intravenous; MAP, mean arterial pressure; MCF, maximal clot firmness. Adapted with permission [77▪▪].

doses to prevent thromboembolic adverse events [1▪▪,92].

In addition to all factor concentrates, one should take the two following drugs into consideration: first, tranexamic acid (TXA), which stops hyperfibrinolysis, reduces the need for blood products and decreases mortality [94] and second, desmopressin, which enhances platelet adherence [94–99]. There is actually clear evidence that the early use of TXA is favorable for patients. One study, including 40 trauma patients (55% penetrating, 45% blunt trauma), all received TXA in the prehospital setting showing that this is feasible without delaying treatment or creating severe adverse events [100▪▪]. However, patients' outcome could not be assessed because of the study design and the limited sample size. The most known study, named CRASH-2, showed that early (within first 3 h) administration of TXA in the emergency room reduces mortality significantly [94]. Furthermore, TXA is cost effective and has been integrated into military trauma algorithms [101▪▪]. A recent systematic Cochrane review showed that TXA clearly reduces blood transfusions in patients requiring emergency or urgent surgery [102▪].

Regarding desmopressin, the European Trauma Guidelines recommend a single dose for trauma patients treated with aspirin [1▪▪].

TRANSFUSION AND PATIENT OUTCOME

Today, in many countries, the widespread approach is to transfuse bleeding trauma patients with FFP and RBCs at a 1 : 1 ratio. Halmin *et al.* [103] recently published a cohort study on the association between death in trauma and FFP : RBC ratio integrating time-dependent data, as suggested by Ho *et al.* [104]. In their retrospective cohort study including nearly 750 patients from one single trauma center, they analyzed time-dependent transfusions and the relative risk of death comparing low and high FFP : RBC ratios. They could find no significant association between the low plasma ratio and the risk of death. On the other side, when analyses were made excluding the time factor, a strong effect of high plasma ratios was seen, clearly pointing out a survival bias [103]. This high FFP : RBC regimen is supported by observational studies mainly from recent wars, showing lower mortality in bleeding patients receiving equal volumes of plasma and RBCs as compared with patients treated with a lower FFP : RBC ratio. The rationale for this practice is still unclear with several studies failing to show any survival benefits of increased plasma use, perhaps because of a failure to account for the timing of transfused units. The FFP : RBC ratio measured 24 h after admission was based primarily on war casualties, in which it was realized that RBCs alone have no effect on coagulation but the addition of FFP ameliorates coagulation.

The observation of a higher survival rate in patients having received an equivalent number of FFP and RBC transfusion at 24 h after admission, however, suffers from this 'survival bias'. Several studies have addressed this issue. Ho *et al.* [104,105] were able to show that there is a time-dependent covariate regarding high FFP : RBC ratios and so far, the current available evidence is inconclusive. Any retrospective analysis favors patients having received high FFP : RBC ratio because only they survived long enough to receive high amounts of FFP. Those dying early did not survive long enough to have FFPs being ready to be administered [106,107▪▪]. This dilemma can only be solved with prospective randomized studies. Nascimento *et al.* [107▪▪] indeed published in 2013 such a prospective randomized controlled study with 78 patients assessing the feasibility of such a study and the effect on mortality and complications in severe trauma patients. Patients were randomly assigned to a fixed ratio of 1 : 1 : 1 transfusion (1 unit of RBC, FFP and platelets) ($n = 40$) or to a laboratory guided transfusion protocol which served as the control group ($n = 38$) [107▪▪]. The all-cause 28-day mortality was 32% in the fixed-ratio group compared to 14% in the control group and thus increased by a relative risk of 2.27 (95% CI 0.98–9.63). Event-free survival was 54% in the patients with fixed ratios compared to 78% in the control group ($P = 0.053$). The fixed-ratio transfusion protocol was feasible but associated with large plasma wastage and a near significantly higher mortality [107▪▪].

There is a great need for further studies on this subject to clearly identify the optimal treatment of massively bleeding trauma patients. Furthermore, it has recently been shown that there is a clear causation between blood transfusions and bad outcome, this may also be true in trauma patients and thus one should consider giving as little blood as possible and as much as necessary in order to have a better outcome [108]. This can be guided by a clear algorithm that has to be followed by the whole staff in charge. Theusinger *et al.* [77▪▪] recently published a good example for a feasible algorithm.

CONCLUSION

Transfusion in trauma has to be an individual decision for a specific patient, not for a specific laboratory value. Transfusion management must aim on reducing or even avoiding the use of allogeneic blood products. This may lead to a new gold

standard with cost reduction and amelioration of outcome of major trauma patients.

Acknowledgements

None.

Conflicts of interest

Oliver M. Theusinger has received honoraria or travel support for consulting or lecturing from the following companies: CSL Behring Schweiz, Zurich, Switzerland; Vifor SA, Villars-sur-Glâne, Switzerland; Roche Pharma (Schweiz) AG, Reinach, Switzerland; Pentapharm AG, München, Germany; TEM International, München, Germany.

Philipp Stein has no conflict of interest.

Donat R. Spahn academic department is receiving grant support from the Swiss National Science Foundation, Berne, Switzerland (grant numbers: 33CM30_124117 and 406440-131268); the Swiss Society of Anesthesiology and Reanimation (SGAR), Berne, Switzerland (no grant numbers are attributed); the Swiss Foundation for Anesthesia Research, Zurich, Switzerland (no grant numbers are attributed); Bundesprogramm Chancengleichheit, Berne, Switzerland (no grant numbers are attributed); CSL Behring, Berne, Switzerland (no grant numbers are attributed); Vifor SA, Villars-sur-Glâne, Switzerland (no grant numbers are attributed).

Dr Spahn was the chairman of the ABC Faculty and a member of the ABC Trauma Faculty both of which are managed by Thomson Physicians World GmbH, Mannheim, Germany and sponsored by an unrestricted educational grant from Novo Nordisk A/S, Bagsvärd, Denmark. In the past 5 years, Dr Spahn has received honoraria or travel support for consulting or lecturing from the following companies: Abbott AG, Baar, Switzerland; AstraZeneca AG, Zug, Switzerland; Bayer (Schweiz) AG, Zürich, Switzerland; Baxter S.p.A., Roma, Italy; B. Braun Melsungen AG, Melsungen, Germany; Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; Bristol-Myers Squibb, Rueil-Malmaison Cedex, France; CSL Behring GmbH, Hattersheim am Main, Germany and Bern, Switzerland; Curacyte AG, Munich, Germany; Ethicon Biosurgery, Sommerville, New Jersey, USA; Fresenius SE, Bad Homburg v.d.H., Germany; Galenica AG, Bern, Switzerland (including Vifor SA, Villars-sur-Glâne, Switzerland); GlaxoSmithKline GmbH & Co. KG, Hamburg, Germany; Janssen-Cilag AG, Baar, Switzerland; Novo Nordisk A/S, Bagsvärd, Denmark; Octapharma AG, Lachen, Switzerland; Organon AG, Pfäffikon/SZ, Switzerland; Oxygen Biotherapeutics, Costa Mesa, California, USA; Pentapharm GmbH (now Tem Innovations GmbH), Munich, Germany; Roche Pharma (Schweiz) AG, Reinach, Switzerland and Schering-Plough International, Inc., Kenilworth, New Jersey, USA.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■■ Spahn DR, Bouillon B, Cerny V, *et al.* Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013; 17:R76.

This study is the updated version of the European Trauma guideline published in 2007 and updated in 2010. Key changes include new recommendations on the appropriate use of vasopressors and inotropic agents and reflect an awareness of the growing number of patients in the population at large treated with antiplatelet agents and/or oral anticoagulants. A significant addition is a new section that discusses the need for every institution to develop, implement and adhere to an evidence-based clinical protocol to manage traumatically injured patients. The remaining recommendations have been reevaluated and graded based on literature published since the last edition of the guideline. Consideration was also given to changes in clinical practice that have taken place during this time period as a result of both new evidence and changes in the general availability of relevant agents and technologies.

2. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. World J Surg 2007; 31:1507–1511.
3. Champion HR, Bellamy RF, Roberts CP, Leppaniemi A. A profile of combat injury. J Trauma 2003; 54:S13–S19.
4. ■■ Rossaint R, Bouillon B, Cerny V, *et al.* The STOP the Bleeding Campaign. Crit Care 2013; 17:136.

This study deals with the fact that traumatic injuries worldwide are responsible for over 5 million deaths annually. Bleeding caused by traumatic injury-associated coagulopathy is the leading cause of potentially preventable death among trauma patients. Despite these facts, awareness of this problem is insufficient and treatment options are often unclear. The STOP the Bleeding Campaign, therefore, aims to increase awareness of this fact and its appropriate management by publishing European guidelines for the management of the bleeding trauma patient, by promoting and monitoring the implementation of these guidelines and by preparing promotional and educational material, organizing activities and developing health quality management tools. The campaign aims to reduce the number of patients who die within 24 h after arrival in the hospital due to exsanguination by a minimum of 20% within the next 5 years.

5. Esposito TJ, Sanddal TL, Reynolds SA, Sanddal ND. Effect of a voluntary trauma system on preventable death and inappropriate care in a rural state. J Trauma 2003; 54:663–669.
6. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma 2006; 60:S3–11.
7. British Committee for Standards in Haematology. Retter A, Wyncoll D, Pearse R, *et al.* Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. Br J Haematol 2013; 160:445–464.
8. Clinical Transfusion Medicine Committee of the AABB. Carson JL, Grossman BJ, Kleinman S, *et al.* Red blood cell transfusion: a clinical practice guideline from the AABB∗. Ann Intern Med 2012; 157:49–58.
9. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012; 4:CD002042.
10. Frith D, Goslings JC, Gaarder C, *et al.* Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010; 8:1919–1925.
11. Frith D, Brohi K. The acute coagulopathy of trauma shock: clinical relevance. Surgeon 2010; 8:159–163.
12. ■ Spahn DR, Goodnough LT. Alternatives to blood transfusion. Lancet 2013; 381:1855–1865.

This study summarizes the current roles of alternatives to blood in the management of medical and surgical anemias.

13. ■ Spahn DR, Shander A, Hofmann A. The chiasm: transfusion practice versus patient blood management. Best Pract Res Clin Anaesthesiol 2013; 27:37–42.

This publication encourages the implementation of patient blood management.

14. ■■ Shander A, Hofmann A, Isbister J, Van Aken H. Patient blood management: the new frontier. Best Pract Res Clin Anaesthesiol 2013; 27:5–10.

Blood transfusions face many issues, including questionable safety and efficacy, increasing costs and limited supply. The need to provide effective care for a relatively small population of patients who could not be transfused for various reasons gave rise to 'bloodless medicine and surgery', which was subsequently proposed as a care strategy for all patients, with the goal of minimizing the use of allogeneic blood components. The next evolution came from the shift from a 'product-centered' approach toward a 'patient-centered' approach, that is, a focus on patient outcome rather than use of blood components, which gave birth to 'patient blood management'.

15. College of American Pathologists, American Society of Anesthesiologists, Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists, Society of Critical Care Medicine, Italian Society of Transfusion Medicine and Immunohaematology, American Association of Blood Banks. Shander A, Gross I, Hill S, *et al.* A new perspective on best transfusion practices. Blood Transfus 2013; 11:193–202.
16. ■■ Williamson LM, Devine DV. Challenges in the management of the blood supply. Lancet 2013; 381:1866–1875.

In the the next 5–10 years, blood availability in developed countries will need to increase again to meet the demands of aging populations. Increasing of the blood supply raises many challenges; new approaches to recruitment and retainment of future generations of blood donors will be needed, and care will be necessary to avoid taking too much blood from these donors. Personalized medicine could be applied to match donors to patients, not only with extended blood typing, but also by using genetically determined storage characteristics of blood components. Growing of red cells or platelets in large quantities from stem cells is a possibility in the future, but challenges of cost, scaling up and reproducibility remain to be solved.

17. Ives C, Inaba K, Branco BC, *et al.* Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. J Am Coll Surg 2012; 215:496–502.
18. Johansson PI, Stensballe J, Ostrowski SR. Current management of massive hemorrhage in trauma. Scand J Trauma Resusc Emerg Med 2012; 20:47.
19. Strobel E. Hemolytic transfusion reactions. Transfus Med Hemother 2008; 35:346–353.
20. ■ Kenz HE, Van der Linden P. Transfusion-related acute lung injury. Eur J Anaesthesiol 2014; 31:345–350.

This article describes transfusion-related lung injury, its occurrence, its supposed pathomechanism and possible treatment algorithms.

21. Rana R, Fernandez-Perez ER, Khan SA, *et al.* Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion 2006; 46:1478–1483.
22. ■ Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet 2013; 382:984–994.

This article describes transfusion-related lung injury, its occurrence, its supposed pathomechanism and possible treatment algorithms.

23. ■ Prestia K, Bandyopadhyay S, Slate A, *et al.* Transfusion of stored blood impairs host defenses against Gram-negative pathogens in mice. Transfusion 2014. [Epub ahead of print]

This original article enlightens the adverse host reactions after transfusion of stored or older blood in mice. Consecutively lowered defense host mechanisms against bacteria are also considered to be of relevance in the human body, this work reveals possible mechanisms.

24. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology 2010; 113:482–495.
25. Bernard AC, Davenport DL, Chang PK, *et al.* Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009; 208:931–937.
26. Weinberg JA, McGwin G Jr, Marques MB, *et al.* Transfusions in the less severely injured: does age of transfused blood affect outcomes? J Trauma 2008; 65:794–798.
27. Vandromme MJ, McGwin G Jr, Marques MB, *et al.* Transfusion and pneumonia in the trauma intensive care unit: an examination of the temporal relationship. J Trauma 2009; 67:97–101.
28. Juffermans NP, Vlaar AP, Prins DJ, *et al.* The age of red blood cells is associated with bacterial infections in critically ill trauma patients. Blood transfusion 2012; 10:290–295.
29. Keller ME, Jean R, LaMorte WW, *et al.* Effects of age of transfused blood on length of stay in trauma patients: a preliminary report. J Trauma 2002; 53:1023–1025.
30. Murrell Z, Haukoos JS, Putnam B, Klein SR. The effect of older blood on mortality, need for ICU care, and the length of ICU stay after major trauma. Am Surg 2005; 71:781–785.
31. Spinella PC, Carroll CL, Staff I, *et al.* Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care 2009; 13:R151.
32. Zallen G, Offner PJ, Moore EE, *et al.* Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg 1999; 178:570–572.
33. Weinberg JA, McGwin G Jr, Vandromme MJ, *et al.* Duration of red cell storage influences mortality after trauma. J Trauma 2010; 69:1427–1431.
34. Snyder HS. Significance of the initial spun hematocrit in trauma patients. Am J Emerg Med 1998; 16:150–153.
35. Zehtabchi S, Sinert R, Goldman M, *et al.* Diagnostic performance of serial haematocrit measurements in identifying major injury in adult trauma patients. Injury 2006; 37:46–52.
36. Ryan ML, Thorson CM, Otero CA, *et al.* Initial hematocrit in trauma: a paradigm shift? J Trauma Acute Care Surg 2012; 72:54–59.
37. Thorson CM, Ryan ML, Van Haren RM, *et al.* Change in hematocrit during trauma assessment predicts bleeding even with ongoing fluid resuscitation. Am Surg 2013; 79:398–406.
38. Kinoshita Y, Yamane T, Takubo T, *et al.* Measurement of hemoglobin concentrations using the astrim noninvasive blood vessel monitoring apparatus. Acta Haematol 2002; 108:109–110.
39. Berkow L, Rotolo S, Mirski E. Continuous noninvasive hemoglobin monitoring during complex spine surgery. Anesth Analg 2011; 113:1396–1402.
40. Nguyen BV, Vincent JL, Nowak E, *et al.* The accuracy of noninvasive hemoglobin measurement by multiwavelength pulse oximetry after cardiac surgery. Anesth Analg 2011; 113:1052–1057.
41. ■ Joseph B, Hadjizacharia P, Aziz H, *et al.* Continuous noninvasive hemoglobin monitor from pulse ox: ready for prime time? World J Surg 2013; 37:525–529.

This article deals with noninvasive hemoglobin measurement in trauma patients and reveals the lack of sufficient current accuracy in severly injured patients.

42. Moore LJ, Wade CE, Vincent L, *et al.* Evaluation of noninvasive hemoglobin measurements in trauma patients. Am J Surg 2013; 206:1041–1047.
43. Seldon TH, Lundy JS, Adams RC. A blood transfusion service; dangers and safeguards. Anesthesiology 1946; 7:122–131.
44. Wu WC, Schifftner TL, Henderson WG, *et al.* Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007; 297:2481–2488.
45. Musallam KM, Tamim HM, Richards T, *et al.* Preoperative anaemia and postoperative outcomes in noncardiac surgery: a retrospective cohort study. Lancet 2011; 378:1396–1407.
46. Pattakos G, Koch CG, Brizzio ME, *et al.* Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. Arch Intern Med 2012; 172:1154–1160.
47. Chaiwat O, Lang JD, Vavilala MS, *et al.* Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology 2009; 110:351–360.
48. Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. Crit Care Med 2006; 34:S102–S108.
49. ■■ Villanueva C, Colomo A, Bosch A. Transfusion for acute upper gastrointestinal bleeding. N Engl J Med 2013; 368:1362–1363.

A large randomized controlled trial comparing liberal with restrictive transfusion triggers. Restrictive transfusion strategy improves outcomes in patiens with acute upper gastrointestinal bleeding.

50. Carson JL, Terrin ML, Noveck H, *et al.* Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–2462.
51. McIntyre L, Hebert PC, Wells G, *et al.* Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? J Trauma 2004; 57:563–568.
52. Smith MJ, Stiefel MF, Magge S, *et al.* Packed red blood cell transfusion increases local cerebral oxygenation. Crit Care Med 2005; 33:1104–1108.
53. Leal-Noval SR, Munoz-Gomez M, Arellano-Orden V, *et al.* Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. Crit Care Med 2008; 36:1290–1296.
54. Zygun DA, Nortje J, Hutchinson PJ, *et al.* The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury. Crit Care Med 2009; 37:1074–1078.
55. Carlson AP, Schermer CR, Lu SW. Retrospective evaluation of anemia and transfusion in traumatic brain injury. J Trauma 2006; 61:567–571.
56. Salim A, Hadjizacharia P, DuBose J, *et al.* Role of anemia in traumatic brain injury. J Am Coll Surg 2008; 207:398–406.
57. Fluckiger C, Bechir M, Brenni M, *et al.* Increasing hematocrit above 28% during early resuscitative phase is not associated with decreased mortality following severe traumatic brain injury. Acta Neurochir 2010; 152:627–636.
58. Yang CJ, Hsiao KY, Su IC, Chen IC. The association between anemia and the mortality of severe traumatic brain injury in emergency department. J Trauma 2011; 71:E132–E135.
59. ■ Sisak K, Manolis M, Hardy BM, *et al.* Acute transfusion practice during trauma resuscitation: who, when, where and why? Injury 2013; 44:581–586.

In this publication, distinct patterns of early transfusion triggers are revealed to guide transfusion indications in contrast to conventional hemoglobin values as transfusion triggers.

60. ■ Callcut RA, Cotton BA, Muskat P, *et al.* Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. J Trauma Acute Care Surg 2013; 74:59–65.

A large trial comprising 1245 trauma patients of which 237 had a massive transfusion. Individual clinical triggers for transfusion such as INR and positive results for focused assessment with sonography for trauma were identified to predict the likelihood of massive transfusion.

61. Maegele M, Brockamp T, Nienaber U, *et al.* Predictive models and algorithms for the need of transfusion including massive transfusion in severely injured patients. Transfus Med Hemother 2012; 39:85–97.
62. Zollinger A, Hager P, Singer T, *et al.* Extreme hemodilution due to massive blood loss in tumor surgery. Anesthesiology 1997; 87:985–987.
63. Dai J, Tu W, Yang Z, Lin R. Case report: intraoperative management of extreme hemodilution in a patient with a severed axillary artery. Anesth Analg 2010; 111:1204–1206.
64. de Araujo Azi LM, Lopes FM, Garcia LV. Postoperative management of severe acute anemia in a Jehovah's Witness. Transfusion 2014; 54:1153–1157.

65. Hare GM. Tolerance of anemia: understanding the adaptive physiological ■ mechanisms which promote survival. Transfus Apher Sci 2014; 50:10–12.
Physiological compensation mechanisms play a vital role to overcome acute severe anemia. Cardiovascular and cellular responses are key to maintaining survival. Molecular mechanisms, such as neuronal nitric oxide synthase and hypoxia-inducible factor, may promote survival. Oxidation of hemoglobin to methemoglobin by nitric oxide synthase may be a marker of anemia-induced tissue hypoxia.

66. Klein HG, Spahn DR, Carson JL. Red blood cell transfusion in clinical practice. Lancet 2007; 370:415–426.

67. Meier J, Kemming GI, Kisch-Wedel H, *et al.* Hyperoxic ventilation reduces 6-h mortality at the critical hemoglobin concentration. Anesthesiology 2004; 100:70–76.

68. Pape A, Steche M, Laout M, *et al.* The limit of anemia tolerance during ■ hyperoxic ventilation with pure oxygen in anesthetized domestic pigs. Eur Surg Res 2013; 51:156–169.
This animal study reveals the body limits of whole body hypoxic anemia, also in the context of variable inspiratory fractions of oxygen.

69. Lauscher P, Kertscho H, Schmidt O, *et al.* Determination of organ-specific ■■ anemia tolerance. Crit Care Med 2013; 41:1037–1045.
In this trial, pigs were randomized into three different groups and hemodiluted with hydroxyethyl starch comparing no hemodilution vs. hemoglobin of 4.0 g/dl and vs. the critical hemoglobin level of 2.7 g/dl. In the hemodiluted state, 10 mg/kg of pimonidazole was injected, which forms protein adducts in hypoxic cells. Interestingly, metabolic parameters and oxygen consumption did not show that tissue oxygenation was restricted before reaching a hemoglobin level of 2.7 g/dl. Kidneys and skeletal muscle showed enhanced pimonidazole binding and vascular endothelial growth factor expression at a hemoglobin level of 4 g/dl. Other organs such as heart, brain and liver showed no signs of tissue hypoxia at a hemoglobin level of 4 g/dl.

70. Pape A, Kertscho H, Stein P, *et al.* Neuromuscular blockade with rocuronium bromide increases the tolerance of acute normovolemic anemia in anesthetized pigs. Eur Surg Res 2012; 48:16–25.

71. McCullough JN, Zhang N, Reich DL, *et al.* Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 1999; 67:1895–1899.

72. Meier J, Pape A, Loniewska D, *et al.* Norepinephrine increases tolerance to acute anemia. Crit Care Med 2007; 35:1484–1492.

73. Nienaber U, Innerhofer P, Westermann I, *et al.* The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury 2011; 42:697–701.

74. Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Peiniger S, Nienaber U, Lefering R, *et al.* Balanced massive transfusion ratios in multiple injury patients with traumatic brain injury. Crit Care 2011; 15:; R68.

75. Pape H-C, Neugebauer E, Ridley SA, *et al.* Cost-drivers in acute treatment of severe trauma in europe: a systematic review of literature. Eur J Trauma Emerg Surg 2009; 35:61–66.

76. Walsh TS. Red cell transfusion triggers in critically ill patients: time for some new TRICCs? Crit Care 2010; 14:170.

77. Theusinger OM, Stein P, Spahn DR. Applying 'patient blood management' in ■■ the trauma center. Curr Opin Anaesthesiol 2014; 27:225–232.
This review highlights the use of TXA, POC testing, algorithm-based treatment of trauma-associated coagulopathy with factor concentrates to reduce blood loss and transfusion requirements to improve outcome. In addition, the management of patients on new oral anticoagulants, drugs with renewed interest and the tolerance of relatively low hemoglobin levels in the context of trauma is discussed.

78. Theusinger OM, Schroder CM, Eismon J, *et al.* The influence of laboratory ■■ coagulation tests and clotting factor levels on Rotation Thromboelastometry (ROTEM(R)) during major surgery with hemorrhage. Anesth Analg 2013; 117:314–321.
This study confirms the clinical assumption that EXTEM, INTEM and APTEM are associated with fibrinogen and platelets levels; INTEM-CT significantly to aPTT and FIBTEM significantly to fibrinogen. Factor VIII shows a significant correlation with all ROTEM parameters except CT of EXTEM, INTEM, FIBTEM, and clot formation time and maximal clot firmness of APTEM.

79. Theusinger OM, Levy JH. Point of care devices for assessing bleeding ■■ and coagulation in the trauma patient. Anesthesiol Clin 2013; 31:55–65.
Severe trauma is associated with bleeding, coagulopathy, and transfusion of blood and blood products, all contributing to higher rates of morbidity and mortality. This review focuses on POC devices to monitor coagulation in trauma. Close monitoring of bleeding and coagulation as well as platelet function in trauma patients allows goal-directed transfusion and an optimization of the patient's coagulation, reduces the exposure to blood products, reduces costs, and probably improves clinical outcome. Noninvasive hemoglobin measurements are not to be used in trauma patients because of a lack in specificity and sensitivity.

80. Theusinger OM, Nurnberg J, Asmis LM, *et al.* Rotation thromboelastometry (ROTEM) stability and reproducibility over time. Eur J Cardiothorac Surg 2010; 37:677–683.

81. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 2008; 106:1366–1375.

82. Mahambrey T, Pendry K, Nee A, *et al.* Critical care in emergency department: ■ massive haemorrhage in trauma. Emerg Med J 2013; 30:9–14.
This article addresses current concepts in hemostatic resuscitation. Recent guidelines on the diagnosis and treatment of coagulopathy in major trauma, and the role of component and adjuvant therapies, are considered. Finally, the potential role of thromboelastography and rotational thromboelastometry are discussed.

83. Kozek-Langenecker S, Sorensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. Crit Care 2011; 15:R239.

84. Schochl H, Nienaber U, Maegele M, *et al.* Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011; 15:R83.

85. Theusinger OM, Baulig W, Seifert B, *et al.* Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth 2011; 106:505–511.

86. Theusinger OM. The inhibiting effect of factor XIII on hyperfibrinolysis. Anesth Analg 2012; 114:1149–1150.

87. Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice? Curr Opin Anaesthesiol 2009; 22:305–312.

88. Dirkmann D, Gorlinger K, Gisbertz C, *et al.* Factor XIII and tranexamic acid but not recombinant factor VIIa attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood. Anesth Analg 2012; 114:1182–1188.

89. Gorlinger K, Dirkmann D, Hanke AA, *et al.* First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology 2011; 115:1179–1191.

90. Theusinger OM, Felix C, Spahn DR. Strategies to reduce the use of blood products: a European perspective. Curr Opin Anaesthesiol 2012; 25:59–65.

91. Theusinger OM, Madjdpour C, Spahn DR. Resuscitation and transfusion management in trauma patients: emerging concepts. Curr Opin Crit Care 2012; 18:661–670.

92. Sorensen B, Spahn DR, Innerhofer P, *et al.* Clinical review: prothrombin complex concentrates: evaluation of safety and thrombogenicity. Crit Care 2011; 15:201.

93. Schochl H, Nienaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; 14:R55.

94. CRASH-2 collaborators. Roberts I, Shakur H, *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011; 377:1096–1101.

95. Ruggeri ZM, Mannucci PM, Lombardi R, *et al.* Multimeric composition of factor VIII/von Willebrand factor following administration of DDAVP: implications for pathophysiology and therapy of von Willebrand's disease subtypes. Blood 1982; 59:1272–1278.

96. Castaman G, Goodeve A, Eikenboom J. European Group on von Willebrand D. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica 2013; 98:667–674.

97. Beynon C, Sakowitz OW, Unterberg AW. Multiple electrode aggregometry in antiplatelet-related intracerebral haemorrhage. J Clin Neurosci 2013; 20:1805–1806.

98. CRASH-2 goes viral. Lancet 2011; 378:1758.

99. CRASH-2 trial collaborators. Shakur H, Roberts I, *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; 376:23–32.

100. Lipsky AM, Abramovich A, Nadler R, *et al.* Tranexamic acid in the prehospital ■■ setting: Israel Defense Forces' initial experience. Injury 2014; 45:66–70.
The authors show that TXA may be successfully given in the prehospital setting without any apparent delays in evacuation. In light of recent evidence, the ability to give TXA closer to the time of wounding represents an important step toward improving the survival of trauma victims with hemorrhage, even before definitive care is available. TXA could be considered a viable option for use by advanced life support providers at or near the point of injury.

101. Roberts I, Shakur H, Coats T, *et al.* The CRASH-2 trial: a randomised ■■ controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 2013; 17:1–79.
This analysis shows that the early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 h of injury is unlikely to be effective.

102. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing ■ mortality in emergency and urgent surgery. Cochrane Database Syst Rev 2013; 1:CD010245.
The authors show by a prognostic model that one can obtain valid predictions of mortality in patients with traumatic bleeding. TXA can be administered safely to a wide spectrum of bleeding trauma patients and should not be restricted to the most severely injured. It has to be evaluated whether or not this model used in clinical practice has an impact on the management and outcomes of trauma patients.

103. Halmin M, Bostrom F, Brattstrom O, *et al.* Effect of plasma-to-RBC ratios in trauma patients: a cohort study with time-dependent data∗. Crit Care Med 2013; 41:1905–1914.

104. Ho AM, Dion PW, Yeung JH, *et al.* Prevalence of survivor bias in observational studies on fresh frozen plasma:erythrocyte ratios in trauma requiring massive transfusion. Anesthesiology 2012; 116:716–728.

105. Ho AM, Dion PW, Yeung JH, *et al.* Simulation of survivorship bias in observational studies on plasma to red blood cell ratios in massive transfusion for trauma. Br J Surg 2012; 99 (Suppl 1):132–139.

106. Brown LM, Aro SO, Cohen MJ, *et al.* A high fresh frozen plasma: packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. J Trauma 2011; 71:S358–S363.

107. ■■ Nascimento B, Callum J, Tien H, *et al.* Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patients with severe trauma: a randomized feasibility trial. CMAJ 2013; 185:E583–E589.
This article shows a near significant higher mortality in the fixed ratio (1 : 1 : 1 PRB, FFP, platelets) transfusion group compared to a laboratory guided protocol.

108. Isbister JP, Shander A, Spahn DR, *et al.* Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev 2011; 25:89–101.

Acute traumatic coagulopathy

Andrew Cap[a] *and Beverley Hunt*[b]

Purpose of review
Mortality from trauma remains a global public health challenge, with most preventable deaths due to bleeding. The recognition of acute traumatic coagulopathy as a distinct clinical entity characterized by early coagulation dysfunction, arising prior to medical intervention, has revolutionized trauma management over the last decade. The aim of this article is to review our current understanding of acute traumatic coagulopathy.

Recent findings
We focus on recent advances in the mechanistic understanding of acute traumatic coagulopathy, particularly the changes in coagulation factors, physiological anticoagulants, endothelial activation, fibrinolysis and platelet dysfunction. Evolving diagnostic and therapeutic approaches are discussed, including viscoelastic coagulation monitoring and the role of tranexamic acid and blood products.

Summary
Emphasis is now placed on early prevention, diagnosis, and aggressive initial treatment of coagulopathy and fibrinolysis with haemostatic blood products and tranexamic acid in addition to red cell units in order to reduce bleeding and improve clinical outcomes.

Keywords
acute traumatic coagulopathy, endothelial activation, fibrinolysis, hemostatic resuscitation, hypoperfusion, microparticles, platelet dysfunction, tranexamic acid, viscoelastic coagulation monitoring

INTRODUCTION

Mortality from trauma is a major global health issue, causing over 4 million deaths a year [1]. Most potentially preventable deaths are due to bleeding, especially in wartime, but immediate management has changed dramatically and improved outcome [2]. This article will focus on our current understanding of acute traumatic coagulopathy (ATC).

WHAT IS ACUTE TRAUMATIC COAGULOPATHY?

The past decade has seen an explosion of publications describing an entity variously termed 'acute traumatic coagulopathy' (ATC), 'acute coagulopathy of trauma shock', or 'trauma induced coagulopathy,' describing an early coagulopathy associated with high bleeding risk and poor outcomes (Table 1) [3–12]. There is uncertainty about the underlying pathophysiological mechanisms and whether traumatic injury induces a unique coagulopathy when compared with other forms of major haemorrhage (e.g., obstetric or vascular) because no comparative studies have been undertaken. Nevertheless, the recognition that early coagulation changes following trauma portend poor outcomes has radically altered trauma resuscitation and improved outcomes [13].

CLASSIFICATION AND NAMING OF TRAUMA-ASSOCIATED COAGULOPATHIES

There are different approaches to classifying ATC, including by timescale in which temporal phases are described. The first phase is an immediate activation of multiple haemostatic pathways, including fibrinolysis, in association with tissue injury. The second phase is due to therapy-related factors during

[a]Medical Corps, US Army, Uniformed Services University, Blood Research Program, US Army Institute of Surgical Research, JBSA-FT Sam Houston, San Antonio, Texas, USA and [b]Departments of Haematology, Pathology and Lupus Guy's & St Thomas' NHS Foundation Trust, London, UK

Correspondence to Beverley Hunt, Departments of Haematology, Pathology and Lupus Guy's & St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK. Tel: +44 207 188 2736; fax: +44 207 188 2717; e-mail: Beverley.Hunt@gstt.nhs.uk

Curr Opin Crit Care 2014, 20:638–645
DOI:10.1097/MCC.0000000000000158

KEY POINTS

- Traumatic injury generates an acute coagulopathy defined usually by a prolongation of the prothrombin time.
- ATC is associated with increased morbidity and mortality.
- The pathogenesis of ATC relates to excessive stimulation of fibrinolysis and coagulation, changes in platelet function, and generation of microparticles.
- We argue that the changes of ATC are not driven by aPC.

resuscitation, and postresuscitation there is an acute phase response leading to a prothrombotic state, predisposing to venous thromboembolism. In some patients, especially if resuscitated late or inadequately, disseminated intravascular coagulation (DIC) may ensue.

The concept of ATC stems from the recognition that a prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT) at hospital admission, prior to resuscitation, is associated with a three-fold to four-fold higher mortality rate and is independently associated with increased transfusion requirements, organ injury, septic complication, and critical care length of stay [4]. This supports the rationale for giving traumatic coagulopathy a distinct name to emphasize these clinically important associations. For the purposes of this review, the term ATC will be used.

THE CLINICAL RELEVANCE OF ACUTE TRAUMATIC COAGULOPATHY

The role of ATC in forcing change in trauma management cannot be overstated. Previously, patients were initially resuscitated with red cell concentrates, with attention being paid to coagulopathy later. Retrospective data from the US military and civilian institutions described improved outcomes in those administered fresh whole blood [13,14] or fresh frozen plasma, cryoprecipitate and platelets in combination with red blood cells and tranexamic acid (TXA), with limitation of colloid or crystalloid infusions [13,15–19]; a practice known as 'haemostatic resuscitation' [20]. It may be that current transfusion strategies can be improved to further improve survival after ATC [21], and the results of the randomized controlled trials are awaited [22]. In North America, the difficulty in managing ATC has sparked a renewed interest in whole blood for trauma resuscitation [23–26]. In contrast, in some European countries, fibrinogen and other factor concentrates have replaced fresh frozen plasma in the management of ATC [27]. The empiric evolution of divergent clinical practice underscores the need for a better mechanistic understanding of ATC and for more clinical research.

Table 1. Suggested definitions and prevalence of acute traumatic coagulopathy

Study	Number of included patients	Definition of ATC	Average ISS	% penetrating injury	Time to blood sample	% of patients with ATC
Brohi *et al.*, 2003 [4]	1088	PT, APTT, TT >1.5x ULN	20[a]	25	73 min	24.4
Macleod *et al.*, 2003 [5]	10790	APTT >34 s or PT >14 s	9[b]	NS	106 min	28 – PT 8 – APTT
Brohi *et al.*, 2007 [6]	208	PT, APTT, TT >1.5x ULN	17[a]	25	32 min	NS
Chironi *et al.*, 2007 [7]	88	INR >1.6 or APTT >60 s or platelets <100x10^9/l or Fg <1g/l	22[b]	NS	'On admission'	28
Maegele *et al.*, 2007 [8]	8724	Quick's <70% or platelets <100x10^9/l	24[b]	4	69 min to admission	34.2
Niles *et al.*, 2008 [9]	391	INR ≥1.5	17[a]	92	'On admission'	38
Frith *et al.*, 2010 [10]	3646	PTr >1.2	22[a]	10	60 min to admission	36
Floccard *et al.*, 2010 [11]	45	ISTH DIC score ≥1	25[b]	0	25 min	56
Davenport *et al.*, 2011 [12]	300	ROTEM EXTEM CA5 ≤35 mm	12[a]	21	77 min	8 – PT 23 – CA5

The ISTH DIC uses a five-step diagnostic algorithm to calculate a coagulopathy score. Parameters included in the calculation include platelet count, fibrinogen, PT and FDP levels. Points are assigned to each laboratory parameter and a final score is determined.
NS, not stated.
[a]Median.
[b]Mean.
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INJURY-RELATED FACTORS CONTRIBUTING TO ACUTE TRAUMATIC COAGULOPATHY

The following may occur to varying degrees in each individual, predisposing to or amplifying ATC.

Consumption and loss

Coagulation factors and platelets are consumed during the formation of clots, as well as lost from the intravascular compartment during bleeding. Anaemia due to red cell loss has a major effect on primary haemostasis through reduction of axial blood flow and thus reduction of platelet and plasma margination to blood vessel walls and sites of injury [28], such that there is an inverse correlation between the haematocrit and in-vitro bleeding time [29].

Dilution

Autodilution results from reversal of Starling forces and consequent shifts of interstitial fluid into the vascular compartment. Dilution is aggravated by replacement of lost whole blood with crystalloid, colloid and red cell transfusion. The volume of fluid administered both *in vitro* and *in vivo* is proportional to the resultant coagulopathy [8,30].

Hormonal and cytokine-induced changes

Following tissue injury, levels of cytokines and hormones, such as adrenaline and vasopressin, rise, and cytokine, hormone and thrombin production lead to endothelial cell activation (ECA) [31]. Vasopressin stimulates production of tissue plasminogen activator (t-PA) and Weibel Palade body release, which increases von Willebrand factor levels and expression of P-selectin on the endothelium, enhancing platelet recruitment. Cytokines, such as TNF and IL-1, as well as thrombin and continued hypoxia, cause ECA and effect a slow change in endothelial cell phenotype from antithrombotic to prothrombotic, which in inadequately resuscitated patients leads to DIC. ECA downregulates thrombomodulin and fibrinolysis (PAI-1 levels increase), causes cleavage of glycosaminoglycans from the cell surface, limiting activation of antithrombin, increases platelet-activating factor production, increases endothelial permeability and *in vitro* upregulates the expression of tissue factor (TF) [31,32].

Hypoxia, acidosis and hypothermia

This triad predisposes to bleeding by impairing the function of platelets and coagulation proteases while increasing fibrinolysis [33]. Hypoxia exacerbates ECA and coagulopathic changes are most pronounced once pH is less than 7.1 [34] and temperatures less than 33°C [35].

Immune system activation

Tissue damage and shock are associated with platelet release of soluble CD40 ligand, a potent immune activator [36▪]. Immune stimulation, including complement activation, is associated with release of damage-associated molecular patterns, such as mitochondrial damage-associated molecular patterns and histone-complexed DNA [37,38▪]. Immune activation can aggravate tissue damage through mechanisms including proteolytic degradation and oxidative stress, thus amplifying coagulation activation.

CHARACTERIZATION OF ACUTE TRAUMATIC COAGULOPATHY

In two large observational studies, one-quarter of trauma patients had prolongation of an APTT and/or PT at admission which was independently associated with bleeding and death [3]. ATC was found in patients who received little or no intravenous fluid therapy, negating the long-held belief that iatrogenic haemodilution is the main causative factor in traumatic coagulopathy [6,10,12,39]. Fibrinolysis also appears to play an important role in contributing to traumatic coagulopathy [40,41▪], as suggested by the reduction in mortality due to use of TXA in CRASH-2 [42,43].

Much of the work characterizing ATC has been based on standard plasma-based tests resulting in definitions based on abnormal APTT, PT, TT, INR or PTr, low platelet count, low fibrinogen level or an ISTH DIC score of at least 1–4 (nonovert DIC) or ≥ 5 (overt DIC) (Table 2) [3,40,44–47], including a description of the ISTH DIC score. Viscoelastic tests have been used to identify ATC [12], but there is no universally accepted assay or definition.

PATHOPHYSIOLOGY OF ACUTE TRAUMATIC COAGULOPATHY

Conceptually, it seems ATC is due to massive stimulation of coagulation and fibrinolysis by damaged tissues. Tissue damage *per se* leads to exposure of the subendothelial matrix, which contains TF, driving localized coagulation, and collagen which binds to platelet glycoprotein VI and vWF – glycoprotein Ib, causing platelet activation. In keeping with this hypothesis, reduced clotting factor and physiological anticoagulant levels (range 35–98%) [11,48,49]

Table 2. Visco elastic parameters used by different authors to define fibrinolysis

Study	TEG or ROTEM	Value used	Normal range (%)	Clinical setting	Prevalence of TEG hyperfibrinolysis (%)
Levrat *et al.*, 2008 [44]	ROTEM	LI30 LI60	<2 <43	Trauma	6
Carroll *et al.*, 2009 [45]	TEG	LY60	<15	Trauma	2
Kashuk *et al.*, 2010 [40]	r-TEG	LY60	<15	Trauma	18
Tauber *et al.*, 2011 [46]	ROTEM	LI60	>85	Trauma	7.3
Ostrowski *et al.*, 2011 [47]	TEG	Lys30	<8	Trauma	1

LI30 or LI60, percentage of maximum clot strength present at 30 or 60 min; LY60, percentage fibrinolysis after 60 min; Lys30, decrease in maximal amplitude over 30 min after the maximal amplitude has been reached; ROTEM, rotational thrombelastometry (TEM International, GmbH, Munich, Germany); r-TEG, rapid TEG; TEG, (TEG; Haemoscope Corp, Niles, Illinois, USA).
Reproduced with permission [3].

and high thrombin-generating capacity [6,11,39, 50–52], as well as moderately reduced platelet counts [5,52] are found, that is, a consumptive coagulopathy. The most consumed coagulation factors following injury are fibrinogen and factor V [48,53], which are likely due, in part, to inactivation by activated protein C (aPC) or free plasmin [54,55], although the relative contributions of each are uncertain.

Thrombin is a central molecule in haemostasis – its generation not only converts fibrinogen to fibrin, resulting in fibrin strand formation, but it also activates platelets, leukocyctes and endothelium. Thrombin stimulates the production of t-PA from the endothelium, an effect previously known as secondary fibrinolysis. Stimulation of t-PA release from the endothelium by other factors, such as hypoxia, adrenaline and vasopressin, is known as primary fibrinolysis. High t-PA levels are reported in coagulopathic trauma patients [6,52]. In addition, when bound to the endothelial receptor thrombomodulin, thrombin activates protein C.

It has been argued that aPC is a major driver of ATC through its cleavage of factors Va and VIIIa, as well as binding of PAI-1, thereby possibly controlling fibrinolysis [12,39,54]. This mechanism is problematic for several reasons. Firstly, both platelet and plasma factor Va pools are resistant to aPC cleavage at concentrations of aPC relevant to either ATC or even pharmacologic dosing of recombinant human aPC in sepsis [56▪▪]. Furthermore, a normal platelet concentration of 200 000/mm^3 was able to eliminate aPC anticoagulant effects at suprapathophysiologic concentrations of aPC. In this study, aPC had no discernable effect on fibrinolysis in the presence or absence of platelets [56▪▪]. Secondly, PAI-1 is a potent inhibitor of aPC in the presence of the ubiquitous glycoprotein, vitronectin [57]. It has been hypothesized that the binding and inactivation of aPC by the vitronectin/PAI-1 complex could lead to PAI-1 depletion and thus promotion of fibrinolysis. This is unlikely given that PAI-1 circulates at roughly 10 times higher concentrations than aPC [58,59]. Furthermore, catalytic aPC neutralization of PAI-1 is a goal of pharmacologic manipulation, not likely a primary physiologic function of aPC [60,61]. We argue that it is the enormously increased production of t-PA, secondary to adrenaline, vasopressin and thrombin, not failure of inhibition which drives fibrinolysis during ATC.

After the immediate haemostatic effects resulting from tissue injury, further changes are orchestrated by ECA. As mentioned, thrombin and various cytokines cause ECA, as do hypoxia and hypoperfusion [62]. The importance of hypoperfusion in the pathogenesis of ATC has come from patient data [9,10,39,40,49,63,64] animal models, such as the rat trauma model [10,63] and in-vitro data [62,64]. These studies show that as shock indices increase (as measured by base deficit) the PT, PTr and INR values rise [4,10,12,61,62] and coagulation factor levels fell [10,62]. The largest of these studies ($n = 3646$) showed that ATC (PTr >1.2) was only evident with significant hypoperfusion (base deficit >6 mmol/l) combined with severe injury (ISS >15) [10].

The importance of fibrinolysis in ATC has come to the fore recently, for CRASH-2 reported a one-third reduction in bleeding mortality in trauma patients given TXA, a competitive inhibitor of plasminogen activation [42,43]. Other clinical data have shown that the degree of fibrinolysis is correlated with transfusion requirement [44] and mortality [44,65–68]. A sensitive marker of fibrinolysis is plasmin–antiplasmin complex, and levels are increased in nearly 60% of trauma patients [68]. Increased plasmin generation and fibrin products [69], such as D-dimers, [6,7,39,49,65,70] are found in bleeding trauma patients.

As time from injury increases, the prothrombotic effects of ECA gradually predominate,

especially if hypoxia and acidosis continue. This is partly mediated by release of phosphatidylserine-positive microparticles [71]; the endothelium switches from a net production of t-PA to a net production of PAI-1 [6,7,52,72]. A thrombotic coagulopathy and fibrinolytic shutdown ensues, thus probably explaining why treatment at this stage with an antifibrinolytic may worsen outcome [43].

Platelets play a central role in both primary haemostasis and the widely accepted cell-based model of coagulation. Platelets are resistant to collagen, ADP and arachidonic acid stimulation following trauma [73,74]. This platelet dysfunction, still of unclear cause, likely explains the many observations of improved outcomes associated with platelet transfusion despite platelet counts previously thought to be adequate [75–77]. Indeed, it appears that lower admission platelet count predicts mortality even within the normal range [78]. There is a suggestion that transfused platelet quality may be a determinant of trauma outcome [79].

Microparticles derived from blood and endothelial cells contribute to normal haemostasis. TF and thus fibrin incorporation into clots is dependent on the interaction between P-selectin glycoprotein ligand 1/TF-bearing microparticles from leukocytes and P-selectin on platelets adherent to damaged tissue [80]. Procoagulant microparticle production increases in trauma [81] and contributes to prothrombotic changes [82].

It has been argued by some that the initial picture seen in ATC is due to DIC [52,83]. However, although the early coagulation screen changes of ATC may resemble DIC resulting in a positive ISTH DIC score, there is no evidence of inappropriate disseminated clot formation on histological examination [84] – clot formation occurs only at the site of injury, so by definition early ATC is not DIC.

THE CLINICAL IMPORTANCE OF IDENTIFYING COAGULOPATHY

The hypothesis that the extent of coagulation activation will relate to the degree by which blood is exposed to TF on damaged tissues is supported by data showing that the severely injured are more likely to have ATC [4], have haemorrhagic shock [39], require transfusion support [61] and are most at risk of worsening coagulopathy and death [3,85,86].

Prediction of coagulopathy

A variety of scoring systems have been published for adults and children with injury, which aim to predict which patients will develop severe haemorrhage and thus shift clinical management from a reactive to a proactive approach [87–92]. None of the scoring systems, however, have the sensitivity to identify all patients at risk of coagulopathy and massive blood loss; any patient with major injury should therefore be assumed to be at risk [91].

METHODS FOR ACUTE TRAUMATIC COAGULOPATHY DIAGNOSIS AND MONITORING OF HAEMOSTATIC CHANGES

Standard laboratory tests

These include PT-based assays (PT, PTr and INR), APTT and Clauss fibrinogen. The PT/INR has been suggested as the more sensitive test to the multiple coagulation factor deficiencies, and therefore a better marker of ATC [53]. The current advantages of using standard tests are that every laboratory can provide these results; they have a use in guiding plasma product administration and predicting mortality [9].

Originally, the PT and APTT tests were designed to evaluate clotting factor deficiencies, not acquired coagulopathy, and are not predictors of later bleeding in these circumstances [93]. Moreover, they do not evaluate platelet number and function, fibrinolysis, thrombin generation or the interactions between coagulation proteases and phospholipid surfaces. Furthermore, turnaround times from sampling to obtaining results from the routine laboratory may be over an hour [12]. It is for these reasons that plasma-based coagulation tests have limited value in the immediate management of ATC, but they do have a major value in longitudinal monitoring during ongoing bleeding to guide the use of appropriate blood components.

Viscoelastic tests

Increasingly, TEG and ROTEM are being used in the trauma setting [46,65,68,73]. Overall, minimally injured patients tend to have normal traces, and moderate or severe trauma may be associated with TEG changes [65,71,94]. TEG and ROTEM have a role in the assessment of severe fibrinolytic activity but are not sensitive enough to detect more limited lytic activity [69]. Increased fibrinolytic activity, when detected by viscoelastic testing, is associated with a poor prognosis. Schochl *et al.* [67] and other authors arbitrarily used the term 'hyperfibrinolysis' for lysis greater than a certain maximal amplitude on ROTEM testing (Schochl uses 15%). However, confusion has arisen with this TEG/ROTEM-associated terminology because traditionally hyperfibrinolysis describes a situation in which fibrinolytic

activity is greater than fibrin formation, clot integrity is threatened, and there is clot breakdown [45] rather than a loose term used simply to describe increased evidence of fibrinolysis (Table 2). Therefore, there is a suggestion that the term 'TEG hyperfibrinolysis' be used in relation to the TEG viscoelastic measurements [95].

There is as yet no agreed viscoelastic definition of ATC, although the changes seen include the following: increases in clotting time and clot formation time, and reduction in clot amplitude and maximal clot amplitude [12,47,63,67]. One study [12] using ROTEM reported an EXTEM CA5 (clot amplitude at 5 min) value of <36 mm as diagnostic of ATC. Another study [95] suggests that TEG or ROTEM A10 correlates best with platelet count and fibrinogen level and predicted transfusion needs. Advocates for viscoelastic testing argue that the ability to distinguish different haemostatic abnormalities provides a means of individualizing coagulation management [44,68,96]. However, there are no validated ROTEM and TEG algorithms in trauma and external quality assurance schemes are at an early stage. As with standard laboratory tests, viscoelastic tests are routinely performed at 37°C, and results will underestimate coagulation disturbances in a hypothermic patient.

CONCLUSION

Despite the many advances in our understanding of ATC in the last decade, further clinical observational studies are required to further our understanding of the pathophysiology of traumatic coagulopathy and thus inform the direction of future studies to improve haemostatic management and outcome.

Acknowledgements

None.

Conflicts of interest

Disclaimer: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

Neither author has any conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. WHO. World Health Organisation. Global Health Indicators. 2011. http://www.who.int/whosis/whostat/EN_WHS2011_Part2.pdf.
2. Eastridge BJ, Mabry RL, Seguin P, *et al.* Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg 2012; 73 (Suppl 5):S431–S437.
3. Curry NS, Davenport RA, Hunt BJ, Stanworth SJ. Transfusion strategies for traumatic coagulopathy. Blood Rev 2012; 26:223–232.
4. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54:1127–1130.
5. MacLeod JB, Lynn M, McKenney MG, *et al.* Early coagulopathy predicts mortality in trauma. J Trauma 2003; 55:39–44.
6. Brohi K, Cohen MJ, Ganter MT, *et al.* Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008; 64:1211–1217.
7. Chironi GN, Boulanger CM, Simon A, *et al.* Endothelial microparticles in diseases. Cell Tissue Res 2009; 335:143–151.
8. Maegele M, Lefering R, Yucel N, *et al.* Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007; 38:298–304.
9. Niles SE, McLaughlin DF, Perkins JG, *et al.* Increased mortality associated with the early coagulopathy of trauma in combat casualties. J Trauma 2008; 64:1459–1465.
10. Frith D, Goslings JC, Gaarder C, *et al.* Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010; 8:1919–1925.
11. Floccard B, Rugeri L, Faure A, *et al.* Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury 2012; 43:26–32.
12. Davenport R, Manson J, De'Ath H, *et al.* Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011; 39:2652–2658.
13. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. Blood Rev 2009; 23:231–240.
14. Perkins JG, Cap AP, Spinella PC, *et al.,* 31st Combat Support Hospital Research Group. Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients (CME). Transfusion 2011; 51:242–252.
15. Borgman MA, Spinella PC, Perkins JG, *et al.* The ratio of blood products transfused affects the mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007; 63:805–813.
16. Pidcoke HF, Aden JK, Mora AG, *et al.* Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: increased plasma and platelet use correlates with improved survival. J Trauma Acute Care Surg 2012; 73 (Suppl 5):S445–S452.
17. Spahn DR, Bouillon B, Cerny V, *et al.* Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013; 17:R76.
18. 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; 10:1342–1351.
19. Morrison JJ, Ross JD, Dubose JJ, *et al.* Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surg 2013; 148:218–225.
20. Johansson PI, Stensballe J. Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets–a review of the current literature. Transfusion 2010; 50:701–710.
21. Khan S, Brohi K, Chana M, *et al.,* International Trauma Research Network (INTRN). Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. J Trauma Acute Care Surg 2014; 76:561–567.
22. Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. Hematology Am Soc Hematol Educ Program 2013; 2013:656–659.
23. Spinella PC, Reddy HL, Jaffe JS, *et al.* Fresh whole blood use for hemorrhagic shock: preserving benefit while avoiding complications. Anesth Analg 2012; 115:751–758.
24. Cotton BA, Podbielski J, Camp E, *et al.,* Early Whole Blood Investigators. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg 2013; 258:527–532.
25. Murdock AD, Berséus O, Hervig T, *et al.* Whole blood: the future of traumatic hemorrhagic shock resuscitation. Shock 2014; 41 (Suppl 1):62–69.
26. Cap AP. The school of hard knocks: what we've learned and relearned about transfusion in a decade of global conflict. Transfus Med 2014; 24:135–137.
27. Fries D, Innerhofer P, Perger P, *et al.* Coagulation management in trauma-related massive bleeding. - Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI). Anasthesiol Intensivmed Notfallmed Schmerzther 2010; 45:552–561.
28. Valeri CR, Khuri S, Ragno G. Nonsurgical bleeding diathesis in anemic thrombocytopenic patients: role of temperature, red blood cells, platelets, and plasm-clotting proteins. Transfusion 2007; 47:S206–S248.
29. Eugster M, Reinhart WH. The influence of the haematocrit on primary haemostasis in vitro. Thromb Haemost 2005; 94:1213–1218.
30. Bolliger D, Szlam F, Molinaro RJ, *et al.* Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth 2009; 102:793–799.

31. Hunt BJ, Jurd KM. Endothelial cell activation. BMJ 1998; 316:1328–1329.
32. Johansson PI, Sorensen AM, Perner A, *et al.* Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? A prospective observational study. Crit Care 2011; 15:R272.
33. Dirkmann D, Radü-Berlemann J, Görlinger K, Peters J. Recombinant tissue-type plasminogen activator-evoked hyperfibrinolysis is enhanced by acidosis and inhibited by hypothermia but still can be blocked by tranexamic acid. J Trauma Acute Care Surg 2013; 74:482–488.
34. Martini WZ, Pusateri AE, Uscilowicz JM, *et al.* Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma 2005; 58:1002–1009.
35. Wolberg AS, Meng ZH, Monroe DM 3rd, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004; 56:1221–1228.
36. ■ Johansson PI, Windeløv NA, Rasmussen LS, *et al.* High sCD40L levels early after trauma are associated with enhanced shock, sympathoadrenal activation, tissue and endothelial damage, coagulopathy and mortality. J Thromb Haemost 2012; 10:207–216.

Novel findings suggesting sCD40L may mediate and/or be a product of tissue and endothelial damage.

37. Zhang Q, Raoof M, Chen Y, *et al.* Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464:104–107.
38. ■ Johansson PI, Sørensen AM, Perner A, *et al.* Blood levels of histone-complexed DNA fragments are associated with coagulopathy, inflammation and endothelial damage early after trauma. J Emerg Trauma Shock 2013; 6:171–175.

Increased histone-complexed DNA fragments were associated with ISS and markers of hyperfibrinolysis.

39. Brohi K, Cohen MJ, Ganter MT, *et al.* Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245:812–818.
40. Kashuk JL, Moore EE, Sawyer M, *et al.* Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg 2010; 252:434–444.
41. ■ Raza I, Davenport R, Rourke C, *et al.* The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013; 11:307–314.

Detailed investigation of fibrinolysis in trauma patients.

42. Shakur H, Roberts I, Bautista R, *et al.,* CRASH-2 trial collaborators. 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; 376:23–32.
43. Roberts I, Shakur H, Afolabi A, *et al.,* CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011; 377:1096–1101.
44. Levrat A, Gros A, Rugeri L, *et al.* Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth 2008; 100:792–797.
45. Carroll RC, Craft RM, Langdon RJ, *et al.* Early evaluation of acute traumatic coagulopathy by thromboelastography. Transl Res 2009; 154:34–39.
46. Tauber H, Innerhofer P, Breitkopf R, *et al.* Prevalence and impact of abnormal ROTEM assays in severe blunt trauma: results of the 'Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study'. Br J Anaesth 2011; 107:378–387.
47. Ostrowski SR, Sørensen AM, Larsen CF, Johansson PI. Thrombelastography and biomarker profiles in acute coagulopathy of trauma: a prospective study. Scand J Trauma Resusc Emerg Med 2011; 19:64.
48. Jansen JO, Scarpelini S, Pinto R, *et al.* Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma 2011; 71:S435–S440.
49. Shaz BH, Winkler AM, James AB, *et al.* Pathophysiology of early trauma-induced coagulopathy: emerging evidence for hemodilution and coagulation factor depletion. J Trauma 2011; 70:1401–1407.
50. Dunbar NM, Chandler WL. Thrombin generation in trauma patients. Transfusion 2009; 49:2652–2660.
51. Chandler W. Procoagulant activity in trauma patients. Am J Clin Pathol 2010; 134:90–96.
52. Hayakawa M, Sawamura A, Gando S, *et al.* Disseminated intravascular coagulation at an early phase of trauma is associated with consumption coagulopathy and excessive fibrinolysis both by plasmin and neutrophil elastase. Surgery 2011; 149:221–230.
53. Yuan S, Ferrell C, Chandler WL. Comparing the prothrombin time INR versus the APTT to evaluate the coagulopathy of acute trauma. Thromb Res 2007; 120:29–37.
54. Cohen MJ, Call M, Nelson M, *et al.* Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012; 255:379–385.
55. Omar MN, Mann KG. Inactivation of factor Va by plasmin. J Biol Chem 1987; 262:9759–9765.
56. ■■ Campbell JE, Meledeo MA, Cap AP. Comparative response of platelet fV and plasma fV to activated protein C and relevance to a model of acute traumatic coagulopathy. PLoS One 2014; 9:e99181.

Shows that APC is not the driver of ATC.

57. Rezaie AR. Vitronectin functions as a cofactor for rapid inhibition of activated protein C by plasminogen activator inhibitor-1. Implications for the mechanism of profibrinolytic action of activated protein CJT J Biol Chem. 2001; 276:15567–15570.
58. Lijnen HR. Pleiotropic functions of plasminogen activator inhibitor-1. J Thromb Haemost 2005; 3:35–45.
59. Griffin JH1, Fernández JA, Gale AJ, Mosnier LO. Activated protein C. J Thromb Haemost 2007; 5 (Suppl 1):73–80.
60. Okajima K, Koga S, Kaji M, *et al.* Effect of protein C and activated protein C on coagulation and fibrinolysis in normal human subjects. Thromb Haemost 1990; 63:48–53.
61. Komissarov AA, Andreasen PA, Declerck PJ, *et al.* Redirection of the reaction between activated protein C and a serpin to the substrate pathway. Thromb Res 2008; 122:397–404.
62. Faller DV. Endothelial cell responses to hypoxic stress. Clin Exp Pharmacol Physiol 1999; 26:74–84.
63. Darlington DN, Craig T, Gonzales MD, *et al.* Acute coagulopathy of trauma in the rat. Shock 2013; 39:440–446.
64. Pinksy DJ, Yan SF, Lawson C, *et al.* Hypoxia and modification of the endothelium: implications for regulation of vascular homeostatic properties. Semin Cell Biol 1995; 6:283–294.
65. Sawamura A, Hayakawa M, Gando S, *et al.* Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res 2009; 124:608–613.
66. Schöchl H, Frietsch T, Pavelka M, Jámbor C. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 2009; 67:125–131.
67. Schöchl H, Nieaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; 14:R55.
68. Hunt BJ, Raza I, Brohi K. The incidence and magnitude of fibrinolytic activation in trauma patients: a reply to a rebuttal. J Thromb Haemost 2013; 11:1437–1438.
69. Kushimoto S, Gando S, Saitoh D, *et al.* Clinical course and outcome of disseminated intravascular coagulation diagnosed by Japanese Association for Acute Medicine criteria. Comparison between sepsis and trauma. Thromb Hemost 2008; 100:1099–1105.
70. Rugeri L, Levrat A, David JS, *et al.* Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Hemost Thromb 2007; 5:289–295.
71. Castellino FJ, Chapman MP, Donahue DL, *et al.* Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. J Trauma Acute Care Surg 2014; 76:1169–1176.
72. Chen JP, Rowe DW, Enderson BL. Contrasting post-traumatic serial changes for D-dimer and PAI-1 in critically injured patients. Thromb Res 1998; 94:175–185.
73. Kutcher ME, Redick BJ, McCreery RC, *et al.* Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012; 73: 13–19.
74. Perkins JG, Cap AP, Spinella PC, *et al.* An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. J Trauma 2009; 66 (Suppl 4):S77–S84.
75. Zink KA, Sambasivan CN, Holcomb JB, *et al.* A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009; 197:565–570.
76. Brown LM, Call MS, Margaret Knudson M, *et al.* A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. J Trauma 2011; 71 (Suppl 3):S337–S342.
77. Stansbury LG, Hess AS, Thompson K, *et al.* The clinical significance of platelet counts in the first 24 hours after severe injury. Transfusion 2013; 53:783–789.
78. Inaba K, Branco BC, Rhee P, *et al.* Impact of the duration of plateletstorage in critically ill trauma patients. J Trauma 2011; 71:1766–1773.
79. Falati S, Liu Q, Gross P, *et al.* Accumulation of tissue factor into developing thrombi in vivo is dependent upon microparticle P-selectin glycoprotein ligand 1 and platelet P-selectin. J Exp Med 2003; 197: 1585–1598.
80. Morel N, Morel O, Petit L, *et al.* Generation of procoagulant microparticles in cerebrospinal fluid and peripheral blood after traumatic brain injury. J Trauma 2008; 64:698–704.
81. Park MS, Owen BA, Ballinger BA, *et al.* Quantification of hypercoagulable state after blunt trauma: microparticle and thrombin generation are increased relative to injury severity, while standard markers are not. Surgery 2012; 151:831–836.
82. Gando S, Sawamura A, Hayakawa M. Trauma, shock and disseminated intravascular coagulation: lessons from the classical literature. Ann Surg 2011; 254:10–19.
83. Rizoli S, Nascimento B, Key N, *et al.* Disseminated intravascular coagulopathy in the first 24 hours after trauma: the association between ISTH score and anatomopathologic evidence. J Trauma 2011; 71:S441–S447.

84. Maegele M, Lefering R, Wafaisade A, *et al.* Trauma Registry of Deutsche Gesellschaft für Unfallchirurgie (TR-DGU). Revalidation and update of the TASH-score: a scoring system to predict the probability for massive transfusion as a surrogate for life-threatening haemorrhage after severe injury. Vox Sang 2011; 100:231–238.

85. Cancio LC, Wade CE, West SA, Holcomb JB. Prediction of mortality and of the need for massive transfusion in casualties arriving at combat support hospitals in Iraq. J Trauma 2008; 64:S51–S56.

86. Maegele M, Lefering R, Wafaisade A, *et al.* Revalidation and update of the TASH-score: a scoring system to predict the probability for massive transfusion as a surrogate for life-threatening haemorrhage after severe injury. Vox Sang 2011; 100:231–238.

87. Ruchholtz S, Pehle B, Lewan U, *et al.* The emergency room transfusion score (ETS): prediction of blood transfusion requirement in initial resuscitation after severe trauma. Transfus Med 2006; 16:49–56.

88. Schreiber MA, Perkins J, Kiraly L, *et al.* Early predictors of massive transfusion in combat casualties. J Am Coll Surg 2007; 205:541–545.

89. Yücel N, Lefering R, Maegele M, *et al.* Trauma associated severe hemorrhage (TASH)-score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma 2006; 60:1228–1237.

90. Reed MJ, Lone N, Walsh TS. Resuscitation of the trauma patient: tell me a trigger for early haemostatic resuscitation please! Crit Care 2011; 15:126.

91. Stanworth SJ, Morris TP, Gaarder C, *et al.* Reappraising the concept of massive transfusion in trauma. Crit Care 2010; 14:R239.

92. Dzik WH. Predicting hemorrhage using preoperative coagulation screening assays. Curr Hematol Rep 2004; 3:324–330.

93. Johansson PI, Stissing T, Bochsen L, Ostrowski SR. Thrombelastography and thromboelastometry in assessing coagulopathy in trauma. Scand J Trauma Resusc Emerg Med 2009; 17:45.

94. Hunt BJ, Segal H. Hyperfibrinolysis. J Clin Pathol 1996; 49:958.

95. Meyer AS1, Meyer MA, Sørensen AM, *et al.* Thrombelastography and rotational thromboelastometry early amplitudes in 182 trauma patients with clinical suspicion of severe injury. J Trauma Acute Care Surg 2014; 76:682–690.

96. Kaufmann CR, Dwyer K, Crews JD, *et al.* Usefulness of thromboelastography in assessment of trauma patient coagulation. J Trauma 1997; 42:716–722.

Airway and ventilator management in trauma patients

Stefan K. Beckers[a,c], *Jörg C. Brokmann*[b], *and Rolf Rossaint*[a]

Purpose of review
Securing the airway to provide sufficient oxygenation and ventilation is of paramount importance in the management of all types of emergency patients. Particularly in severely injured patients, strategies should be adapted according to useful recent literature findings.

Recent findings
The role of out-of-hospital endotracheal intubation in patients with severe traumatic brain injury as prevention of hypoxia still persists, and the ideal neuromuscular blocking agent will be a target of research. Standardized monitoring, including capnography and the use of standardized medication protocols without etomidate, can reduce further complications. Prophylactic noninvasive ventilation may be useful for patients with blunt chest trauma without respiratory insufficiency.

Summary
An algorithm-based approach to airway management can prevent complications due to inadequate oxygenation or procedural difficulties in trauma patients; therefore, advanced equipment for handling a difficult airway is needed. After securing the airway, ventilation must be monitored by capnography, and normoventilation involving the early use of protective ventilation with low-tidal volume and moderate positive end-expiratory pressure must be the target.
After early identification of patients with blunt chest trauma at risk for respiratory failure, noninvasive ventilation might be a treatment strategy, which should be evaluated in future research.

Keywords
airway management, emergency management, intubation, prehospital, ventilation

INTRODUCTION

Effective management of the airway is a central issue in emergency and critical care medicine for providing sufficient oxygenation and ventilation and for preventing gastric, debris or blood aspiration in trauma patients. Endotracheal intubation (ETI) as a standard procedure in anesthesiology and intensive care medicine continues to be the gold standard for protecting the airway in the emergency medicine settings, both pre and in-hospital [1]. Algorithm-based strategies are well established and widely accepted in international course strategies for the prehospital (e.g., prehospital trauma life support) and in-hospital (e.g., advanced trauma life support) treatment of trauma patients, in which 'A' represents the 'airway' and 'B' subsumes all diagnostic and procedural tasks for 'breathing' [2–4].

INDICATIONS FOR AIRWAY MANAGEMENT IN TRAUMA

Severe multiple injuries are always associated with impaired tissue oxygenation and the risk of overall damage to the affected human organism. Therefore, oxygen uptake is essential. In many patients, adequate oxygenation can only be sufficiently provided via controlled or assisted mechanical ventilation using a secured airway. Following international recommendations and guidelines, ETI represents the gold standard for this task [1,3,5]. In detail, there are widely accepted, specific recommendations for the application of ETI and further ventilation in trauma patients for hypoxia ($SpO2 < 90\%$), despite the administration of oxygen (e.g., by nasal or face mask) and after exclusion of a

[a]Department of Anaesthesiology, [b]Emergency Department, University Hospital Aachen, RWTH Aachen University and [c]Emergency Medical Service, Fire Department, Aachen, Germany

Correspondence to Professor Rolf Rossaint, MD, PhD, Department of Anesthesiology, University Hospital, RWTH Aachen University, Pauwelsstr. 30, D–52074 Aachen, Germany. Tel: +49 241 80 88179; fax: +49 241 80 82304; e-mail: Rrossaint@ukaachen.de

Curr Opin Crit Care 2014, 20:626–631
DOI:10.1097/MCC.0000000000000160

KEY POINTS

- Adequate airway and ventilator management focus on preventing hypoxia, hypocapnia or hypercapnia.
- The role of ETI in patients with severe TBI and respective strategies for out-of-hospital management remains unclear, and more work is required to determine the ideal neuromuscular blocking agent.
- After securing the airway with a standardized medication protocol for RSI, ventilation must be monitored by capnography, and normoventilation that involves the early use of protective ventilation with low-tidal volume and moderate PEEP should be the target.
- NIV is a useful prophylactic strategy in patients suffering from blunt chest trauma to reduce the occurrence of respiratory failure, but it requires further study.

tension pneumothorax. First, severe traumatic brain injury (TBI) is categorized with a Glasgow Coma Scale of less than nine for in-hospital and out-of-hospital emergency situations [5,6]. In fact, studies have demonstrated that ETI in patients with TBI improved not only the hemodynamic parameters and end-tidal carbon dioxide but also survival [7,8]. Patients with multiple trauma and TBI often suffer from hypoxia in combination with hemodynamic instability, and in these cases, ETI is indicated to prevent further secondary brain damage [9,10]. Indications of ETI in trauma patients are as follows:

(1) hypoxia (SpO2 < 90%);
(2) impending airway obstruction (e.g., hemorrhage, swelling);
(3) severe TBI, categorized with a Glasgow Coma Scale of less than nine;
(4) severe chest trauma with respiratory failure;
(5) hemodynamic instability (RRsys < 90 mmHg) related to trauma.

Another certain indication for ETI is severe chest trauma with respiratory failure, for example, as a result of pulmonary contusion or serial rib fractures with an unstable thorax, if other basic procedures are not effective for ensuring sufficient oxygenation [5]. However, registry results from a matched-pair analysis must be considered for risk stratification, wherein no benefit for ETI can be observed in patients with severe thoracic trauma without respiratory insufficiency [11]. Concerning the time point of emergency anesthesia and ETI, studies have suggested the prehospital use of ETI, or at least its use in the trauma room [12,13], and it is classified as well tolerated and effective, with success rates of 98.7 and 96.6%, respectively [13,14]. A retrospective evaluation of overall 4317 patients (3571 prehospital vs. 746 in-hospital ETI) showed that in-hospital ETI was particularly associated with an increased risk of a poor outcome ($P < 0.0001$) [15]. Conversely, a regional evaluation examined different airway management techniques for out-of-hospital patients with TBI in association with the outcome and found poor outcomes following rapid sequence induction (RSI), in contrast to the widespread assumption that aggressive airway management is associated with better outcomes [9,16▪]. A recently published study evaluated data from the Resuscitation Outcomes Consortium Hypertonic Saline Trial in a secondary analysis and examined the associations between out-of-hospital and emergency department airway management with respect to outcome in patients with isolated severe TBI or hemorrhagic shock. Overall, 1116 patients with TBI and 528 with hemorrhagic shock were included, and the authors reported that out-of-hospital airway management is linked to a tendency to increased mortality, particularly in presence of hemorrhagic shock, but without statistical difference [17▪▪]. Based on these facts, the conclusion of Boer *et al.* [18], that is, that there is broad consensus that 'adequate airway management, prevention of hypoxia, hypocapnia or hypercapnia, prevention of hypotension and control of hemorrhage represent preclinical therapeutic modalities that may contribute to improved survival in severe TBI' remains current. In fact, their postulation that randomized controlled trials (RCTs) are particularly helpful for evaluating the optimal strategies for different emergency medical systems must be highly emphasized. Nevertheless, beside such studies we might learn also a lot from comparative effectiveness research using large prospective registries.

PREPARATION AND FACTORS TO CONSIDER

Oxygenation of the organism, not the endotracheal placement of a tube itself, is of chief importance in the airway management procedure [19▪]. Therefore, preoxygenation, if feasible, which is performed using a facemask with high-flow oxygen in patients in whom it is still feasible, is useful for providing optimal ETI conditions not only for an expected difficult airway setting but also in severely injured patients [3,20]. However, preoxygenation before ETI should be limited to 3–5 min, since doubling the time of oxygenation from 4 to 8 min was on the one hand not associated with significant improvement in the arterial pO_2 and on

the other hand associated with the potential risk of delayed airway management procedures in critical patients [21].

Moreover, it has to be realized that the conditions for patients who require ETI in the out-of-hospital emergency setting are challenging and influenced by several factors that are worth considering [3]. A 10-year evaluation of 6088 trauma patients with airway management identified direct injury of the head or neck with loss of the normal anatomy of the upper airway, pharyngeal tumor and laryngospasm as the main risk factors for difficult airway management situations [12]. In fact, difficult situations for ETI are often obvious, such as maxillofacial trauma, which is known as an independent predictor for difficult airway management [22]; facial bleeding or neck tumors, in which strategies should anticipate possible complications [23,24]. The summary of possible aggravating factors to consider in prehospital ETI is given as follows [24,25] (compilation of factors that can complicate prehospital intubation. The corresponding categories can be almost 1 : 1 transferred for in-hospital situations.):

(1) patient site
    (a) blood, secretions or vomit;
    (b) traumatic or thermal damage of the upper respiratory tract;
    (c) inflammation or swelling of the upper airways;
    (d) subcutaneous emphysema;
    (e) immobilization of the cervical spine;
    (f) no or limited preoxygenation;
    (g) inadequate depth of anesthesia;
    (h) no neuromuscular blockade;
    (i) usually no awake intubation features are available in the airways that are anticipated to be difficult;
(2) due to situation and site
    (a) simultaneous tasks or procedures to provide (e.g., chest compressions);
    (b) environmental conditions (e.g., lighting, noise);
    (c) restricted access to patient;
    (d) limited equipment;
    (e) differing teams;
    (f) missing or not successfully communicated standards;
    (g) lack of competent support on-site.

Table 1 identifies general risk factors associated with a difficult airway [26]. The following list gives an overview of the recommendations for securing the airway in emergency medical settings (given by the Working Group in Emergency Medicine of the German Society for Anesthesiology and Intensive Care Medicine) [25].

Table 1. Identified risk factors associated with a difficult airway

History	Previously noted difficulties
	Male
	Age 40–59
	Diabetes
	Acromegaly
	Rheumatoid arthritis
	Obstructive sleep apnea
	Head and neck surgery, radiation
Physical exam	Obesity
	Upper airway trauma, burn or swelling
	Large tongue
	Receding jaw
	High arched palate
	Prominent upper incisors
	Short thick neck
	Fixed or 'high' larynx
	Mouth opening <4 cm
	Mallampati class 3 or 4
	Thyromental distance <6 cm
	Reduced head/neck mobility

Adapted from [19▪,26].

(1) Critical review of the indication for invasive airway management;
(2) If possible, application of an adequate preoxygenation with high FiO2 before any invasive airway management [ETI or extraglottic airway (EGA)];
(3) Endotracheal tube as the gold standard, but only if at least 100 documented ETIs occur in patients under supervision and carried out 10 ETIs/year;
(4) EGA as the primary access when the above-mentioned requirements cannot be fulfilled and if 10 applications are documented under supervision and three EGAs/year were performed, or an alternative for difficult intubation;
(5) Use of EGA with drainage and placing a stomach tube or an intubating laryngeal mask airway;
(6) Use of video laryngoscopy is possible as an alternative when there is sufficient internal clinical experience;
(7) Optimized mask ventilation (two-handed, double C-handle), optimal head positioning +/− matching Guedel and with a high FiO2 between two intubation attempts, particularly in children;

(8) No application of cricoid pressure as prophylaxes for aspiration;
(9) Continuous capnography after each airway management procedure;
(10) Communication of standards and corporate training of emergency teams.

MEDICATION

Airway management for ETI as part of emergency anesthesia should be performed as RSI to ensure that the airway is secured as quickly and safely as possible [27–29]. This approach is described to be sufficient and effective in the hands of experienced anesthesiologists [12], whereas a nonstructured usage is associated with increased patient mortality [3]. For RSI, the application of a neuromuscular blocking agent and a sedative agent is necessary. For many years, etomidate was the first-line medication because of its hemodynamic stability, but several studies have called the previous strategies into question. One retrospective study [30] showed an increased risk for acute respiratory distress syndrome with multiorgan failure and a prolonged length of hospital stay and ventilator days for patients treated with a single dose of etomidate. Additionally, a prospective and randomized trial reported a prolonged stay in the ICU and an increased rate of ventilator days and length of hospital stay following etomidate use [31].

For the analgetic part of emergency anesthesia, fentanyl or sufentanil for hemodynamically stable patients and ketamine for hemodynamically unstable patients are commonly used; anesthetic agents are often used depending on the different conditions, such as the hemodynamic status, pattern of injuries and experience of the user [32,33].

Recent literature follows this line of research and supports the substitution of etomidate by ketamine without negatively influencing the hemodynamic parameters in both prehospital [34▪] and in-hospital settings [35]. Additionally, Ballow *et al.* [35] reported an RSI medication protocol for simplifying the airway management strategy to avoid potential complications.

With respect to the neuromuscular blocking agent used, a Cochrane database review [36] evaluated 58 studies concerning the question of rocuronium vs. succinylcholine for RSI intubation, and 37 of these studies were included in the updated analyses in 2008. This analysis reported no significant difference in intubation conditions when succinylcholine was compared with 1.2 mg/kg rocuronium, but the study team finally concluded that succinylcholine was clinically superior because of its shorter duration of action. In fact, another observational study including 1045 patients demonstrated more successful RSI with fewer intubation attempts for succinylcholine compared with rocuronium [37], but prospective randomized trials are needed to clarify this topic.

ALTERNATIVE TECHNIQUES

Even if ETI remains the gold standard for airway management in trauma patients, alternative equipment should be available and techniques must be considered in a structured approach after a maximum of three insufficient attempts [27–29]. In fact, several adjuncts and technical equipment have been developed [38] for use if ETI is not possible, but specific training is required to efficiently handle these tools. A commonly used tool is the laryngeal mask airway and its different variations, such as the intubating laryngeal mask airway, which has proven successful after failed direct laryngoscopy in patients with predicted difficult airways [39,40]. Using video-guided airway management technology, this invention might represent a theoretically optimal solution in cases of predicted or unpredicted difficult airways. In an RCT using the direct laryngoscope or the GlideScope (Verathon Inc., Bothell, USA) video laryngoscope, 623 in-hospital patients were included; there was no difference in survival to hospital discharge in the observed patients [41▪]. However, use of GlideScope was associated with longer intubation times than direct laryngoscopy and in the subgroup of severe head injury trauma patients was associated with a greater incidence of hypoxia ($SaO2 \leq 80\%$) and mortality.

VENTILATION AND MONITORING

The complication with the utmost fatal consequence in airway management with ETI is undiscovered esophageal intubation, which has an incidence rate reported to range from less than 1 [42] to 17% [43], with mortality rates reaching 80% [44]. Therefore, it is widely accepted that strategies to prevent esophageal intubation, such as a standardized check, verification of endotracheal tube placement and ventilation monitoring, are necessary. It is evident that the inclusion of capnography can sufficiently detect esophageal misplacement [45,46], so it is therefore also part of the international guidelines and recommendations for treating patients with cardiac arrest [1,47▪]. Additionally, capnography is also the gold standard for ensuring adequate ventilation during mechanical ventilation and is effective for preventing hypocapnia and hypercapnia as well as hypoventilation and hyperventilation. Further, particularly for patients with

Table 2. Outcomes associated with noninvasive ventilation

Study (design)	Severity of hypoxemia	Need for intubation due to failure of NIV	Nosocomial infection	Pneumothorax	Mortality
Hernandez *et al.* (2010) [56] (RCT)	PaO2/FiO2 ≤200 for >8 h	12% in NIV vs. 40% in high-flow oxygen group	8% in NIV vs. 12% in high-flow oxygen group	24% in NIV vs. 12% in high-flow oxygen group	4% in NIV vs. 4% in high-flow oxygen group
Gunduz *et al.* (2005) [57] (RCT)	PaO2/FiO2 ≤300	17%[a]	9%	–	9%
Bolliger and Van Eeden (1990) [58] (RCT)	PaO2/FiO2 ≥150	–	13.8%	5.5%	0

Data are reported as rates (%) for all variables.
NIV, noninvasive ventilation; RCT, randomized controlled trial.
[a]The rate of intubation was not reported in the journal text, and patients requiring ETI were excluded from the analysis.
Adapted from [55▪▪].

TBI, excessive deviations in both directions should be prevented because the data support a trend to mortality reduction [48–51]; a particularly low $PaCO_2$ upon arrival in the emergency department is associated with fatal outcomes [52].

Observational studies suggest that even in patients with normal lung function, the use of a large tidal volume could result in lung injury [53,54]; thus, a tidal volume of 6 ml/kg predicted body weight or even less is part of the protective ventilation recommendations.

A recently published systematic review [55▪▪] examined the safety and efficacy of noninvasive ventilation (NIV) in patients with blunt chest trauma. These authors stated that although only nine studies were included in their analysis (three RCTs, two retrospective cohort studies and four observational studies without a control group), there might be a role for the early use of NIV in these patients. This finding is based on the data from one RCT, which suggested that the early identification of at-risk patients with the consequent initiation of NIV resulted in lower intubation rates (12 vs. 40%) [56]. Table 2 [55▪▪,56–58] summarizes the outcomes (only the analyzed RCTs are displayed) associated with NIV.

CONCLUSION

A strategic and algorithm-based systematic approach to airway management can prevent complications that arise due to inadequate oxygenation or procedural difficulties in trauma patients; therefore, advanced equipment for handling difficult airways must be available. Additionally, standardized monitoring, including capnography and the use of standardized medication protocols without etomidate, can reduce further complications. Overall, the role of ETI in patients with severe TBI and strategies for out-of-hospital management remain unclear, and identifying the ideal neuromuscular blocking agent is a subject for future research.

Ventilation can affect the outcome of severely injured patients; therefore, ensuring normoventilation and preventing hyperventilation should be helpful.

After the early identification of patients with blunt chest trauma at risk for respiratory failure, NIV might be a treatment strategy, even if this has had to be the subject of research in the future.

Acknowledgements

None.

Conflicts of interest

The views expressed in this review are those of the authors and do not reflect any official policy or position.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Deakin CD, Nolan JP, Soar J, *et al.* European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. Resuscitation 2010; 81:1305–1352.
2. American College of Surgeons Committee on Trauma ATLS. Student Course. Manual 8th ed. Chicago: American College of Surgeons; 2008.
3. Paal P, Herff H, Mitterlechner T, *et al.* Anaesthesia in prehospital emergencies and in the emergency room. Resuscitation 2010; 81:148–154.
4. Wolfl CG, Gliwitzky B, Wentzensen A. Standardised primary care of multiple trauma patients. Prehospital Trauma Life Support und Advanced Trauma Support. Unfallchirurg 2009; 112:846–853.
5. Dunham CM, Barraco RD, Clark DE, *et al.* Guidelines for emergency tracheal intubation immediately after traumatic injury. J Trauma 2003; 55:162–179.
6. Badjatia N, Carney N, Crocco TJ, *et al.* Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehosp Emerg Care 2008; 12 (Suppl 1):S1–S52.
7. Bernard S, Smith K, Foster S, *et al.* The use of rapid sequence intubation by ambulance paramedics for patients with severe head injury. Emerg Med 2002; 14:406–411.
8. Klemen P, Grmec S. Effect of prehospital advanced life support with rapid sequence intubation on outcome of severe traumatic brain injury. Acta Anaesthesiol Scand 2006; 50:1250–1254.
9. Jeremitsky E, Omert L, Dunham CM, *et al.* Harbingers of poor outcome the day after severe brain injury: hypothermia, hypoxia, and hypoperfusion. J Trauma 2003; 54:312–319.

10. Stahel PF, Smith WR, Moore EE. Hypoxia and hypotension, the 'lethal duo' in traumatic brain injury: implications for prehospital care. Intensive Care Med 2008; 34:402–404.

11. Ruchholtz S, Waydhas C, Ose C, *et al.* Prehospital intubation in severe thoracic trauma without respiratory insufficiency: a matched-pair analysis based on the Trauma Registry of the German Trauma Society. J Trauma 2002; 52:879–886.

12. Stephens CT, Kahntroff S, Dutton RP. The success of emergency endotracheal intubation in trauma patients: a 10-year experience at a major adult trauma referral center. Anesth Analg 2009; 109:866–872.

13. Sise MJ, Shackford SR, Sise CB, *et al.* Early intubation in the management of trauma patients: indications and outcomes in 1,000 consecutive patients. J Trauma 2009; 66:32–40.

14. Fakhry SM, Scanlon JM, Robinson L, *et al.* Prehospital rapid sequence intubation for head trauma: conditions for a successful program. J Trauma 2006; 60:997–1001.

15. Arbabi S, Jurkovich GJ, Wahl WL, *et al.* A comparison of prehospital and hospital data in trauma patients. J Trauma 2004; 56:1029–1032.

16. ▪ Sobuwa S, Hartzenberg HB, Geduld H, Uys C. Outcomes following prehospital airway management in severe traumatic brain injury. S Afr Med J 2013; 103:644–646.

Observational study reporting no improved outcomes after prehospital ETI.

17. ▪▪ Wang HE, Brown SP, MacDonald RD, *et al.* Association of out-of-hospital advanced airway management with outcomes after traumatic brain injury and hemorrhagic shock in the ROC hypertonic saline trial. Emerg Med J 2014; 31:186–191.

Secondary analysis of a large group of patients reporting that out-of-hospital airway management is linked to increased mortality, particularly in presence of hemorrhagic shock.

18. Boer C, Franschman G, Loer SA. Prehospital management of severe traumatic brain injury: concepts and ongoing controversies. Curr Opin Anaesthesiol 2012; 25:556–562.

19. ▪ Niven AS, Doerschug KC. Techniques for the difficult airway. Curr Opin Crit Care 2013; 19:9–15.

Recently published review summarizing all important facts in respect of management of the difficult airway.

20. Mort TC. Preoxygenation in critically ill patients requiring emergency tracheal intubation. Crit Care Med 2005; 33:2672–2675.

21. Mort TC, Waberski BH, Clive J. Extending the preoxygenation period from 4 to 8 mins in critically ill patients undergoing emergency intubation. Crit Care Med 2009; 37:68–71.

22. Cogbill TH, Cothren CC, Ahearn MK, *et al.* Management of maxillofacial injuries with severe oronasal hemorrhage: a multicenter perspective. J Trauma 2008; 65:994–999.

23. Combes X, Jabre P, Jbeili C, *et al.* Prehospital standardization of medical airway management: incidence and risk factors of difficult airway. Acad Emerg Med 2006; 13:828–834.

24. Timmermann A, Eich C, Russo SG, *et al.* Prehospital airway management: a prospective evaluation of anaesthesia trained emergency physicians. Resuscitation 2006; 70:179–185.

25. Timmermann A, Byhahn C, Wenzel V, *et al.* Handlungsempfehlung für das präklinische Atemwegsmanagement: Für Notärzte und Rettungsdienstpersonal. Anästh Intensivmed 2012; 53:294–308.

26. Pearce A. Evaluation of the airway and preparation for difficulty. Best Pract Res Clin Anaesthesiol 2005; 19:559–579.

27. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 2004; 99:607–613.

28. Wang HE, Yealy DM. How many attempts are required to accomplish out-of-hospital endotracheal intubation? Acad Emerg Med 2006; 13:372–377.

29. American Society of Anesthesiologists. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003; 98:1269–1277.

30. Warner KJ, Cuschieri J, Jurkovich GJ, *et al.* Single-dose etomidate for rapid sequence intubation may impact outcome after severe injury. J Trauma 2009; 67:45–50.

31. Hildreth AN, Mejia VA, Maxwell RA, *et al.* Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. J Trauma 2008; 65:573–579.

32. Jabre P, Combes X, Lapostolle F, *et al.* Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicenter randomised controlled trial. Lancet 2009; 374:293–300.

33. Morris C, Perris A, Klein J, *et al.* Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? Anaesthesia 2009; 64:532–539.

34. ▪ Price B, Arthur AO, Brunko M, *et al.* Hemodynamic consequences of ketamine vs etomidate for endotracheal intubation in the air medical setting. Am J Emerg Med 2013; 31:1124–1132.

Recently published retrospective data suggesting substitution of etomidate by ketamine.

35. Ballow SL, Kaups KL, Anderson S, Chang M. A standardized rapid sequence intubation protocol facilitates airway management in critically injured patients. J Trauma Acute Care Surg 2012; 73:1401–1405.

36. Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev 2008; 16:CD002788.

37. Hiestand B, Cudnik MT, Thomson D, Werman HA. Rocuronium versus succinylcholine in air medical rapid-sequence intubation. Prehosp Emerg Care 2011; 15:457–463.

38. Hernandez MR, Klock PA, Ovassapian A. Evolution of the extraglottic airway: a review of its history, applications, and practical tips for success. Anesth Analg 2012; 114:349–368.

39. Ferson DZ, Rosenblatt WH, Johansen MJ, *et al.* Use of the intubating LMAFastrach in 254 patients with difficult-to-manage airways. Anesthesiology 2001; 95:1175–1181.

40. Frappier J, Guenoun T, Journois D, *et al.* Airway management using the intubating laryngeal mask airway for the morbidly obese patient. Anesth Analg 2003; 96:1510–1515.

41. ▪ Yeatts DJ, Dutton RP, Hu PF, *et al.* Effect of video laryngoscopy on trauma patient survival: a randomized controlled trial. J Trauma Acute Care Surg 2013; 75:212–219.

This RCT showed no influence on survival to hospital discharge by using the GlideScope. In fact, usage was associated with longer intubation times than direct laryngoscopy.

42. Wang HE, Sweeney TA, O'Connor RE, *et al.* Failed prehospital intubations: an analysis of emergency department courses and outcomes. Prehosp Emerg Care 2001; 5:134–141.

43. Katz SH, Falk JL. Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. Ann Emerg Med 2001; 37:32–37.

44. Timmermann A, Russo SG, Eich C, *et al.* The out-of-hospital esophageal and endobronchial intubations performed by emergency physicians. Anesth Analg 2007; 104:619–623.

45. ▪ Silvestri S, Ralls GA, Krauss B, *et al.* The effectiveness of out-of-hospital use of continuous end-tidal carbon dioxide monitoring on the rate of unrecognized misplaced intubation within a regional emergency medical services system. Ann Emerg Med 2005; 45:497–503.

46. Grmec S, Mally S. Prehospital determination of tracheal tube placement in severe head injury. Emerg Med J 2004; 21:518–520.

47. ▪ Spahn DR, Bouillon B, Cerny V, *et al.* Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013; 17:R76.

This guideline summarizes clinical handling of bleeding trauma patients and refers to all important aspects such as ventilation strategy.

48. Bratton SL, Chestnut RM, Ghajar J, *et al.* Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. J Neurotrauma 2007; 24 (Suppl 1):S87–S90.

49. Bullock MR, Povlishock JT. Guidelines for the management of severe traumatic brain injury. Editor's Commentary. J Neurotrauma 2007; 24 (Suppl 1):2 preceding S1.

50. Caulfield EV, Dutton RP, Floccare DJ, *et al.* Prehospital hypocapnia and poor outcome after severe traumatic brain injury. J Trauma 2009; 66:1577–1582.

51. Davis DP, Hoyt DB, Ochs M, *et al.* The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma 2003; 54:444–453.

52. Caulfield EV, Dutton RP, Floccare DJ, *et al.* Prehospital hypocapnia and poor outcome after severe traumatic brain injury. J Trauma 2009; 66:1577–1583.

53. Gajic O, Frutos-Vivar F, Esteban A, *et al.* Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005; 31:922–926.

54. Mascia L, Zavala E, Bosma K, *et al.* High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. Crit Care Med 2007; 35:1815–1820.

55. ▪▪ Duggal A, Perez P, Golan E, *et al.* Safety and efficacy of noninvasive ventilation in patients with blunt chest trauma: a systematic review. Crit Care 2013; 17:R142.

This systematic review examined the safety and efficacy of NIV in patients with blunt chest trauma and suggested NIV after the early identification of patients at risk for respiratory failure.

56. Hernandez G, Fernandez R, Lopez-Reina P, *et al.* Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. Chest 2010; 137:74–80.

57. Gunduz M, Unlugenc H, Ozalevli M, *et al.* A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. Emerg Med J 2005; 22:325–329.

58. Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures: randomized controlled trial comparing ventilatory with nonventilatory management. Chest 1990; 97:943–948.

Fluid resuscitation and vasopressors in severe trauma patients

Anatole Harrois[a,b], *Sophie Rym Hamada*[a], *and Jacques Duranteau*[a,b]

Purpose of review
To discuss the fluid resuscitation and the vasopressor support in severe trauma patients.

Recent findings
A critical point is to prevent a potential increase in bleeding by an overly aggressive resuscitative strategy. Indeed, large-volume fluid replacement may promote coagulopathy by diluting coagulation factors. Moreover, an excessive level of mean arterial pressure may induce bleeding by preventing clot formation.

Summary
Fluid resuscitation is the first-line therapy to restore intravascular volume and to prevent cardiac arrest. Thus, fluid resuscitation before bleeding control must be limited to the bare minimum to maintain arterial pressure to minimize dilution of coagulation factors and complications of over fluid resuscitation. However, a strategy of low fluid resuscitation needs to be handled in a flexible way and to be balanced considering the severity of the hemorrhage and the transport time. A target systolic arterial pressure of 80–90 mmHg is recommended until the control of hemorrhage in trauma patients without brain injury. In addition to fluid resuscitation, early vasopressor support may be required to restore arterial pressure and prevent excessive fluid resuscitation. It is crucial to find the best alchemy between fluid resuscitation and vasopressors, to consider hemodynamic monitoring and to establish trauma resuscitative protocols.

Keywords
coagulopathy, fluid resuscitation, hemorrhagic shock, severe trauma patients, vasopressor

INTRODUCTION

Trauma injury remains the leading cause of death among people aged less than 44 years with 40% of trauma deaths imputable to uncontrolled hemorrhagic shock or its consequences (multiorgan failure) and 50% due to severe traumatic brain injury during the first 24 h of care [1]. In severe trauma patients, the hemodynamic management during the first hours is crucial to insure an acceptable tissue perfusion before hemorrhage control. A critical point of the hemodynamic resuscitation of traumatic hemorrhagic shock is to prevent a potential increase in bleeding by an overly aggressive resuscitative strategy. Excessive fluid resuscitation may promote coagulopathy by diluting coagulation factors and inducing hypothermia. Moreover, an excessive level of mean arterial pressure (MAP) may induce bleeding by preventing clot formation. Delayed fluid resuscitation was reported to increase survival in comparison with immediate fluid resuscitation in penetrative torso injuries [2]. However, fluid resuscitation remains the first-line therapy to restore intravascular volume and arterial pressure, and to prevent cardiac arrest in traumatic hemorrhage. Thus, a strategy of low-volume resuscitation needs to be handled in a flexible way and be balanced considering the severity of the hemorrhage and the transport time. A recent study even showed that prehospital fluid administration decreased in-hospital mortality in trauma patients [3▪▪]. Vasopressor agents may also be transiently required in the presence of life-threatening hypotension. In addition, the early use of vasopressors could limit fluid resuscitation and consecutive hemodilution. Lastly, vasopressors are needed to achieve high

[a]AP-HP, Service d'Anesthésie-Réanimation, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Hôpital de Bicêtre, Le Kremlin-Bicêtre and [b]Laboratoire d'Etude de la Microcirculation, 'Bio-CANVAS: Biomarkers in Cardio-Neurovascular Diseases' UMRS 942, Paris, France

Correspondence to Jacques Duranteau, MD, PhD, Department of Anesthesia and Intensive Care, Bicêtre Hospital, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Assistance Publique Hôpitaux de Paris, 78, rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France. Tel: +33 1 45 21 34 41; fax: +33 1 45 21 28 75; e-mail: Jacques.Duranteau@bct.aphp.fr

Curr Opin Crit Care 2014, 20:632–637
DOI:10.1097/MCC.0000000000000159

KEY POINTS

- Fluid loading is the first resuscitative therapy to reverse hypotension in severe trauma patients.
- A strategy of low fluid resuscitation needs to be handled in a flexible way and be balanced considering the severity of the hemorrhage and the transport time.
- A target systolic blood pressure of 80–90 mmHg until major bleeding control is recommended following trauma without brain injury.
- A vasopressor may be required when hypotension persists despite fluid resuscitation in severe trauma patients.
- A vasopressor should be administered very early with fluid resuscitation to achieve high MAP goals (MAP>80 mmHg) in severe brain-injured patients.

MAP targets ensuring an adequate tissue perfusion in case of severe traumatic brain injury. Thus, clear understanding of the respective roles of fluid resuscitation and vasopressors is crucial to establish trauma resuscitative protocols to improve the initial hemodynamic management of trauma patients.

FLUID RESUSCITATION

Fluid resuscitation is the first step in the hemodynamic management of traumatic hemorrhagic shock. Restoring intravascular volume is effective to reverse tissue hypoperfusion [4,5] and to correct oxygen debt [6] during the initial phase of hemorrhagic shock. However, excessive fluid resuscitation could contribute to the development of the coagulopathy of trauma [7,8] and of tissue edema, which can lead to alterations of tissue perfusion and complications such as abdominal compartment syndrome or adult respiratory distress syndrome [9,10]. In line with this, previous studies supported the concept of transferring the patient as quickly as possible to the trauma center with restrictive fluid resuscitation until the time of bleeding control [2,11]. Thus, fluid administration before bleeding control must be limited to the bare minimum to maintain arterial pressure to minimize dilution of coagulation factors and complications of over fluid resuscitation. Recently, in an observational clinical study conducted in 1200 patients [median ISS = 25 (16–35)] at 10 level 1 trauma centers in the United States, 83 and 89% of the trauma patients who require massive blood transfusions had prehospital (600 ± 735 ml) and first 30 min in emergency department (836 ± 998.8 ml) resuscitative fluids, respectively [3▪▪]. In this study, prehospital intravenous fluid volumes were associated with decreased in-hospital mortality in trauma patients as compared with patients who did not receive prehospital intravenous fluid. As is the rule in US trauma centers, fluid resuscitation was predominantly crystalloid based using normal saline (NaCl 0.9%) or Lactate Ringer [3▪▪]. Thus, the first key message is that fluid resuscitation remains the first-line therapy to restore intravascular volume and correct hypotension and that a strategy of low-volume resuscitation needs to be balanced considering the severity of hemorrhage and the time to transfer the patient. A second key message is that fluid resuscitation has to be guided as soon as possible by hemodynamic monitoring to optimize its adequacy with tissue perfusion.

Concerning the choice of the type of fluid for resuscitation, there is no clear evidence in the literature that indicated one of the fluids is better or worse in trauma patients. The main perceived benefit of colloids is that colloids can induce a more rapid and persistent plasma expansion because of a larger increase in oncotic pressure. However, randomized comparisons of fluid resuscitation with hydroxyethyl starch (HES) 130/0.4 versus normal saline in trauma patients have not always shown a superiority of HES on the recovery of tissue perfusion (i.e., lactate clearance) and showed no difference in fluid requirements and maximum SOFA scores [12]. But, it should be borne in mind that in this latter study patients in the HES group were more severely injured than those in the saline group. As regards a potential effect on mortality, the CHEST study failed to show that a fluid strategy using HES 130/0.4 (versus NaCl 0.9%) decreased the mortality in ICU patients and in particular in the subgroup of trauma patients [13]. In addition, there is continuing concern about the effects of HES on coagulation. HES has the potential to decrease the Von Willebrand factor level and to interfere with the polymerization of fibrinogen and the platelet function. Studies that address the assessment of hemostasis by thromboelastography reported that HES infusion resulted in a weaker clot with a less stable fibrin network and less firm aggregation of platelets than did crystalloid or human albumin [14]. This can lead to greater needs for red blood cells transfusions [12,13]. Because of these effects, the use of HES is discussed at the initial phase of hemorrhagic shock. All in all, alteration of coagulation and potential deleterious kidney effects observed with last generation of HES prompted the European Medicines Agency to drastically limit usage of HES [15▪▪]. The European Medicines Agency recommended not to use HES in sepsis patients and to limit their use in hemorrhagic shock patients only when crystalloids alone are not considered sufficient [15▪▪]. In

addition, HES is contraindicated in the case of coagulopathy.

As regards the other synthetic colloids, coagulation [16] and kidney function alterations [17] have been described with gelatins, but high-quality studies are lacking to know if these recommendations have to be extended to them.

The SAFE study has shown that albumin does not interfere with coagulation and kidney functions [18]. However, in the subgroup of trauma patients, especially in patients with traumatic brain injury, a negative trend in the relative risk of death was observed with albumin (versus saline) [19]. This finding was attributed to the albumin-induced increase in intracranial pressure due to its hypo-osmolarity [20].

Hypertonic saline (HTS, 7.5% saline with or without colloid) has long been considered as an interesting fluid in trauma patients. Potential benefits of HTS include restoration of intravascular volume with the administration of a small volume, reduction of intracranial pressure in trauma brain injury, and modulation of the inflammatory response. However, HTS failed to improve outcomes in patients with hemorrhagic shock or with severe traumatic brain injury [21–23].

VASOPRESSORS

When hypotension persists despite fluid resuscitation, vasopressor agents may be required to restore tissue perfusion and sustain life. In traumatic hemorrhagic shock, the sympathetic response induces both arterial and venous α-adrenergic stimulation. In addition to arterial vasoconstrictive effect, sympathetic response induces venoconstriction in the capacitance vessels (especially at the level of splanchnic circulation), which actively shifts the venous blood volume from the unstressed volume (i.e., the blood volume that fills the blood vessels without generating an intravascular pressure) to the stressed volume with subsequent increase in venous return. In healthy patients, these physiologic adaptations are able to maintain MAP despite a significant amount of blood loss (≈1500–2000 ml) [24]. Sympathetic vasoconstriction also leads to volume transfer from the interstitial to the intravascular compartment [25]. This sympathetic response is crucial to fight against the hemorrhage. However, several factors can make this response less effective in trauma. Sedation is the main competitor with the sympathetic response. In addition, systemic inflammatory response syndrome occurs promptly after trauma with peripheral vasoplegia related to increase of circulating cytokines such as HMGB1 (high-mobility group protein B1) [26], damage associated mitochondrial proteins [27], and excessive NO production [28,29]. Inflammation in trauma is the result of a combination of three elements: the traumatic injury, the tissue hypoxia, and the reperfusion injury. Endogenous opioid peptides also contribute to peripheral vasoplegia during hemorrhagic shock as delta-opioid receptor antagonists can restore MAP in an experimental model of uncontrolled hemorrhagic shock [30]. Moreover, it is clear that a spinal cord injury could be responsible for vasomotor paralysis. Finally, hemorrhagic shock progressively becomes a combination of hypovolemia and vasoplegia.

For all of those reasons, it appears appropriate to support the sympathetic response during moderate-to-severe traumatic hemorrhage by exogenous vasopressor infusion in addition to fluid resuscitation. It is important to understand that fluid resuscitation is more efficient when the cardiovascular system is stressed by the sympathetic response or exogenous vasopressor. In addition, vasopressors are needed to obtain high MAP targets ensuring an adequate tissue perfusion in case of severe trauma brain injury. Moreover, the early use of vasopressors could limit fluid resuscitation and hemodilution. Several experimental studies reported the beneficial effect of exogenous vasopressor infusion (mainly norepinephrine) in addition to fluid resuscitation. Indeed, in a lethal model of uncontrolled hemorrhagic shock in rats, Lee *et al.* [31] observed a higher survival rate in rats receiving a fixed dose of norepinephrine in addition to a fixed fluid resuscitation volume. A similar result was obtained using vasopressin [32▪]. In these last two experimental studies, vasopressors enhanced a sympathetic tone that seems to be more or less exhausted after prolonged hemorrhage. In a study by Poloujadoff *et al.* [33], a MAP-directed resuscitation of uncontrolled hemorrhagic shock in rats was undertaken with fluid alone or fluid and norepinephrine. Either for a targeted MAP of 40 mmHg or 80 mmHg, the survival was higher in groups resuscitated with fluid and norepinephrine than in groups resuscitated with fluid without norepinephrine. Moreover, bleeding amount and resuscitation fluid amount were smaller in groups resuscitated with fluids and norepinephrine [33].

Unfortunately, there are only few clinical trials that have investigated the effects of vasopressors in trauma patients, and their use in hemorrhagic shock remains controversial. Two retrospective studies reported an independent association between vasopressor exposure during the 24 h posttrauma and mortality rate [34,35▪]. However, despite the methodological efforts of authors, a number of limitations must be highlighted because of the retrospective nature of the analysis. In particular, the specific

indications for vasopressor use and the timing of vasopressor use are really unknown. This point is crucial to establish who had vasopressor use as a salvage therapy. The type of vasopressors given is also a crucial point to take into account. For instance, in the Plurad *et al.* [35▪] study, the most commonly used agent was dopamine, which is a dosage dependent and a β-adrenergic drug with weak α-adrenergic effects. Lastly, there is no clear resuscitation protocol in these studies with the risk of changes in hemodynamic resuscitative strategies over the study period. Thus, independently of the quality of these studies, it remains unclear whether vasopressor use is, in itself, detrimental or simply a marker for poor outcome in trauma patients. Cohn *et al.* [36▪▪] performed a prospective, randomized trial of low-dose vasopressin (2.4 IU/h for 5 h at arrival to the emergency department) versus placebo and found a statistically significantly lower requirement for crystalloids, total fluids or blood in the first 24 h and 5 days. Despite the limitations of this study, in particular, the small number of patients and the fact that authors were forced to terminate the trial early because of accrual problems, these results were very encouraging to continue to explore the early use of vasopressors in trauma resuscitative strategies.

Because vasopressors may increase cardiac after load, in particular when there is an excessive infusion rate or impaired left ventricular function, it is essential to assess cardiac function during the initial ultrasound examination. This point is crucial because cardiac dysfunction may be altered in trauma patients after cardiac contusion, pericardial effusion, or secondary to brain injury with intracranial hypertension.

GOALS OF FLUID RESUSCITATION AND BLOOD PRESSURE

As we have seen above, fluid administration before bleeding control must be limited to the bare minimum to maintain arterial pressure to minimize dilution of coagulation factors and complications of over fluid resuscitation. The optimal level of blood pressure during the resuscitation of the hemorrhagic shock patient is still debated. The initial objectives are to control the bleeding as soon as possible and to maintain a level of arterial pressure that provides an adequate level of tissue perfusion that, although lower than normal, is acceptable for short periods. There are no stong data to define the optimal blood pressure level during active hemorrhagic shock [37,38]. However, European guidelines for the management of bleeding trauma patients recommended a target systolic blood pressure of 80–90 mmHg until major bleeding has been stopped in the initial phase following trauma without brain injury [39▪▪]. When traumatic hemorrhagic shock is associated with severe brain injury, cerebral perfusion pressure must be maintained by increasing the MAP at least 80 mmHg to prevent secondary brain injury [39▪▪]. It becomes clear that the major challenges to obtaining the best alchemy between fluid resuscitation and vasopressors are to consider hemodynamic monitoring as soon as possible and to establish clear trauma resuscitative protocols. Hemodynamic monitoring aims at avoiding the side-effects of excessive fluid resuscitation or excessive vasoconstriction due to vasopressors leading to tissue hypoperfusion. It is usually difficult to get sophisticated hemodynamic monitoring at the initial phase of traumatic hemorrhagic shock and invasive arterial pressure is the main parameter that guides resuscitative strategy until the bleeding is controlled. But clearly, we need, as soon as possible, preload and cardiac indices to make the good balance between fluid resuscitation and vasopressors' needs. On the one hand, fluid resuscitation will only be completely effective if vasoconstrictive tonus is present. One the other hand, the vasopressor action will be complete if the unstressed blood volume can be recruited. A balance between these two therapies seems therefore necessary to optimize hemodynamic status of trauma patients with hemorrhagic shock.

Additionally, despite adequate fluid resuscitation and arterial blood pressure stabilization, only blood transfusion can support tissue hemoglobin level. Thus, one key message is that we must consider blood transfusion early during the management of traumatic hemorrhagic shock to improve oxygen delivery.

CONCLUSION

Fluid resuscitation is the first-line therapy to manage hypotension and to prevent cardiac arrest in traumatic hemorrhage. Over fluid resuscitation could contribute to the development of trauma coagulopathy and of tissue edema with alterations of tissue perfusion and complications, such as abdominal compartment syndrome and adult respiratory distress syndrome. Fluid administration before bleeding control must be limited to the bare minimum to maintain arterial pressure to minimize dilution of coagulation factors and complications of over fluid resuscitation. A strategy of low-volume resuscitation needs to be handled in a flexible way and must take into consideration the severity of hemorrhage and the transport time. A target systolic blood pressure of 80–90 mmHg until major bleeding has been stopped is recommended following trauma without brain

injury. In addition to fluid resuscitation, early vasopressor support may be required to maintain arterial pressure. It is clear that vasopressor support prevents or delays cardiovascular collapse until bleeding control. Moreover, early vasopressor support could prevent excessive fluid resuscitation. In addition, vasopressors are needed to obtain high MAP target ensuring an adequate tissue perfusion in case of severe trauma brain injury. To find the best alchemy between fluid resuscitation and vasopressors, it is crucial to consider hemodynamic monitoring as soon as possible and to establish trauma resuscitative protocols with clear hemodynamic goals. Resuscitation protocols that optimize the prehospital and hospital's fluid benefit while conscientiously avoiding an elevated blood pressure until the bleeding is controlled should become standard.

Acknowledgements

None.

Conflicts of interest

J.D. received honoraria for lecturing from the LFB company. A.H and S.R.H have no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Dutton RP, Stansbury LG, Leone S, *et al.* Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. J Trauma 2010; 69:620–626.
2. 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; 331:1105–1109.
3. ■■ Hampton DA, Fabricant LJ, Differding J, *et al.* Prehospital intravenous fluid is associated with increased survival in trauma patients. J Trauma Acute Care Surg 2013; 75 (1 Suppl 1):S9–S15.

An important study in the ongoing debate on the indication of prehospital intravenous fluids and fluid restricted resuscitation protocols. This study reports that prehospital intravenous fluids are associated with decreased in-hospital mortality in trauma patients compared with patients who did not receive prehospital IVF. These authors point out that resuscitation protocols that maximize the prehospital fluid's benefit while conscientiously avoiding an elevated blood pressure should become standard. This study supports that a strategy of low-volume resuscitation needs to be handled in a flexible way.

4. Fang X, Tang W, Sun S, *et al.* Comparison of buccal microcirculation between septic and hemorrhagic shock. Crit Care Med 2006; 34 (Suppl):S447–S453.
5. Vajda K, Szabo A, Kucsa K, *et al.* Microcirculatory heterogeneity in the rat small intestine during compromised flow conditions. Microcirculation 2004; 11:307–315.
6. Siegel JH, Fabian M, Smith JA, *et al.* Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. J Trauma 2003; 54:862–880.
7. Nishi K, Takasu A, Shinozaki H, *et al.* Hemodilution as a result of aggressive fluid resuscitation aggravates coagulopathy in a rat model of uncontrolled hemorrhagic shock. J Trauma Acute Care Surg 2013; 74:808–812.
8. Solomonov E, Hirsh M, Yahiya A, Krausz MM. The effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock after massive splenic injury. Crit Care Med 2000; 28:749–754.
9. Varela JE, Cohn SM, Diaz I, *et al.* Splanchnic perfusion during delayed, hypotensive, or aggressive fluid resuscitation from uncontrolled hemorrhage. Shock 2003; 20:476–480.
10. Zakaria el R, Li N, Matheson PJ, Garrison RN. Cellular edema regulates tissue capillary perfusion after hemorrhage resuscitation. Surgery 2007; 142:487–496.
11. Haut ER, Kalish BT, Cotton BA, *et al.* Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis. Ann Surg 2011; 253:371–377.
12. James MF, Michell WL, Joubert IA, *et al.* Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011; 107:693–702.
13. Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–1911.
14. Hartog CS, Skupin H, Natanson C, *et al.* Systematic analysis of hydroxyethyl starch (HES) reviews: proliferation of low-quality reviews overwhelms the results of well performed meta-analyses. Intensive Care Med 2012; 38:1258–1271.
15. ■■ European Medicines Agency. Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients. http://www.ema.europa.eu. 2013.

Crucial recommendations in the debate on the use of HES in hemorrhagic shock. The European Medicines Agency recommends not to use HES in sepsis patients and to limit their use in hemorrhagic shock patients only when crystalloids alone are not considered sufficient. In addition, HES is contraindicated in the case of coagulopathy.

16. Niemi TT, Miyashita R, Yamakage M. Colloid solutions: a clinical update. J Anesth 2010; 24:913–925.
17. Bayer O, Reinhart K, Sakr Y, *et al.* Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. Crit Care Med 2011; 39:1335–1342.
18. Finfer S, Bellomo R, Boyce N, *et al.* A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350:2247–2256.
19. Myburgh J, Cooper DJ, Finfer S, *et al.*, SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007; 357:874–884.
20. Cooper DJ, Myburgh J, Heritier S, *et al.* Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? J Neurotrauma 2013; 30:512–518.
21. Bulger EM, Jurkovich GJ, Nathens AB, *et al.* Hypertonic resuscitation of hypovolemic shock after blunt trauma: a randomized controlled trial. Arch Surg 2008; 143:139–148.
22. Bulger EM, May S, Brasel KJ, *et al.* Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. JAMA 2010; 304:1455–1464.
23. Bulger EM, May S, Kerby JD, *et al.* Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg 2011; 253:431–441.
24. Cooke WH, Ryan KL, Convertino VA. Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. J Appl Physiol (1985) 2004; 96:1249–1261.
25. Lundvall J, Lanne T. Large capacity in man for effective plasma volume control in hypovolaemia via fluid transfer from tissue to blood. Acta Physiol Scand 1989; 137:513–520.
26. Cohen MJ, Brohi K, Calfee CS, *et al.* Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion. Crit Care 2009; 13:R174.
27. Zhang Q, Raoof M, Chen Y, *et al.* Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464:104–107.
28. Liu LM, Ward JA, Dubick MA. Hemorrhage-induced vascular hyporeactivity to norepinephrine in select vasculatures of rats and the roles of nitric oxide and endothelin. Shock 2003; 19:208–214.
29. Thiemermann C, Szabo C, Mitchell JA, Vane JR. Vascular hyporeactivity to vasoconstrictor agents and hemodynamic decompensation in hemorrhagic shock is mediated by nitric oxide. Proc Natl Acad Sci U S A 1993; 90:267–271.
30. Liu L, Tian K, Zhu Y, *et al.* δ opioid receptor antagonist, ICI 174,864, is suitable for the early treatment of uncontrolled hemorrhagic shock in rats. Anesthesiology 2013; 119:379–388.
31. Lee JH, Kim K, Jo YH, *et al.* Early norepinephrine infusion delays cardiac arrest after hemorrhagic shock in rats. J Emerg Med 2009; 37:376–382.
32. ■ Liu L, Tian K, Xue M, *et al.* Small doses of arginine vasopressin in combination with norepinephrine 'buy' time for definitive treatment for uncontrolled hemorrhagic shock in rats. Shock 2013; 40:398–406.

This study suggested that early application of small doses of Arg vasopressin (0.4 U/kg) + norepinephrine before bleeding control can 'buy' time for the definitive treatment of uncontrolled hemorrhagic shock.

33. Poloujadoff MP, Borron SW, Amathieu R, *et al.* Improved survival after resuscitation with norepinephrine in a murine model of uncontrolled hemorrhagic shock. Anesthesiology 2007; 107:591–596.
34. Sperry JL, Minei JP, Frankel HL, *et al.* Early use of vasopressors after injury: caution before constriction. J Trauma 2008; 64:9–14.

35. Plurad DS, Talving P, Lam L, *et al.* Early vasopressor use in critical injury is ■ associated with mortality independent from volume status. J Trauma 2011; 71:565–570.

In this retrospective analysis of the intensive care unit database at a level I center (from 2001 to 2008), the authors found that vasopressor exposure early after critical injury is independently associated with death, and mortality is increased regardless of fluid status. The vasopressor group was exposed to dopamine, epinephrine, phenylephrine, norepinephrine, or arginine vasopressin within 24 h of admission.

36. Cohn SM, McCarthy J, Stewart RM, *et al.* Impact of low-dose vasopressin on ■■ trauma outcome: prospective randomized study. World J Surg 2011; 35:430–439.

Prospective, randomized trial of early infusion of low dose vasopressin (2.4 IU/h for 5 h at arrival to the emergency department) versus placebo. Authors reported a statistically significantly lower fx1 requirement for crystalloids, total fluids or blood in the first 24 and 5 days. Very encouraging results to continue to explore the early use of vasopressors in trauma.

37. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002; 52: 1141–1146.

38. 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; 70:652–663.

39. Spahn DR, Bouillon B, Cerny V, *et al.* Management of bleeding and coagulo- ■■ pathy following major trauma: an updated European guideline. Crit Care 2013; 17:R76.

This article is the updated version of the European Trauma guideline published in 2007 and updated in 2010. Key changes include new recommendations on fluid resuscitation and appropriate use of vasopressors and inotropic agents. A significant addition is a new section that discusses the need for every institution to develop, implement and adhere to an evidence-based clinical protocol to manage traumatically injured patients.