Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Medical intelligence | Published 20 September 2012, doi:10.4414/smw.2012.13685
Cite this as: Swiss Med Wkly. 2012;142:w13685

Volume replacement after trauma: an update

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Summary

Traditionally, fluid therapy in trauma patients favoured liberal replacement of intravascular fluids to correct fluid loss and optimise macro- and microcirculation. This narrative review examines the background for the changed approach to volume therapy, discusses important clinical studies and points out open questions for future research. Evidence is emerging that low volume resuscitation and permissive hypotension may be associated with improved outcomes. Crystalloids are safe as first line fluids. Colloids have no advantage over crystalloids and may be detrimental in patients with traumatic brain injury. Synthetic colloids may prolong bleeding and increase need for blood products. The role of hypertonic saline is unclear, as recent large-scale trials have been stopped for futility and some safety concerns.

Key words: *crystalloids; colloids; low volume resuscitation; permissive hypotension; hypertonic saline; coagulopathy*

Introduction

Trauma is the leading cause of death worldwide in the age-group below 44 [1]. In Germany, 33,000 to 38,000 individuals suffer from severe trauma every year [2]. Nearly one quarter of trauma patients admitted to hospital show a coagulopathy that further increases their risk of mortality [3, 4] and uncontrolled haemorrhage is most often responsible for potentially preventable deaths [5].

For much of the second half of the 20th century, resuscitating trauma patients called for an aggressive fluid resuscitation regimen. Intravenous fluids were liberally replaced with the intention to restore normal circulatory function and prevent uncorrected haemorrhagic shock, which would lead to interrupted oxygen delivery, cellular ischemia, progressive organ dysfunction, and ultimately irreversible organ failure. However, the practice of trauma resuscitation has changed over the last decades towards damage control resuscitation, a strategy including permissive hypotension, haemostatic resuscitation and damage control surgery which has been widely adopted as the preferred method of resuscitation in patients with haemorrhagic shock [6]. This narrative review examines the background for the changed approach, discusses important clinical studies and points out open questions for future research. High quality randomised controlled studies are mostly lacking in this area. Therefore, guidelines by the American Thoracic Society suggest that intravenous fluid resuscitation in trauma should be guided by the same principles as in sepsis, given that secondary insults after major trauma may incite an inflammatory reaction with altered capillary permeability [7]. Hence, where appropriate, this review also draws on results from recent sepsis trials.

The “lethal triad”: hypothermia, acidosis and coagulopathy

Hypothermia, acidosis and coagulopathy are mutually exacerbating states that commonly occur after injury. Hypothermia follows heat loss at the scene of injury and may also result from medical treatment. It is associated with an increased risk of bleeding and is a significant contributing factor to trauma-associated morbidity and mortality. A core temperature below 35 °C is an independent risk factor for death [8]. Hypoperfusion results in decreased oxygen delivery, anaerobic metabolism with increased lactate production, and metabolic acidosis which further limits endogenous heat production. Coagulopathy was long considered to result from loss of coagulation factors (by consumption and bleeding), dilution due to resuscitation fluids, and dysfunction related to hypothermia and acidosis. Coagulopathy in the context of trauma, however, seems to be more complex although the mechanisms are not completely understood. It results from several independent but interacting mechanisms. Acute traumatic coagulopathy (ATC) requires tissue injury, hypoperfusion, and activation of anticoagulant and fibrinolytic pathways [9]. It is an independent predictor for the need for massive transfusion and death [3, 4]. Patients who develop a coagulopathy have an increased likelihood of prolonged intensive care stay, multi-organ failure (MOF) including renal failure and acute lung injury [10]. There is a lack of consensus on how to diagnose coagulopathy. Commonly, prolongation of activated partial thromboplastin time (aPTT) and/or prothrombin time (PT) by more than 1.5 times the upper limit of normal are regarded as indicative of traumatic coagulopathy [11]. In recent years, viscoelastic point-of-care tests such as thrombelastography (TEG), thrombelastometry (ROTEM) or Sonoclot have been advocated to monitor haemostasis. These methods have the advantage of a rapid turn-around time

and results are available within 10–30 minutes of starting the test. The result is displayed as a real-time graphic of the clot formation. The method shows promise to detect abnormalities of the components of clot formation including information on coagulation factors, fibrinogen and platelets [12]. Data from a prospective cohort study of 334 blunt trauma patients found that significant differences in mortality and need for red blood cell transfusion were detected for defined ROTEM thresholds [13]. However, there are drawbacks to this method which requires external quality testing to ensure repeatable results, as it has not yet been validated in the trauma setting and is expensive. In the absence of large-scale comparative clinical trials, it is still unclear whether the use of TEG or ROTEM improves morbidity or mortality in patients with severe bleeding compared to conventional laboratory parameters [14]. The updated recommendations of the European Task Force for Advanced Bleeding Care in Trauma (2010) recommend that coagulation monitoring to detect post-traumatic coagulopathy should routinely include the measurement of international normalised ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelets [15].

Permissive hypotension

Hypotensive shock has typically been managed by liberal administration of up to 2 litres of bolus crystalloids followed by blood and repeated as necessary to achieve a target blood pressure [16]. However, evidence is emerging that low-volume or hypotensive resuscitation are permissible strategies, particularly for penetrating injuries, until definitive surgical control of bleeding can be established. In 1994 a pivotal RCT was published which compared immediate or delayed fluid resuscitation in 598 adults with penetrating torso injuries who presented with a pre-hospital systolic blood pressure ≤90 mm Hg [17]. Patients assigned to the immediate-resuscitation group received standard fluid resuscitation before they reached the hospital, and those assigned to the delayed-resuscitation group received intravenous cannulation but no fluid resuscitation until they reached the operating room. On arrival at the trauma centre, patients in the delayed resuscitation groups had a significantly lower systolic blood pressure (mean 72 ± 43 mm Hg versus 79 ± 46 mm Hg, $p = 0.02$). This trial found an 8% mortality reduction in the 289 patients who received delayed fluid resuscitation (70% survival) compared with 193 of the 309 patients (62% survival) who received immediate fluid resuscitation. Intra-operative blood loss was similar between the two groups, but patients in the delayed-resuscitation group who survived to the post-operative period tended to develop fewer complications (adult respiratory distress syndrome, sepsis syndrome, acute renal failure, coagulopathy, wound infection, and pneumonia) than those in the immediate-resuscitation group, 23% versus 30%, $p = 0.08$. The duration of hospitalisation was also shorter in the delayed-resuscitation group [17]. A subsequent large randomised controlled trial (RCT) which ran-

Table 1: Clinical studies.
A: Early versus late fluid resuscitation.

Authors	Patients	Study type	Interventions	Outcomes
W.H. Bickell et al. 1994 [17]	598 adults with penetrating torso injuries who presented with a pre-hospital systolic blood pressure of ≤90 mm Hg	RCT	Immediate (pre-clinical) versus delayed (in-hospital) resuscitation	Survived and discharged from hospital: 203/ 289 patients (70%) with delayed fluid resuscitation and 193/309 patients (62%) who received immediate fluid resuscitation ($p = 0.04$). The mean estimated intra-operative blood loss was similar in the two groups. 55/238 patients in the delayed-resuscitation group who survived to the post-operative period, 55 (23%) had one or more complication (ARDS, sepsis syndrome, ARF, coagulopathy, wound infection, and pneumonia), compared with 69/227 patients (30%) in the immediate-resuscitation group ($p = 0.08$). The duration of hospitalisation was shorter in the delayed-resuscitation group.
J. Turner et al. 2000 [18]	1,309 trauma patients	RCT	Comparison of two different preclinical fluid protocols: A usual pre-clinical IV fluid therapy, B no fluids until arrival in hospital unless >1 hour	No difference in mortality rates or composite outcomes between groups. Poor compliance with allocated protocol.

B: Normal versus high volume resuscitation / Hypotensive versus normotensive resuscitation.

Authors	Patients	Study type	Interventions	Outcomes
Z. Balogh et al. 2003 [21]	156 patients with major trauma	Retrospective analysis of a prospective database	Supranormal resuscitation (to achieve a oxygen delivery index (DO_2I) ≥600 ml/min per m^2, n = 85 versus normal resuscitation to achieve a DO_2I ≥500 ml/min per m^2, n = 71, for the first 24 hours in the ICU	The supranormal resuscitation group required more lactated Ringer infusion volume (mean ± SD, 13±2 vs 7±1 l; p <0.05) and had higher $GAPCO_2$ (16 ± 2 vs 7 ± 1 mm Hg; p <0.05), and showed more frequent IAH (42% vs 20%; p <0.05) and ACS (16% vs 8%; p <0.05).
C.A. Morrison et al. 2011 [24]	90 patients in haemorrhagic shock requiring emergent surgery	RCT, interim report	Intra-operative fluid therapy with low mean arterial pressure (target MAP = 50 mm Hg) versus high MAP [HMAP]) arm were managed with standard fluid resuscitation to a target MAP of 65 mm Hg	Primary endpoint 30-day mortality was not different (10/44 [23%]) in the low MAP group versus 13/46 [28%] in the high MAP group. Patients in the low MAP group received less blood products (mean [SD] ml: 1,594 [2,292] vs 2,898 [3,299], $p = 0.03$) and similar intravenous fluid volumes.

domised 1,309 trauma patients to receive or not receive pre-clinical fluids failed to find a difference in mortality but compliance with protocol was poor [18]. A 2004 Health Technology Assessment on the clinical effectiveness and cost-effectiveness of pre-hospital intravenous (IV) fluids in trauma patients [19] which also took into account evidence from observational studies concluded that there was no evidence to suggest that pre-hospital IV fluid resuscitation is beneficial and there was some evidence that it may be harmful and that patients do comparatively well when fluids are withheld. In 2009, a Cochrane meta-analysis of trials which investigated timing and volume of fluid administration for patients with bleeding was performed. However, it did not combine the results quantitatively because the interventions and patient populations were so diverse. The authors summarised that the evidence from randomised controlled trials for or against early or larger volume of intravenous fluid administration was undecided [20].

Several smaller studies have suggested that high-volume resuscitation leads to worse clinical outcomes. Balogh et al. conducted a retrospective analysis of patients with major trauma which suggested that resuscitation targeted to achieve a supra-normal oxygen delivery index (DO_2I) was associated with unfavourable outcomes, including more lactated Ringer infusion, decreased intestinal perfusion, and an increased incidence of abdominal compartment syndrome, multiple organ failure, and death [21]. Another retrospective analysis of 3,137 patients who received crystalloid resuscitation in the emergency department found that fluid volumes of 1.5 L or more were significantly associated with mortality in both elderly (odds ratio [OR]: 2.89, confidence interval [CI]: 1.13–7.41, $p = 0.027$) and non-elderly patients (OR: 2.09, CI: 1.31–3.33, $p < 0.002$). Fluid volumes up to 1 litre were not associated with significantly increased mortality. At 3 litres, mortality was especially pronounced in the elderly (OR: 8.61, CI: 1.55–47.75, $p < 0.014$), when compared with the non-elderly (OR = 2.69, CI:1.53–4.73, $p < 0.0006$) [22]. A matched-pair analysis using data from the Trauma Registry of the German Society for Trauma Surgery with 948 patients in each group found that increasing replacement volume was associated with an increased need for transfusion (pRBCs: low-volume: 7 units, high-volume: 8.3 units; $p < 0.001$) and a reduced ability to coagulate (prothrombin ratio (PR): low-volume: 68%, high-volume: 61.5%; $p < 0.001$) and increased mor-

C: Colloids versus crystalloids.

Authors	Patients	Study type	Interventions	Outcomes
S. Finfer et al. 2004 [28]	6,997 ICU patients	Multicenter blinded RCT	4% albumin versus 0.9% saline	Primary endpoint 28-d mortality was not different between groups (726/3,497 patients died in the albumin group vs. 729/3,500 patients in the saline group, relative risk of death: 0.99; 95%CI: 0.91 to 1.09; $p = 0.87$) There was no difference between groups in the frequency of new single-organ and multiple-organ failure, ICU or hospital LOS, days on mechanical ventilation or days on renal replacement therapy.
J. Myburgh et al. 2007 [33]	460 patients with traumatic head injury	*Post hoc* follow-up study	4% albumin versus 0.9% saline	At 24 months, 71/214 patients in the albumin group (33.2%) had died, compared with 42/206 in the saline group (20.4%) (relative risk: 1.63; 95%CI: 1.17 to 2.26; $p = 0.003$).
M.-Y. Tseng et al., 2008 [34]	160 patients with aneurysmal subarachnoid haemorrhage	*Post-hoc* analysis of prospective data derived from two separate RCTs	Effect of fluid treatment with synthetic colloids 6% pentastarch and 4% gelatine	Synthetic colloids for initial resuscitation seemed to be associated with more requirements for blood transfusions ($p = 0.003$). Multivariate analyses identified that colloid fluids (OR 2.53/l/day, $p = 0.025$) promoted unfavourable outcome at 6 months (OR 4.45, $p = 0.035$), while crystalloids decreased unfavourable outcome (OR 0.27/l/day, $p = 0.005$).
M. F. James et al. 2011 [37, 38]	109 severely injured patients requiring >3 litres of fluid resuscitation	Single-centre blinded RCT	6% HES 130/0.4 versus normal saline	Co-Primary endpoints: volume needed in 24 hours and number of patients tolerating enteral/parenteral feeding by day 5 did not differ between groups. At baseline, patients in the HES group were more severely injured than patients in the saline group (median injury severity score 29.5 vs 18; $p = 0.01$). The HES group required significantly more blood products (packed red blood cell volumes 2,943 (1,628) vs 1,473 (1,071) ml, $p = 0.005$). Total deaths: 12/44 patients (27.2%) HES group and 6/47 patients (17.7%) in the saline group.
A. Perner et al. 2012 [39]	798 patients with severe sepsis	Multi-centre blinded RCT	6% HES 130/0.4 versus Ringer's acetate (RA)	Primary endpoint 90-day mortality: 51% (201/398 patients) in the HES group versus 43% (172/400 patients) in the RA group (relative risk: 1.17; 95%CI: 1.01 to 1.36; $p = 0.03$). In the 90-day period, RRT occurred in 87 (22%) patients in the HES group versus 65 (16%) patients in the RA group (relative risk: 1.35; 95%CI: 1.01 to 1.80; $p = 0.04$) and 38 (10%) and 25 (6%) of patients had severe bleeding (relative risk: 1.52; 95%CI: 0.94 to 2.48; $p = 0.09$).

D: Crystalloid versus other crystalloids.

Authors	Patients	Study type	Interventions	Outcomes
J.H. Waters et al., 2001 [46]	66 patients undergoing aortic reconstructive surgery	Single-centre blinded RCT	Ringer's lactate versus normal saline (NS)	The NS patients developed a hyperchloraemic acidosis and received more bicarbonate therapy (30 ± 62 ml versus 4 ± 16 ml). There were no differences in duration of mechanical ventilation, intensive care unit stay, hospital stay, and incidence of complications

tality (low-volume: 22.7%, high-volume: 27.6%; p <0.01) [23].

The concept of permissive hypotension has only recently been studied in a prospective RCT, and results have now been published of an interim analysis of an ongoing clinical trial which randomised 90 patients in haemorrhagic shock undergoing emergent surgery to intra-operative resuscitation with either low mean arterial pressure where the target mean arterial pressure (MAP) was 50 mm Hg or a high MAP arm where target MAP was 65 mm Hg. Patients in the low MAP group received significantly less blood products and total IV fluids during intra-operative resuscitation than those in the high MAP group. They had significantly lower mortality in the early postoperative period and a non-significant trend for lower mortality at 30 days. Interestingly, although the average MAP for the low MAP group was slightly lower than that of the high MAP group, this difference was not statistically significant. Of note, anaesthesiologists were not allowed to use pharmacological interventions to *lower* the MAP in their patients. A likely explanation for the unexpected similarities in actual MAP is that patients in the low MAP group were able to automatically maintain a blood pressure above the minimum target of 50 mm Hg without requiring further intervention. This study is continuing until a planned total of 271 patients have been enrolled [24].

Theoretically, hypotensive resuscitation may be possibly harmful by deceasing oxygen delivery to the various tissues of the body, further jeopardise tissue perfusion and contribute to the development of subsequent organ failure. On the other hand, reduced fluid administration may minimise dilutional coagulopathy, acidosis and hypothermia effects, and also reduce the risk of clot displacement, by maintaining a lower systolic blood pressure. Of note, blood pressure alone may be a poor marker for adequacy of tissue perfusion and inadequate organ perfusion may be present despite normal blood pressure. Reduced fluid administration may also decrease the risk of oedema formation. However, the exact amount of crystalloid resuscitation associated with higher mortality or morbidity has not been quantified.

Deliberate hypotension in trauma resuscitation is still poorly defined and clinical evidence is inconclusive. Some authors recommend maintaining a target systolic pressure of less than 100 mm Hg in patients who are actively bleeding and in a damage control mode, while the military are content with a palpable radial pulse as a sign of adequate perfusion [25]. A recent systematic review on the clinical effectiveness of permissive hypotension in blunt abdominal trauma with haemorrhagic shock identified only 2 RCTs with mixed types of injuries which found no significant difference between the groups used in each study [26]. Therefore, further large clinical trials are warranted.

Crystalloids or colloids?

There is an ongoing debate about whether crystalloids or colloids should be preferred. The rationale for colloid-based fluid-resuscitation was traditionally based on theoretical reasoning, aiming to maintain or raise plasma oncotic pressure to minimise extravasation of intravascular fluids and hence reduce oedema formation. It was thought that colloids were associated with substantial fluid saving up to 3–4fold or even higher volumes [27]. However, only about 40% larger crystalloid than colloid volumes were actually needed in larger clinical trials to achieve comparable hemodynamic stabilisation [28, 29] and even similar volumes were effective in children with Dengue shock syndrome [30].

In 2003, a critical analysis which reviewed six meta-analyses concluded that trauma patients should continue to be resuscitated with crystalloids [31]. A recently updated systematic review by the Cochrane Collaboration of randomised controlled trials in patients requiring volume replacement also found no difference between types of fluids for

E: Hypertonic saline (alone or with hypertonic colloid) versus saline or other fluids.

Authors	Patients	Study type	Interventions	Outcomes
L. Harutjunyan et al., 2005	32 neurosurgical patients with ICP >20 mm Hg	RCT	7.2% saline in 6% hydroxyethyl starch versus 15% mannitol	Both drugs decreased ICP below 15 mm Hg (p <0.0001); both increased the cerebral perfusion pressure (both, p <0.0001).
C.E. Wade et al., 2003	230 patients with penetrating injuries to the torso	Blinded RCT	250 ml hypertonic saline dextran or normal saline	Primary endpoint survival until discharge from hospital (82.5% vs 75.5%, p = 0.19).
E.M. Bulger et al., 2010 [51]	1,282 patients with blunt trauma and TBI and a pre-hospital GCS score of ≤8 who did not meet criteria for hypovolaemic shock	Multi-centre blinded RCT	A single 250-ml bolus of 7.5% saline/6% dextran 70 (hypertonic saline/dextran), 7.5% saline (hypertonic saline), or 0.9% saline (normal saline) initiated in the out-of-hospital setting.	Primary endpoint: Six-month neurologic outcome by Extended Glasgow Outcome Scale (GOSE) (dichotomized as >4 or ≤4) was not different between groups. Survival at 28 days was 74.3% with hypertonic saline/dextran, 75.7% with hypertonic saline, and 75.1% with normal saline (p = 0.88). Planned enrolment was 2,122 patients, but study was terminated earlier because of meeting pre-specified futility criteria.
E.M. Bulger et al., 2010 [52]	853 severely injured patients with hypovolaemic shock (systolic BP ≤70 mm Hg or systolic BP 71–90 mm Hg with heart rate ≥108 beats per minute)	Multi-centre blinded RCT	250 ml of either 7.5% saline per 6% dextran 70 (hypertonic saline/dextran, HSD), 7.5% saline (hypertonic saline, HS), or 0.9% saline (normal saline, NS) administered by out-of-hospital providers.	Primary endpoint: 28-day survival was not different between groups (HSD 74.5% (0.1; 95%CI: –7.5 to 7.8); HS: 73.0% (–1.4; 95%CI: –8.7–6.0); and NS: 74.4%, p = 0.91. A pre-specified safety subgroup analysis of survival in patients who did not receive blood transfusion showed 28-day mortality in each of the hypertonic resuscitation arms approximately twice the mortality in the NS arm. After additional analyses the study was terminated early for futility in the presence of a potential safety concern.

RCT = randomised controlled trial; ARDS = adult respiratory distress syndrome; ARF= acute renal failure; IAH= urinary bladder pressure measurements >20 mm Hg; $GAPCO_2$ = gastric partial carbon dioxide minus end-tidal carbon dioxide; ACS = abdominal compartment syndrome (as defined by urinary bladder pressure measurements >25 mm Hg with organ dysfunction); PRBC= packed red blood cells; FFP = fresh frozen plasma; LOS = length of stay; GCS = Glasgow Coma Scale; TBI = traumatic brain injury.

the pooled relative risk (RR) of death (RR 1.01, 95%CI: 0.92 to 1.10) [32]. The authors concluded that "There is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs." [32]. Recent RCTs have suggested that colloids may be associated with some risk. In the blinded 7000-patient SAFE trial comparing 4% albumin and 0.9% NaCl, the pre-defined subgroup of trauma patients had a not quite significantly increased risk of death if they received resuscitation with albumin. Mortality rates were 81/596 patients (13.6%) in the albumin group and 59/590 patients (10.0%) in the NaCl group, (RR 1.36 (0.99 to 1.86)) [28]. This was found to be mainly due to patients with traumatic brain injury (TBI). In a *post-hoc* follow-up study, 460 patients with TBI were observed for 2 years. At 24 months, 71 of 214 patients in the albumin group (33.2%) had died, compared with 42 of 206 in the saline group (20.4%) (RR, 1.63; 95%CI: 1.17 to 2.26; $p = 0.003$) [33]. In this study, initial intracranial pressure tended to be higher in the albumin group and the authors speculated that intravascular colloids extravasated into brain tissue in these traumatised patients and contributed to brain oedema [33]. A retrospective analysis of 160 patients with aneurysmal subarachnoid haemorrhage who received synthetic colloids (4% succinylated gelatin or 6% pentastarch) suggested that colloid fluids dose-dependently (l/day) promoted unfavourable outcome at 6 months (OR 2.53, CI 1.13–5.68, $p = 0.025$), while crystalloids decreased unfavourable outcome (OR 0.27/l/day, CI 0.11–0.67, $p = 0.005$). A higher daily dose of synthetic colloids for initial resuscitation seemed to be associated with more requirements for blood transfusions ($p = 0.003$) [34]. Synthetic colloid plasma expanders may negatively affect the haemostatic system beyond their effect on haemodilution [35]. The synthetic colloid hydroxyethyl starch (HES) can reduce von Willebrand factor and interferes with fibrinogen polymerisation and platelet function [35]. Modern HES 130/0.4 is supposed to have less effect on coagulation. A recent systematic review and meta-analysis on haemostatic effects measured by thrombelastographic methods found that HES 130/0.4 administration results in a weaker and smaller clot than crystalloid or albumin haemodilution [36]. This raises concerns that administration of HES 130/0.4 may increase risk of bleeding, concerns which are not alleviated by the results of the first randomised trial on HES 130/0.4 versus normal saline in severe trauma patients [37]. This study was powered for volume need and time to tolerance of feeding which did not differ between groups. There were severe baseline imbalances and HES patients were more severely injured. Therefore, the finding that patients with blunt trauma in the HES group required significantly more blood products [37] or that ICU mortality was higher in the HES (21.4%) than the saline group (11.3%) [38] may be inconclusive. A recent blinded, multi-centre randomised controlled trial in 800 sepsis patients which was powered for 90-day mortality found that patients treated with HES 130/0.4 up to a daily dose of 33 ml/kg had an 8% absolute higher mortality rate than patients treated with Ringer's acetate. The use of blood products was also increased [39]. Gelatines and dextrans also interfere with

Table 2: Reviews and meta-analyses.

Reference	Condition	Type of review	Focus of review	Outcomes and conclusions
I. Kwan et al., 2009 [20]	Trauma patients with bleeding	Systematic review of randomised trials	Early versus delayed, and larger versus smaller volume of fluid administration	Interventions and patient populations were so diverse that no quantitative combination of results was performed. Three trials reported mortality and two coagulation data for early versus delayed fluid administration. Three trials reported mortality and one coagulation data for larger versus smaller volume of fluid administration.
S.B. Rizoli, 2003 [31]	Trauma patients	Critical analysis of six meta-analysis	Crystalloids versus colloids	Conclusion: considering all weaknesses and nuances of interpretation, the meta-analyses reviewed suggest that trauma patients should continue to be resuscitated with crystalloids.
P. Perel, I. Roberts, 2011 [32]	Patients with trauma, burns, or sepsis, or undergoing surgery	Meta-analysis of RCTs	Crystalloids versus colloids	No evidence from RCTs that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. For meta-analyses of HES vs crystalloid, modified gelatine vs crystalloid, dextran vs crystalloid, there were no statistically significant differences in mortality.
J. Dretzke et al., 2004 [19]	Trauma patients with no head injury who have haemorrhage-induced hypotension due to trauma	Health technology Assessment report	Pre-hospital intravenous (IV) fluid replacement, compared with no IV fluid replacement or delayed fluid replacement	The review found no evidence to suggest that pre-hospital IV fluid resuscitation is beneficial, and some evidence that it may be harmful. This evidence is however not conclusive, particularly for blunt trauma. Further research is required on hypotensive (cautious) resuscitation versus delayed or no fluid replacement, particularly in blunt trauma.
F. Bunn et al., 2008 [48]	Fluid resuscitation in critically ill patients	Meta-analysis of RCTs	Hypertonic versus near isotonic crystalloid	Fourteen trials with a total of 956 participants were included. Pooled relative risk for death in trauma patients was 0.84 (95%CI: 0.69 to1.04); in patients with burns 1.49 (0.56 to 3.95); and in patients undergoing surgery 0.51 (0.09 to 2.73). In the one trial that gave data on disability using the Glasgow outcome scale, the relative risk for a poor outcome was 1.00 (0.82 to 1.22). There is not enough clinical data to say which fluid is better.
A. Alsawadi 2012 [26]	Blunt abdominal trauma with haemorrhagic shock	Systematic review of randomised trials	Clinical effectiveness of permissive hypotension	Two randomised controlled trials with mixed types of injuries in the included patients found no significant difference between the groups used in each study.

coagulation and may prolong bleeding [35]. Despite many decades of clinical use, evidence for the safety of these plasma expanders is rather poor or non-existent as has recently been shown for gelatine [40].

Current recommendations for critically ill patients [41] and patients with sepsis [42] caution against the use of synthetic colloids. The recently issued interdisciplinary German S3 guidelines treatment of polytrauma/severe injuries [43] recommend to use crystalloids, and not to use albumin for pre-clinical resuscitation. However, in case colloids are considered in hypotensive trauma patients HES 130/0.4 is specifically recommended [43]. This seems problematic considering latest clinical evidence in sepsis patients [39]. The CHEST trial [44] which has enrolled 7000 ICU patients to compare fluid therapy with HES 130/0.4 versus normal saline is expected to come up with results within this year. Pre-specified subgroups include patients admitted for trauma without traumatic brain injury, and patients with traumatic brain injury, whereas patients with severe traumatic intracranial haemorrhage are excluded.

Regarding use of different types of isotonic crystalloids, it is important to note that appropriate comparisons between different types of crystalloids are missing. Hence, preference of one type of crystalloid over another is mainly based on inference from experimental studies or smaller trials [45]. It has been suggested that peri-operative resuscitation with normal saline may result in hyperchloraemic acidosis [46] however the clinical relevance of this observation is unclear. Acetated dialysis fluids may predispose to increased hypotension in patients requiring dialysis [47].

Hypertonic / hyperosmolar solutions

Hypertonic salt solutions (HTS) – in the context of "small-volume resuscitation" – are considered to have a greater ability to expand blood volume by causing an osmotic shift of fluid from the intracellular and interstitial spaces to the extravascular compartment. On one hand, the osmotically active substance may have a positive effect on patients with brain injury by improving macro-circulation in combination with a reduction of intracranial pressure. On the other hand, hypertonic solutions may also have important disadvantages. In case of ongoing haemorrhage, hypertonic solutions may perpetuate bleeding from injured vessels; head injuries may be associated with a disrupted blood brain barrier, which can cause sodium to leak into brain tissue and worsen cerebral oedema. According to a 2008 meta-analysis of the Cochrane Collaboration on the effects of hypertonic crystalloid on mortality in patients with hypovolaemia, clinical studies had so far not provided enough data to be conclusive. 14 trials with a total of 956 participants were included. RR for death in trauma patients was 0.84 (95%CI: 0.69 to1.04), in patients with burns 1.49 (95%CI: 0.56 to 3.95) and in patients undergoing surgery 0.51 (95%CI: 0.09 to 2.73) [48].

Hyper-osmolar solutions – salt solutions in combination with 6–10% dextran 60/70 or 6–10% HES – have also been advocated as beneficial mainly based on small and short-term studies. For example, both 7.2% NaCl/HES 200/0.5 and 15% mannitol reduced intracranial pressure (ICP) below 20 mm Hg and for up to 30 min after infusion in 32 neurosurgical patients, and mean arterial pressure (MAP) was higher after HTS-HES [49]. In 230 patients with penetrating torso injuries who were randomly administered either 250 ml hypertonic saline dextran (HSD) or normal saline in a blinded fashion, systolic blood pressure was increased whereas survival in hospital was similar (82.5% vs 75.5%, $p = 0.19$) [50].

Fortunately, a pivotal large-scale multi-centre RCT has recently been published which compared HTS, HTS-dextran and normal saline in two separate cohorts, one with TBI (n = 1,087) [51] and one with haemorrhagic shock (n = 853) [52]. The study was powered for primary endpoints of neurological outcome at 6 months after TBI and 28 day survival, respectively. The TBI study was terminated early due to futility: an interim analysis was unable to find an improvement in neurological status or mortality at 6 months. The second study demonstrated no significant difference in mortality at 28 days, and this study was terminated because the subgroup of patients without need of blood transfusion showed a higher although statistically non-significant increase in 28-day mortality rate when treated with HTS.

Conclusion

Volume therapy in trauma patients is changing. Traditionally, liberal replacement of intravascular fluids was favoured to correct fluid loss and optimise macro- and microcirculation. High quality randomised controlled studies accounting for different types and severity of injury, use of vasopressors, inotropes and blood component management are mostly lacking in this area. Evidence is emerging that low volume resuscitation and permissive hypotension may be associated with improved outcomes. Crystalloids are safe as first line fluids. Colloids have no advantage over crystalloids and may be detrimental in patients with traumatic brain injury. Synthetic colloids may prolong bleeding and increase need for blood products. The role of hypertonic saline is unclear, as recent large-scale trials have been stopped for futility and some safety concerns.

Funding / potential competing interests: There was no additional study funding by extra-departmental sources for this work. Michael Bauer is funded in part by the Centre for Sepsis Control and Care (CSCC). The CSCC is an Integrated Research and Treatment Centre funded by the German Federal Ministry of Ministry of Education and Research. Michael Bauer and Christiane Hartog receive CSCC research grants. Michael Bauer is supported by grants from the German Research Council (DFG). Authors declare that they have no competing interests.

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