Critical Care

PERSPECTIVE

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Are crystalloid-based fluid expansion strategies still relevant in the first hours of trauma induced hemorrhagic shock?

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Abstract

Background Crystalloid-based fluid resuscitation has long been a cornerstone in the initial management of trauma-induced hemorrhagic shock. However, its benefit is increasingly questioned as it is suspected to increase bleeding and worsen coagulopathy. The emergence of alternative strategies like permissive hypotension and vasopressor use lead to a shift in early trauma care practices. Critical appraisal of current evidence is necessary to guide clinicians and outline research perspectives.

Main text Current guidelines for managing trauma-induced hemorrhagic shock suggest titrating fluids and using vasopressors to achieve minimal blood pressure targets until hemorrhage is controlled. In case of traumatic brain injury with severe hemorrhage, blood pressure target increases. The scientific literature supporting these recommendations is limited, and several aspects remain the subject of ongoing scientific debate. The aim of this review is to evaluate the existing evidence on low-volume fluid resuscitation during the first hours of trauma management, with an emphasis on its integration with permissive hypotension, vasopressor use and cerebral perfusion pressure in traumatic brain injury. The review also highlights the limitations of current guidelines, particularly the lack of robust evidence supporting specific type of fluid, volumes and administration protocols tailored to specific trauma scenarios and populations. Emerging technologies such as point-of-care diagnostics, integrated monitoring systems, and machine learning hold promise for enhancing clinical decision-making in trauma care. These innovations could play a crucial role, ultimately helping clinicians address critical unanswered questions in trauma management and improve patient survival.

Conclusions Crystalloid-based resuscitation remains relevant in early trauma care, but its application must be reassessed considering recent evidence and evolving practices. Further research is essential to refine fluid resuscitation guidelines, particularly in defining safe fluid volumes and the role of vasopressors. The integration of advanced monitoring technologies may offer new opportunities to optimize trauma care and improve outcomes.

Keywords Trauma-induced hemorrhagic shock, Fluid resuscitation, Crystalloid fluids, Permissive hypotension, Vasopressors, Trauma care, Advanced monitoring

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Introduction

Despite major growth and improvements in trauma systems, circulatory shock remains a leading cause of trauma deaths worldwide [1, 2]. The highest mortality rates in severe hemorrhage have been observed in the first hours following trauma giving prehospital care a significant role [3]. By decreasing intravascular blood volume, severe hemorrhage can lead to a state of shock defined as inadequate tissue perfusion due to decreased cardiac output [4]. Aimed at restoring intravascular volume and therefore cardiac output, fluid resuscitation is a cornerstone of prehospital trauma care [5]. Its clinical benefit remains however insufficiently characterized and documented harm stems from excessive fluid resuscitation [5, 6]. Indeed, aggressive fluid resuscitation has been suspected of exacerbating acute bleeding by increasing hydrostatic pressure and decreasing clot firmness [7]. Permissive hypotension based on maintaining blood pressure at lower-than-normal levels to ensure minimal organ perfusion emerged to address such concerns [8]. Restrictive fluid expansion strategies combined with vasopressor use could represent an alternative [9].

Current recommendations suggest for traumatic hemorrhagic shock without severe head injury, to titrate fluids and use vasopressors to maintain permissive hypotension (target systolic blood pressure 80–90 mmHg) until hemorrhage control [9]. If traumatic brain injury is associated to severe hemorrhage, guidelines recommend targeting a systolic blood pressure > 110 mmHg. Isotonic crystalloid solutions are recommended as first line for fluid expansion. The level of evidence for these recommendations is however weak and several aspects remain a matter of scientific controversy. The aim of this perspective is to review the available evidence on low volume fluid resuscitation in the first six hours of trauma management and its articulation with permissive hypotension, vasopressor use and cerebral perfusion pressure in traumatic brain injury (TBI). Although they represent exciting alternatives, this review will not address the use of blood products. Further evidence is required to establish their benefit or harm in early trauma resuscitation [10]. Blood products are also not immediately available in all systems, and in consequence fluids remain a first line treatment. This perspective will focus on the evidence and rationale of crystalloid fluids in humans in the first hours of trauma induced hemorrhagic shock. A structured search of literature was conducted and restricted to human studies only. The supplementary material details the search and selection strategy.

Low volume resuscitation

Experts recommend the initiation of fluid expansion strategies in trauma induced circulatory shock [9, 11]. Circulatory shock can be suspected in the prehospital setting if there is an absence of radial pulse and/or hypotension (SBP < 90 mmHg). Indeed, presence of a radial pulse is believed to be a reliable indicator of a SBP over 80 mmHg [12]. It is critical to underline that only a small proportion of trauma patients present signs of circulatory shock in the first six hours. Indeed, a recent analysis of the UK-TARN and German-DGU database showed that only 3,5% of trauma patients in the UK received prehospital fluids [13]. Furthermore, this study showed a reduction of fluid volumes over the last decade with median volumes of < 1000 ml administered in both countries. Indeed, serious concerns about fluid expansion safety arose in the last decades. Potential harm stems from amplification of coagulopathy through dilution and hypothermia, endothelial dysfunction from hyperchloremic acidosis, renal dysfunction, increased infections and ARDS and abdominal and limb compartment syndrome in excessive fluid use [6, 14, 15]. Overzealous fluid expansion is suspected of bleeding intensification through an increase in vascular hydrostatic pressure. This concept is based on fragile evidence from vascular surgery suggesting that increased pressure could result in clot dislodgement [7].

Low volume resuscitation aims to maintain some perfusion while limiting the risk of adverse effects. The benefit of restrictive fluid expansion strategies on mortality has been confirmed by prospective observational studies and many randomized controlled trials [16–18]. The pooled external validity of these studies is limited due to heterogenous study populations and administered fluid volumes [5]. Recent data suggest potential harm of overly restrictive fluid strategies, since they might fail to maintain tissue perfusion. One observational study demonstrated increased mortality after a prehospital fluid volume of less than 250 ml or more than 1250 ml in shocked trauma patients [19]. Prospective estimation of the safe amount of fluid expansion remains to be established.

Current guidelines advocate for goal directed fluid administration with repeated 250 ml fluid boluses until recuperation of radial pulse and/or specific blood pressure levels (80–90 mmHg SBP and/or 50–60 mmHg MAP) before bleeding control [9]. These strategies have however never been assessed in prospective interventional studies. Recent data suggests that the elderly could benefit from higher blood pressure goals and whether more fluid would be the appropriate tool to obtain these pressure levels remains unknown [20]. We also do not

know whether penetrating and blunt trauma differ with respect to the effect of fluid resuscitation.

Normal saline was the historic first line fluid but seems to increase kidney injuries through chloride overload [21]. Randomized control trials have shown that balanced crystalloids improve survival after high volume fluid expansion beyond 1500 ml [21].

A summary of the scientific evidence cited above on low volume resuscitation is provided in Table 1.

Permissive hypotension

During permissive hypotension, clinicians tolerate lower arterial blood pressures until hemorrhage control. The rationale is to avoid the "pop the clot" phenomenon and harm from excessive fluids [22]. This strategy is advocated by several guidelines [9, 23].

Bickel et al. performed the first randomized controlled trial (RCT) in 1994 and demonstrated a lower mortality in the group managed with permissive hypotension in penetrating trauma [24]. Since then, two RCTs [18, 25] found no difference in mortality comparing permissive hypotension and normotension; two other RCTs [16, 26] and one meta-analysis combining all five RCTs [8] indicate a survival benefit of permissive hypotension. Two meta-analyses pooled prospective and retrospective studies and suggest a lower mortality with permissive hypotension [27, 28]. Owattanapanich et al. [28] pooled 24 studies with weak to moderate heterogeneity (I2: 27%; $p=0.11$). This meta-analysis points towards a decrease in mortality, transfusion of red blood cells concentrates, fluid volumes and incidence of multi-organ dysfunction syndrome (MODS) and ARDS with no impact on the incidence of acute kidneys injury (AKI) [28].

These studies and trials face criticism. The findings from the Bickel trial significantly contribute to the outcomes of the meta-analyses. Since 1994 trauma management and case-mix have considerably changed and the results apply strictly to penetrating trauma. All mentioned RCT share issues with regarding blinding, incomplete protocol reporting and external validity and a high percentage of penetrating trauma. All trials report inconsistent and heterogenous SBP and MAP targets and a small or no difference in target systolic blood pressure between the two groups, raising doubt about the rigorous application of permissive hypotension. For instance, Schreiber et al. [16] observed a lower mortality in the permissive hypotension group; yet the SBP in the interventional group was not different from the control group (105 vs 99 mmHg; 95% CI −3 to 16, $p>0.05$). The same observation applies to the Bickell trial.

Despite this weak level of evidence, permissive hypotension remains one the best studied components of trauma resuscitation. Guidelines advocate to aim for permissive hypotension until hemorrhage control is obtained. Retrospective data indicate an association between prolonged permissive hypotension and organ hypoperfusion and multiorgan failure [29]. One retrospective study in patients with severe trauma found an association between the duration of hypotension in the resuscitation period and myocardial injury [30]. Permissive hypotension seems to increase mortality in elderly patients and should be carefully considered [20]. The safety of permissive hypotension among patients with chronic arterial hypertension remains to be investigated. Further randomized data is required to understand the maximum duration and the place of permissive hypotension.

A summary of the scientific evidence cited above on permissive hypotension is provided in Table 2.

Vasopressors

The physiologic response to hemorrhagic shock transitions from an initial sympathoexcitatory and vasoconstrictive phase to a sympathoinhibitory phase characterized by uncontrolled vasodilation and endotheliopathy, both facilitators of multi-organ failure [31]. The negative reinforcement of an exhausted sympathoexcitatory response provides the rationale to administer vasopressors in traumatic shock [32]. Vasopressors could prevent or counteract this late-stage vasodilation yet might cause a dilemma [33, 34]. Restoration of a vascular tone and perfusion pressure may exacerbate tissue hypoperfusion and organ dysfunction and raises the question of vasopressor efficacy and safety in traumatic shock [32].

Unfortunately, available observational evidence paints a complex picture. Early investigations into vasopressors in trauma highlighted potential risks. One study associated the use of various vasoactive agents within 12 h post-injury like phenylephrine, norepinephrine, or vasopressin and indicated increased mortality [35]. Collier et al. observed increased mortality risk among trauma patients given vasopressin within 72 h of hospitalization [36]. Analysis of trauma patients exposed to any vasoactive drug within the first 24 h post-admission revealed significantly higher mortality rates compared to unexposed patients. Several retrospective studies echoed these findings [37, 38]; one study reporting quadrupled risk of anastomosis failure after vasopressor use in post-damage control laparotomy [39]. A 2017 systematic review on the early administration of vasopressors concluded to an increased mortality but, as discussed by the authors, these results carry a high risk of bias because of prognostic imbalance and selection bias [40].

First, these studies are characterized by a high risk of bias, insufficient confounder control, very heterogeneous,

Table 1 Available evidence on low volume fluid resuscitation

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Retrospective														
Balogh Z. et al	2003	Arch Surg	Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome	USA	Single center	Prehospital & in-hospital	Major injury (≥ 2 abdominal organs, ≥ 2 bone fractures, complex pelvic fracture, flail chest and/or major vascular injury), and blood loss (≥ 6 RBC units anticipated for the first 12 h) and shock (arterial base deficit ≥ 6 mEq during the first 12 h upon admission). Or trauma victim 65 years old or older with any 2 criteria	Patients with GCS ≤ 8 and abnormal head CT and assessment by attending neurosurgeon of moderate or severe risk of worsening cerebral oedema	Aggressive (DO_2I ≥ 600 mL/min/m2) versus Normal (DO_2I ≥ 500 mL/min/m2)	156 (85/71)	No primary outcome designated	Lactated Ringer infusion volume at ICU admission, gastric partial carbon dioxide minus end-tidal carbon dioxide, intra-abdominal hypertension (Urinary bladder pressure > 20 mmHg), acute compartment syndrome (Urinary bladder pressure > 25 mmHg with organ dysfunction), multiorgan failure, mortality	Secondary outcomes: Intra-abdominal hypertension aggressive group 42% versus 20% normal group ($p < 0.05$) Acute compartment syndrome 16% versus 8% ($p < 0.05$) Multiorgan failure 22% versus 9% ($p < 0.05$) Death 27% versus 11% ($p < 0.05$)	Aggressive resuscitation was associated with higher rates of intraabdominal hypertension, acute compartment syndrome, multiorgan failure, death
Edwards M et al	2010	Am Surg	Defining hypotension in moderate to severely injured trauma patients: raising the bar for the elderly	USA	Multicenter (5 level I and 8 level II trauma centers)	Prehospital	Patients with ISS > 9 and head-AIS < = 3 admitted between 1998 and 2005	Head-AIS > 3, dead on arrival, missing data (age, sex, ISS, GCS score, SBP or death)	SBP in 3 age groups: 20–49, 50–69, > 70 years old	24,438	Optimal definition of hypotension by age group controlling for sex, ISS, and GCS	No secondary ouctomes listed	Primary outcome: Hypotension thresholds were: 100mHg for 20–49 years old, 120 mmHg for 50–69 years old, 140mmhg for people 70 years old or more	Different thresholds of hypotension depending on patient's age

Table 1 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Brown JB et al	2013	J Trauma Acute Care surg	Goal directed resuscitation in the prehospital setting: a propensity-adjusted analysis	USA	Multicenter (7 hospitals)	Prehospital & in-hospital	Blunt injury and ISS > 15 and scene transport and known volume of prehospital crystalloid and initial SBP recorded	Patients younger than 18, older than 90 years, cervical spinal cord injury, patients with isolated traumatic brain injury	High (> 500 mL) versus Low (< 500 mL) prehospital IV fluids	1216 (394/822)	30-day in hospital mortality, acute traumatic coagulopathy defined as INR > 1,5)	Stratification between prehospital hypotension or normotension. Multivariate cox regression analysis Hypotension defined as SBP < 90 mmHg	Primary outcome: 30-day in hospital mortality: High versus Low HR 2.45 (95% CI 1.25;4.83) $p = 0.01$ Secondary outcome: Acute traumatic coagulopathy: in the group with prehospital hypotension High versus Low volumes OR 2.55 (95% CI 0.88;7.39) $p = 0.08$, in the group without prehospital hypotension OR 2.21 (95% CI 1.01;4.86) $p = 0.04$	Prehospital infusion of crystalloids > 500 mL was associated with worse outcomes in patients without prehospital hypotension. Volumes > 500 mL were associated with corrected hypotension. Goal directed strategies are necessary
Zitek T et al	2021	Am J Emerg Med	Is the use of greater than 1L of intravenous crystalloids associated with worse outcomes in trauma patients?	USA	Single center	Prehospital & in-hospital	Trauma patients at least 18 years old with a heart rate ≥ 100 bpm or with SBP ≤ 90 mmHg	Cardiac arrest, neurogenic shock, transfer from another facility, discharged from emergency department, left against medical advice, missing data	IV administration of > 1L crystalloids between EMS and within 3 h after arrival to the emergency department	878 (388/490)	Inhospital mortality	Length of stay, Number of red blood cells transfused, multivariate analysis	Primary outcome: Mortality: OR 0.84 (95% CI 0.44; 1.62) $p = 0.61$	Use of greater than 1L IV crystalloids was not associated with increased in-hospital mortality

Table 1 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Bath MF et al	2024	Critical care	Trends in pre-hospital volume resuscitation of blunt trauma patients: a 15-year analysis of the British (TARN) and German (Trauma register DGU) national registries	Germany & UK	Multicenter (2 national trauma databases)	Pre-hospital	Adult patients in UK and Germany national trauma databases between 2004 and 2018 with a blunt trauma and an ISS > 15	Combined blunt and penetrating injury, transfer from other hospital, isolated head injuries	Volume of fluid expansion	68,510 UK 82,551 Germany	Assess changes and trends in volume resuscitation practice	Rates of trauma-induced coagulopathy and in hospital mortality	Primary outcome: UK: slope − 1.12 (95% CI − 1.14 to − 1.11) $p < 0.001$ Germany: slope − 15.4 (95% CI − 15.6 to − 15.3) $p < 0.001$	Year on year decrease in the volume of pre-hospital fluid administered
Prospective														
Semle MW et al	2018	N Engl J Med	Balanced crystalloids versus saline in critically ill adults	USA	Single center	In hospital	Adults 18 admitted to a participating intensive care unit	None listed	Saline 0,9% (S) versus lactated Ringer or plasmalyte A (B)	15,802 (7942/7860)	Major adverse kidney event within 30 days (composite of death from any cause, new renal replacement therapy, persistent renal dysfunction)	In-hospital death before ICU discharge at 30–60 days, ICU-free days, ventilator free days, vasopressor free days, days alive and free or renal replacement therapy during the first 28 days after enrollment	Primary outcomes: Major adverse kidney event B 14.3% versus 15.3% in S, OR 0.91 95% CI (0.84;0.99) $p = 0.04$ Secondary outcomes: In hospital 30-days mortality: 10.3% in B versus 11.1% in S ($p = 0.06$). Incidence of new renal replacement therapy 2.5% versus 2.9% ($p = 0.008$)	Higher proportion of major adverse kidney events in the saline group

Table 1 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Deeb AP et al	2023	J Am Coll Surg	Optimal prehospital crystalloid resuscitation volume in trauma patients at risk for hemorrhagic shock	USA	Multicenter (9 trauma centers)	Prehospital	Trauma patients transported by air from scene with SBP < 70 mmHg or SBP 70–90 mmHg with a heart rate > 108 bpm	None listed	Prehospital crystalloid volume	405	24-h mortality	Fluid volumes for patients with traumatic brain injury, subgroup analyses, IL6 and syndecan-1 rates	Primary outcome: Lowest 24-h mortality range of 250–1250 mL overall Under 250 mL adjusted OR of death 2.46 (95% CI 1.31;4.83) $p = 0.007$ Over 1250 mL adjusted OR 2,57 (95% CI 1.24;5.45) $p = 0.012$	U shaped relationship between IV fluids and 24-h mortality with highest survival between 250 and 1250 mL
Randomized controlled trials														
Dutton RP et al	2002	J trauma	Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality	USA	Single center	In-hospital	Traumatic injury with evidence of ongoing hemorrhage, and SBP < 90 mmHg at least once within the first hour	Pregnancy, central nervous system injury impairing consciousness or motor function, older than 55 years, previous history of coronary artery disease or diabetes	Low: Target SBP of 70 mm Hg (LSBP) Control: target SBP > 100 mm Hg (CSBP) Using fluid titration	110 (55/55)	ISS, duration of active hemorrhage	none listed	Primary outcomes: ISS (mean ± SD): CSBP 19.55 ± 11.6 versus LSBP 23.91 ± 13.8 ($p = 0.08$) Duration of active hemorrhage (hours): CSBP 2.97 ± 1.75 versus in LSBP 2.57 ± 1.46 h, $p = 0.20$)	No significant difference in ISS and duration of hemorrhage using lower SBP targets

Table 1 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Schreiber MA et al	2015	J Trauma Acute Care surg	A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial	USA & Canada	Multicenter (USA & Canada)	Prehospital & in-hospital	Blunt or penetrating trauma, with SBP ≤ 90 mmHg, and ≥ 15 years old or > 50 kg if age unknown and GCS > 8	Out of hospital cardiopulmonary resuscitation, drowning or asphyxia by hanging, burns > 20%, prisoner status, evidence of pregnancy, > 250 mL fluids received before randomization, > 4 h between call and randomization	Controlled resuscitation (CR) (250 mL of fluid if no radial pulse or SBP < 70 mmHg and additional boluses to reach goals) Vs Standard resuscitation (SR) (2L initially and additional to maintain SBP > 110mHg) Duration: from out-of hospital enrollment to 2 h into hospital stay or bleeding control	192 (97/95)	Early crystalloid volume & 24-h mortality	Sub-group analyses (blunt vs penetrating trauma), 24-h fluid volumes, in-hospital mortality, admission vital signs, admission hematologic assays, renal function, ICU free days, ventilator free days, out of hospital days, protocol violations	Primary outcomes: Early crystalloid volume (mean): 1 L (SD 1.5) in CR versus 2 L (SD 1.4) in SR: mean difference 1.00 (95% CI 0.59–1.41) 24 h-mortality 5.2% CR, 14.7% SR, adjusted OR 0.39 (95% CI 0.12–1.26)	Controlled resuscitation is feasible and safe
Systematic reviews & meta-analysis														
Hébert et al	2023	CJEM	The efficacy of prehospital IV fluid management in severely injured adult trauma patients: a systematic review and meta-analysis	International	6 observational studies, 1 randomized controlled trial	Prehospital	Trauma defined as any cause of blunt or penetrating injury and severity quantified to a corresponding prehospital systolic blood pressure of 90 mmHg or shock index greater than 1. Primary endpoint of interest: 30-day-all cause mortality	Pregnancy, isolated head or spinal cord injury, burns, cardiac arrest, non-hemorrhagic causes of shock	Not applicable	3050	30-day all cause mortality	No secondary outcomes listed	Primary outcome: Mortality: RR 0.99 (95% CI 0.88;1.22)	No difference in mortality when comparing standard resuscitation to restricted resuscitation

Scientific articles were sorted by design: retrospective, prospective observational, randomized controlled trials and systematic-reviews and meta-analyses. Within each category the articles were tabulated in chronological order

AIS, abbreviated injury scale; DO_2I, oxygen delivery index; GCS, Glasgow Coma Scale; HR, hazard ratio; INR, international normalized ratio; ISS, injury severity score; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure; UK, United Kingdom; USA, United States of America

Table 2 Available evidence on permissive hypotension

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	Blood pressure boundaries	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Retrospective															
Lou X et al	2018	Medicine	Preoperative fluid management in traumatic shock	China	Single center	In-hospital	>60 years old; obvious symptoms of traumatic shock; an Abbreviated Injury Score (AIS) 90—an Injury Severity Score (ISS) between 16 and 75, and a prehospital time was within the range of 15 min to 2 h after injury	Cardiac arrest, hospital transfers, severe brain injury, severe heart, lung, and liver disorders	Group A: 72 patients were given aggressive fluid infusion at 20 to 30 mL/min to restore normal mean arterial pressure (MAP) of 65 to 75 mmHg Group B: 72 patients were slowly given restrictive hypotensive fluid infusion at 4 to 5 mL/min to maintain MAP of 50 to 65 mmHg Group C: 75 patients were given personalized infusion to achieve MAP of 75 to 85 mmHg	Mean arterial pressure target: Group A: 65–75 mmHg Group B: 50–65 mmHg Group C: 75–85 mmHg	219 (Group A: 72 Group B: 72 Group C: 75)	Mortality rates at 6 and 24 h	No secondary outcomes listed	Primary outcome: A lower mortality rate at 6 and 24 h after operation was observed in the Group C subjects ($p < 0.05$, compared with group B)	Personalized management of fluid resuscitation in traumatized aged patients with appropriate volume and MAP (>75 mmHg), suggesting increased survival rate compared to the permissive hypotensive group
Stroda A et al	2023	Eur J Trauma Emerg Surg	Association between hypotension and myocardial injury in patients with severe trauma	Germany	Single center	In-hospital	Severely injured ISS ≥ 16, adult (≥ 18 years)	Dead immediately after arrival, no measurement of troponin T at arrival, blood pressure values were missing	The duration of arterial hypotension (MAP < 65 mmHg) during resuscitation period	Mean arterial pressure target: < 65 mmHg	343 (143/200)	Myocardial injury 72 h after trauma	In-hospital death, acute kidney injury, major adverse cardiovascular events	Primary outcome: Hypotension and myocardial injury: OR 1.22 (95%CI 1.04–1.42) Secondary outcomes: Hypotension and in-hospital death: OR 1.23 (95%CI 1.05–1.44) Hypotension and acute kidney injury: OR 1.0 (95%CI 0.85–1.18) Hypotension and major adverse cardiovascular events: OR 1.22 (95%CI 1.04–1.44)	Duration of permissive hypotension < 65 mmHg during resuscitation period is independently associated with myocardial injury

Table 2 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	Blood pressure boundaries	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Randomized controlled trials															
Bickell HW et al	1994	N Engl J Med	Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries	USA	Single center	Prehospital & in-hospital Preoperative	Torso penetrating trauma who had a systolic blood pressure (SBP) ≤ 90 mm Hg	Revised Trauma Score of zero at the scene of the injury, fatal gunshot wound to the head, minor injuries not requiring operative intervention	Delayed-resuscitation group (in which intravenous fluid resuscitation was delayed until operative intervention) Standard immediate-resuscitation group (in which intravascular fluid resuscitation was given before surgical intervention)	Not mentioned	598 (289/309)	Survival to discharge	Length of hospital stay, length of ICU stay estimated intraoperative blood loss	Primary outcome: The overall rate of survival was significantly higher in the delayed-resuscitation group than in the immediate-resuscitation group (70% vs. 62%, $p = 0.04$)	For hypotensive patients with penetrating torso injuries, delay of aggressive fluid resuscitation until operative intervention improves the outcome
Dutton RP et al	2002	J Trauma	Hypotensive Resuscitation during Active Hemorrhage: Impact on In-Hospital Mortality	USA	Single center	Prehospital & in-hospital Preoperative & intraoperative	Trauma (blunt and penetrative) hemorrhagic shock with systolic blood pressure (SBP) < 90 mmHg	Central nervous system injury, impairing their level of consciousness or motor function, older than 55, previous medical history of diabetes or coronary artery disease	Intervention: target SBP of 70 mm Hg (low) Control: target SBP > 100 mm Hg (conventional)	Systolic blood pressure target: 70 mmHg	110 (55/55)	In-hospital mortality	Duration of active hemorrhage, Injury Severity Scale	Primary outcome: Overall survival was 92.7%, with four deaths in each group Secondary outcomes: No difference in secondary outcomes	Permissive hypotension did not affect mortality in this study
Morrison CA et al	2011	J Trauma	Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial	USA	Single center	In-hospital Intraoperative	Patients undergoing laparotomy or thoracotomy for blunt and penetrating trauma with systolic blood pressure (SBP) < 90 mmHg	Central nervous system injury, older than 45, previous medical history of myocardial infarction, renal disease, cerebrovascular disease, coronary artery disease	Group with minimum mean arterial pressure (MAP) of 50 mm Hg (experimental arm, LMAP) Group 65 mm Hg (control arm, HMAP)	Mean arterial pressure target: 50 mmHg	90 (44/46)	30-day mortality	Length of stay in: ICU, hospital, length of mechanical ventilation, postoperative hemoglobin levels, platelet levels, international normalized ratio [INR] values, and base deficit values, 24-h mortality, development of postoperative complications	Primary outcome: HR 1.10 (95%CI 0.96–1.07; $p = 0.58$) Secondary outcomes: LMAP patients had a lower 24 h-mortality, were significantly less likely to develop immediate postoperative coagulopathy, had significantly lower INR than those in the HMAP group. Others secondary outcomes were similar	No significant difference in terms of 30-day mortality

Table 2 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	Blood pressure boundaries	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Carrick MM et al	2016	J Trauma	Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma	USA	Single center	In-hospital Intra-operative	Penetrating trauma with systolic blood pressure (SBP) ≤ 90 mmHg requiring laparotomy or thoracotomy for control of hemorrhage	None listed	Group with minimum mean arterial pressure (MAP) of 50 mm Hg (experimental arm, LMAP) Group 65 mm Hg (control arm, HMAP)	Mean arterial pressure target: 50 mmHg	168 (86/82)	24 h and 30 days mortality	Stroke, myocardial infarction, acute kidney injury, coagulopathy, infection	Primary outcome: No significant survival advantage existed for the LMAP group at 30 days ($p = 0.48$) or 24 h ($p = 0.27$) Secondary outcomes: Secondary outcomes were similar for the LMAP and HMAP groups. Acute kidney injury occurred less often in the LMAP group (13% vs. 30%, $p = 0.01$)	This study was unable to demonstrate that hypotensive resuscitation could significantly improve 30-day mortality
Schreiber et al	2015	J Trauma	A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial	USA	Multicenter (USA & Canada)	Pre-hospital & in-hospital Preoperative & intra-operative	Trauma (blunt and penetrating) with out-of-hospital systolic blood pressure (SBP) ≤ 90 mmHg	Evidence of a severe traumatic brain injury, out-of-hospital cardiopulmonary resuscitation	Controlled ressuscitation: SBP ≥ 70 mmHg Standard ressuscitation: SBP ≥ 110 mmHg	Systolic blood pressure target: 70 mmHg	192 (97/95)	24 h mortality for all trauma 24 h mortality for blunt trauma 24 h mortality for penetrating trauma	ICU-free days, ventilator-free days, renal failure	Primary outcome: All trauma: OR 0.39 (95%CI 0.12, 1.26) Blunt trauma: OR 0.17 (95%CI 0.03, 0.92) Penetrating trauma: OR 1.93 (95%CI 0.19, 19.17) Secondary outcomes: No significant difference	No mortality difference in all trauma Controlled resuscitation may offer an early survival advantage in blunt trauma

Table 2 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	Blood pressure boundaries	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Systematic reviews with meta-analyses															
Albreiki M et al	2018	Eur J Trauma Emerg Surg	Permissive hypotensive resuscitation in adult patients with traumatic hemorrhagic shock: a systematic review	International	5 randomized controlled trials 2 prospective cohorts 3 retrospective cohorts	Pre-hospital & in-hospital Preoperative & intraoperative	Not applicable	Evidence of a severe traumatic brain injury, out-of-hospital cardiopulmonary resuscitation	Not applicable	Not applicable	3384	Mortality	No secondary outcomes listed	Primary outcome: The mortality rates among patients resuscitated with permissive hypotension and normotension in the selected randomized controlled trials were 21.5% (123/570) and 28.6% (168/587) respectively, whilst the total mortality rate of the patients enrolled in non-comparative studies was 9.97% (279/2797)	Permissive hypotension resuscitation can create better survival rate among trauma patients
Tran A et al	2018	J Trauma	Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: A systematic review and meta-analysis of randomized controlled trials	USA	5 randomized controlled trials	Pre-hospital & in-hospital Preoperative & intraoperative	Not applicable	Patients with isolated head injuries (and all but one study excluded traumatic brain injury patients)	Not applicable	Not applicable	1157 (570/587)	Mortality	Blood loss volumes, blood product utilization, volumes of crystalloid administration, coagulopathy, sepsis, renal failure, Acute Respiratory Distress Syndrome (ARDS)	Primary outcome: OR 0.70 (95%CI 0.53–0.92) Secondary outcomes: Patients receiving permissive hypotension have lower reported blood loss volumes, reduced blood product utilization and lower volumes of crystalloid administration Coagulopathy, renal failure, sepsis, ARDS were similar between groups	Based on the pooled findings of 5 RCT, there is a survival benefit for lower blood pressure targets as compared to conventional resuscitation thresholds

Table 2 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	Blood pressure boundaries	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Owattanapanich N et al	2018	Scand J Trauma Resusc Emerg Med	Risks and benefits of hypotensive resuscitation in patients with traumatic hemorrhagic shock: a meta-analysis	International	24 studies (randomized controlled trials, prospective and retrospective cohorts)	Prehospital & in-hospital Preoperative & intraoperative	Not applicable	Studies of patients who were pregnant, traumatic brain injuries, insufficient mortality data	Not applicable	Not applicable	2955 (1473/1482)	Mortality	Use of packed red blood cells, use of fluid resuscitation, acute kidney injury, multiple organ dysfunction syndrome, acute respiratory distress syndrome	Primary outcome: Decreased mortality was observed in the hypotensive resuscitation group (RR: 0.50; 95% CI 0.40–0.61). Heterogeneity was observed (I2: 27%; degrees of freedom: 23; $p=0.11$) Secondary outcomes: Less use of packed red blood cells and fluid resuscitation. A protective effect was observed relative to both multiple organ dysfunction and acute respiratory distress syndrome No significant difference was observed for acute kidney injury	This meta-analysis revealed benefits of hypotensive resuscitation relative to mortality in traumatic hemorrhagic shock patients

Scientific articles were sorted by design: retrospective, prospective observational, randomized controlled trials and systematic-reviews and meta-analyses. Within each category the articles were tabulated in chronological order

AIS, Abbreviated Injury Scale; ICU, Intensive Care Unit; MAP, mean arterial pressure; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure

non-routine use of various vasoactive agents as late last-line therapeutic and varying blood pressure thresholds. Second, the mechanism of traumatic injury (blunt vs penetrating) is associated with different patterns of tissue damage and inflammation and may condition the response to vasopressors [32]. Yet numerous observational studies do not differentiate between these trauma mechanisms. Studies with a more robust methodology and better confounder control such as propensity score or inverse probability weighting paint a more nuanced picture. One recent propensity score study from the Japanese registry aligns with historic findings with an increased mortality after vasopressor use [41]. One French propensity score cohort study [42] did not demonstrate a higher mortality after norepinephrine, nor did a US cohort exploring the mortality of patients undergoing emergency surgery with vasopressor administration except for epinephrine [43]. A US-French retrospective study applying an inverse probability weighting and doubly robust approach to a cohort of 2164 patients with blunt trauma and hemorrhagic shock did not observe any effect of norepinephrine administration on mortality [44].

Further evidence in favor of vasopressor use in hemorrhagic shock stems from two recent randomized controlled trials (RCTs). One small (n = 78) study found early low-dose vasopressin administration resulted in a reduced total 24 h fluid requirement compared to the no-vasopressin group. The rates of adverse events, organ dysfunction and 30-day mortality were similar [45]. Another RCT revealed that continuous vasopressin infusion reduced total blood product consumption, the primary outcome criterion, without increasing mortality [46]. In summary, vasopressors could play a role in management of shocked trauma patients, but further evidence from randomized studies is required.

A summary of the scientific evidence cited above on vasopressor use is provided in Table 3.

Traumatic brain injury

Current doctrine focuses on the reduction of secondary tissue injury in traumatic brain injury (TBI) [47]. Restoration of cerebral perfusion pressure (CPP) in circulatory shock is critical to ensure oxygen delivery to the brain. Guidelines advocate in favor of an initial systolic blood pressure target over 110 mmHg in patients with severe TBI and advise against permissive hypotension strategies [9]. Clinicians must therefore prioritize between two conflicting clinical strategies of either neuroprotection or hemorrhage limitation. Furthermore, in traumatology shock can arise from multiple causes that do not necessarily involve severe hemorrhage (tension pneumothorax, neurogenic hypotension, pericardial effusion). Such differential diagnoses highly complexify the clinician's dilemma if TBI is suspected.

The evidence underlying current guidelines in favor of increased blood pressure targets consists unfortunately of observational studies suggesting increased mortality rates among patients with prehospital or admission hypotension with TBI [48, 49]. Fuller et al. in 2013, estimated odds of death to be doubled for an admission SBP below 100 mmHg and tripled below 90 mmHg among a population of patients with AIS head scores above 2 [48]. Observational studies indicate a U-shaped relationship between prehospital blood pressure and in hospital mortality in TBI suggesting that hypertension could be also detrimental to survival [50, 51]. Recent observational data suggests that elderly patients could benefit from higher blood pressure levels highlighting the existence of potential high-risk subgroups [20]. The body of evidence supporting the existence of a unique lower threshold defining critical hypotension is limited. Spaite et al. for instance observed a linear association between SBP and mortality [52]. In their cohort, two patients with a SBP difference of 10 mmHg differed in their odds of death by 18.8%.

Despite the low level of evidence, hypotension appears to be a major secondary insult among patients with TBI that must be avoided at all costs. However, safe blood pressure levels as well as the definition of specific subgroups of patients at higher risk remain unclear and must be addressed by future RCTs.

Treatment of hypotension among patients with TBI can be achieved through fluid expansion strategies. Hypotonic crystalloids must be avoided as they maximize vasogenic oedema and have been shown to increase mortality [53]. Hypertonic solutions have failed to show increased survival rates and improvements in neurologic outcomes after severe TBI [54, 55]. Current guidelines therefore recommend the use of 0,9% sodium chloride as it is easily accessible and more cost effective. The safety and efficacy of vasopressor use in combination to fluid expansion strategies in TBI remains uncertain and must be assessed by future RCTs.

A summary of the scientific evidence cited above on cerebral perfusion pressure in traumatic brain injury is provided in Table 4.

Perspectives

Robust evidence has shown that crystalloid fluid expansion is beneficial to patients in circulatory shock in the first 6 h of their trauma. However, central clinical questions yet remain to be answered:

- Which clinical and/or paraclinical parameters should guide fluid initiation?

Table 3 Available evidence on vasopressors use

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Retrospective														
Collier B et al	2010	J Crit Care	Vasopressin use is associated with death in acute trauma patients with shock	USA	Single center	In-hospital	Trauma patients who received vasopressors within the first 72 h after admission	None listed	Use of vasopressin compared to use of other vasopressors	539 (189/350)	28-day in-hospital mortality	No secondary ouctomes listed	Primary outcome: OR 1.6 (95% CI 1.1–2.4; $p=0.02$)	Vasopressin use is associated with increased mortality in trauma patients with hypotension
Fisher PE et al	2013	Am J Surg	Vasopressor use after initial damage control laparotomy increases risk for anastomotic disruption in the management of destructive colon injuries	USA	Single center	In-hospital	Trauma patients sustaining destructive colon injuries	None listed	Risk factors for anastomotic failure after colon reconstruction after initial damage control laparotomy	171 (68/103)	Anastomotic failure	No secondary ouctomes listed	Primary outcome: 57% of the patients who had leaks received vasopressors, compared with 12% of patients who had no leaks ($P=0.02$)	The use of vasopressors after the initial damage control operation more than quadrupled the leak rate to 50%
Van Haren RM et al	2014	Am Surg	Vasopressor use during emergency trauma surgery	USA	Single center	In-hospital	Trauma patients requiring emergency operative intervention	None listed	Use of vasopressor during operative room (stratification based on type: epinephrine, phenylephrine, ephedrine, norepinephrine, dobutamine, vasopressin)	746 (225/521)	In-hospital mortality	No secondary ouctomes listed	Primary outcome: No difference in mortality between those who received vasopressors and those that did not (5 vs 6%, $p=0.523$), excluded epinephrine	Vasopressors during operative room are not independently associated with mortality
Barpararas et al	2018	Injury	Patterns of Vasopressor Utilization During the Resuscitation of Massively Transfused Trauma Patients	USA	Single center	In-hospital	Trauma patients receiving massive transfusion (≥ 3 units of packed red blood cells, within the first hour from admission	Patients receiving ≤ 2 units of packed red blood cells, patients with spinal cord injury	Use of vasopressor versus no use	120 (70/50)	Overall mortality (5 years study period)	No secondary ouctomes listed	Primary outcome: HR 9.88 (95% CI 1.21, 80.90; $p=0.03$)	Vasopressor use in patients receiving massive transfusion may increase mortality

Table 3 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/comparison	N (intervention/control)	Primary outcome	Secondary outcomes	Finding	Key message
Uchida K et al	2020	BMC Emerg Med	The impact of early administration of vasopressor agents for the resuscitation of severe hemorrhagic shock following blunt trauma	Japan	Single center	In-hospital	Blunt trauma patients with hemorrhagic shock	Patients with a probability of survival score calculated by the Trauma and Injury Severity Score (TRISS) of ≥ 0.6, patients in cardiopulmonary arrest, early death (< 24 h)	Survivors versus non-survivors	40 (21/19)	In-hospital mortality	No secondary ouctomes listed	Primary outcome: Max catecholamine index was significantly higher in non-survivors (2 [0–4] versus 14 [10–18]; $p = 0.008$)	Vasopressor administration and high-dose use for resuscitation of hemorrhagic shock following severe blunt trauma are potentially associated with increased mortality
Aoki et al	2018	Crit Care Med	Use of Vasopressor Increases the Risk of Mortality in Traumatic Hemorrhagic Shock: A Nationwide Cohort Study in Japan	Japan	Multicenter	In-hospital	Hemorrhagic shock with systolic hypotension (< 90 mmHg) and the requirement of blood transfusion within the first 24 h	< 16 years old, patients with an AIS equal to 6, patients with severe traumatic brain injury or spinal cord injury, cardiopulmonary arrest or resuscitation	Use of vasopressor for traumatic hemorrhagic shock within the first 24 h	Overall: 3551 (459/3092) Propensity matched: 596 (298/298)	In-hospital mortality	Emergency department mortality	Primary outcome: In-hospital mortality: OR 2.168 (95% CI 1.442–3.320; $p = 0.001$) Secondary outcome: Emergency department mortality: OR 0.676 (95% CI 0.260–1.719; $p = 0.17$)	Use of vasopressor for traumatic hemorrhagic shock was associated with mortality after controlling for biases (trauma severity; volume of fluid resuscitation)
Gauss T et al	2018	Br J Anaesth	Effect of early use of noradrenaline on in-hospital mortality in hemorrhagic shock after major trauma: a propensity-score analysis	France	Multicenter	Pre-hospital & in-hospital	Trauma patients with hemorrhagic shock (≥ 4 packed red blood cells in the first 6 h of admission)	Glasgow coma scale (GCS) = 3, pre-hospital cardiac arrest, younger than 16 years old	Early administration of norepinephrine	Overall: 518 (201/317) Propensity matched: 200 (100/100)	24 h in-hospital mortality	No secondary ouctomes listed	Primary outcome: After propensity score matching, HR 0.95 (95% CI 0.45–2.01; $p = 0.69$)	The propensity-score-matching analysis showed no effect of early noradrenaline use on in-hospital mortality

Table 3 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Fisher AD et al	2021	Prehosp Emerg Care	Prehospital vasopressor use is associated with worse mortality in combat wounded	USA	Multicenter	Prehospital	Prehospital trauma shock in combat wounded	None listed	Use of vasopressor in prehospital versus no use	Overall: 28,212 (124/28088) Propensity matched: 215 (108/107)	In-hospital mortality	No secondary ouctomes listed	Primary outcome: OR 0.32 (95% CI 0.18–0.56; $p < 0.001$)	Prehospital vasopressor use is associated with worse mortality in combat wounded
Gauss T et al	2022	JAMA Netw Open	Association of Early Norepinephrine Administration With 24-Hour Mortality Among Patients With Blunt Trauma and Hemorrhagic Shock	France and USA	Multicenter	Prehospital & in-hospital	Blunt trauma with systolic blood pressure < 100 mmHg and administration of packed red blood cells, need for procedural hemorrhage control, massive transfusion of blood products (defined as > 10 units packed red blood cells) in the first 24 h after admission, or death from hemorrhage	Patients younger than 18 years, pregnant patients, prehospital cardiac arrest	Administration of norepinephrine	2164 (1498/666)	24 h in-hospital mortality	In-hospital mortality	Primary outcome: 24 h mortality: Average treatment effect ranging from −4.6 (95% CI −11.9 to 2.7) to 2.1 (95% CI −2.1 to 6.3) Secondary outcome: In-hospital mortality: Average treatment effects ranging from −1.3 (95% CI −9.5 to 6.9) to 5.3 (95% CI −2.1 to 12.8)	Early norepinephrine infusion was not associated with 24-h or in-hospital mortality among patients with blunt trauma and hemorrhagic shock
Prospective observational														
Sperry JL et al	2008	J Trauma	Early Use of Vasopressors After Injury: Caution Before Constriction	USA	Multicenter	In-hospital	Blunt injured adults in hemorrhagic shock	Early death (< 48 h)	Early use of vasopressor (norepinephrine, phenylephrine, dopamine, or vasopressin) versus no use	921 (802/119)	Mortality at 12 h post-injury	No secondary ouctomes listed	Primary outcome: HR 1.81 (95% CI 1.1–2.9; $p = 0.013$)	Early use of vasopressors for hemodynamic support after hemorrhagic shock may be deleterious

Table 3 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Randomized controlled trials														
Cohn SM et al	2011	World J Surg	Impact of low-dose vasopressin on trauma outcome: prospective randomized study	USA	Single center	In-hospital	Traumatic injury with systolic blood pressure < 90 mmHg	Patients admitted to the emergency department more than 6 h after the trauma who received more than 4L of fluid and required cardiopulmonary resuscitation	Vasopressin bolus (4 IU), followed by IV infusion (2.4 IU/h) versus placebo (saline serum)	78 (38/40)	30-day in-hospital mortality	Total volume of resuscitation fluid over 5 days, adverse event, organ dysfunction, 5 day mortality	Primary outcome: Mortality was 34% in the experimental group and 28% in the control group ($p = 0.52$)	No difference on 30-day mortality The experimental group required a significantly lower total volume of resuscitation fluid over 5 days than did the control group ($p = 0.04$). The rates of adverse events, organ dysfunction, and 5-day mortality were not significantly different
Sims CA et al	2019	JAMA Surg	Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock	USA	Single center	In-hospital	Trauma patients who received ≥ 6 U of any blood product within 12 h of injury	Prehospital cardiopulmonary resuscitation, emergency thoracotomy, recent corticosteroid use, chronic renal insufficiency, significant coronary artery disease, traumatic brain injury requiring neurosurgical intervention, pregnancy, being younger than 18 years or older than 65 years	Vasopressin bolus (4 IU) then infusion (≤ 0.04 U/min) versus placebo	100 (49/51)	Cumulative volume of blood product transfused within 48 h	Total volume of crystalloids transfused, estimated blood loss, overall fluid balance, total vasopressor requirement within the first 48 h	Primary outcome: Patients who received vasopressin required significantly less blood products (median, 1.4 [interquartile range, 0.5–2.6] versus 2.9 [interquartile range, 1.1–4.8]; $p = 0.01$) Secondary outcome: No difference in secondary outcomes	Low-dose vasopressin during the resuscitation of trauma patients in hemorrhagic shock decreases blood product requirements

Table 3 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Systematic review and meta-analysis														
Hylands M et al	2017	BMJ Open	Early vasopressor use following traumatic injury: a systematic review	Not applicable	6 studies (1 randomized controlled trials and 5 observational studies)	Pre-hospital & in-hospital	Not applicable	Studies that addressed vasopressor use exclusively during the post-operative phase, after arrival to ICU or > 24 h from arrival	Not applicable	Not applicable	In-hospital mortality	No secondary ouctomes listed	Primary outcome: Across observational studies, vasopressor use was associated with increased short-term mortality, with unadjusted risk ratios ranging from 2.31 to 7.39	The balance between benefits and harms of vasopressor therapy during the early phase of resuscitation following traumatic injury is uncertain

Scientific articles were sorted by design: retrospective, prospective observational, randomized controlled trials and systematic-reviews and meta-analyses. Within each category the articles were tabulated in chronological order

GCS, Glasgow Coma Scale; HR, hazard ratio; ICU, Intensive Care Unit; OR, odds ratio; RCT, randomized controlled trial; SBP, systolic blood pressure

Table 4 Available evidence on cerebral perfusion pressure in traumatic brain injury

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Retrospective														
Edwards M et al	2010	Am Surg	Defining hypotension in moderate to severely injured trauma patients: raising the bar for the elderly	USA	Multicenter (5 level I and 8 level II trauma centers)	Pre-hospital	Patients with ISS > 9 and head-AIS ≤ 3 admitted between 1998 and 2005	Head-AIS > 3, dead on arrival, missing data (age, sex, ISS, GCS score, SBP or death)	SBP in 3 age groups: 20–49, 50–69, > 70 years old	24,438	Optimal definition of hypotension by age group controlling for sex, ISS, and GCS	No secondary ouctomes listed	Primary outcome: Hypotension thresholds were: 100mHg for 20–49 years old, 120 mmHg for 50–69 years old, 140 mmhg for people 70 years old or more	Different thresholds of hypotension depending on patient's age
Spaite DW et al	2017	JAMA surg	Mortality and prehospital blood pressure un patients with major traumatic brain injury: implications for the hypotension threshold	USA	Multicenter (8 level I trauma centers)	Pre-hospital	Patients age ≥ 10 years old with moderate/ severe traumatic brain injury (head-AIS > 2) and lowest prehospital SBP 40–119 mmHg	Transfers, death before emergency department arrival, cases with missing data for age or trauma type	SBP	3,844	Inhospital mortality	No secondary ouctomes listed	Primary outcome: Adjusted OR of death of 0.812 (95% CI 0.748–0.883) for each 10-point increase in systolic blood pressure	Linear association between lowest prehospital SBP and mortality
Prospective observational														
Zafar SN et al	2011	J of trauma	Presenting blood pressure in traumatic brain injury: a bimodal distribution of death	USA	Multicenter (national trauma database)	In-hospital	Patients over 16 years with isolated TBI with a head-AIS > 2	Penetrating injuries, patients dead on arrival, injury with AIS > 3 to other regions, patients with missing emergency department SPB data	Emergency department SBP	7,238	Mortality	Length of stay in hospital and ICU, 3-day survival, number of days on ventilator	Primary outcome: Mortality for emergency department SPB < 120 mmHg 21%, for SBP 120–140 9%, > = 140 mmHg 19% ($p < 0.001$)	Higher mortality rates outside of a range of 120–140 mmHg SBP among patients with isolated traumatic brain injury
Hasler RM et al	2012	Resuscitation	Systolic blood pressure below 110 mmHg is associated with increased mortality in penetrating major trauma patients: a multicenter cohort study	UK	Multicenter (UK trauma database)	Pre-hospital	Penetrating trauma patients ≥ 16 years old	Blunt injuries, concomitant brain injury (AIS > 3), transfers from a non-TARN hospital, patients referred to a non-TARN hospital	SBP	3,444	30-day mortality	Multivariable regression, sensitivity analysis	Primary outcome: Reference category: SBP 110–129 mmHg SBP 90–109 mmHg OR 3.03 (95% CI 1.78–5.18) SBP 70–89 mmHg OR 11.6 (95% CI 6.99–19.2) SBP < 70 mmHg OR 36.1, 95% CI 21.4–61.1)	Patients with penetrating trauma with SBP < 120 mmHg should be triaged to high level trauma centers

Table 4 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Fuller G et al	2014	Injury	The association between admission systolic blood pressure and mortality in significant traumatic brain injury: a multicenter cohort study	UK	Multicenter (UK trauma database)	Prehospital	Patients ≥ 16 years old with -head-AIS > 2 admitted directly to specialized neuroscience centers (2005–2012)	Patients transferred to non-TARN hospitals, with missing data, scalp, cranial nerves or vascular injuries	SBP	5057	30-day mortality	Interaction of SBP with extracranial injury or hypoxia, sensitivity analyses	Primary outcome: Reference range of 130–139 mmHg 30-day mortality: Odds of death 19.9 (95% CI 12.7;31.2) for SBP < 70 mmHg Odds of death 5.9 (95% CI 4.3;8.2) for SBP > 200 mmHg	Increased odds of death with SBPs outside 120–140 mmHg range
Rowell SE et al	2016	J Neurotrauma	The impact of prehospital administration of lactated Ringer's solution versus normal saline in patients with traumatic brain injury	USA	Multicenter (10 level I trauma centers)	Prehospital	Patients receiving prehospital ≥ 200 mL Lactated Ringer (LR) or normal 0,9% (NS) saline with an ISS ≥ 9	Age < 16 years, transfer from other hospital, pregnancy, > 20% burn injury, inhalation injury, incarceration, death within 30 min of admission, patients receiving other fluids or blood products, patients receiving both LR and NS	Patients with AIS < 3 vs ≥ 3	791	30-day mortality	Red blood cells and crystalloid use in the first 6 h after admission, physiological and biochemical variables, international normalized ratio, heart rate, SBP	Primary outcome: Patients with AIS > = 3: HR of death at 30 days 1.78 (95% CI 1.04;3.04) ($p = 0.035$) patients with AIS < 3 HR of death at 30 days for 1.49 (95% CI 0.757;2.95) ($p = 0.247$)	Use of LR for prehospital resuscitation in patients with severe TBI was associated with increased 30-day mortality
Randomized controlled trials														
Cooper DJ et al	2004	JAMA	Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial	Australia	Multicenter (multiple trauma centers)	Prehospital	Patients with a traumatic brain injury, a GCS < 9 and SBP < 100 mmHg	Multisystem trauma, penetrating trauma, younger than 18 years old, pregnant, no IV access, serious premorbid disease on identification bracelet, peripheral oedema, proximity to hospital, absent sinus rhythm, or cardiac arrest	Infusion of either 250 mL of 7,5% saline (group S) or Ringer's lactate solution (group RL)	229 (114/115)	GOSE at 6 months	First intracranial pressure and cerebral perfusion pressure, duration of elevated intracranial pressure and inadequate cerebral perfusion pressure, worst oxygenation as lowest PaO2/FiO2 ratio, duration of inotropic support and mechanical ventilation, functional independence measure, Rancho Los Amigos score range	Primary outcome: Median GOSE 6 months 5 (interquartile range 3–6) for intervention and 5 (interquartile range 5–6) for controls $p = 0.45$	Prehospital use of hypertonic saline solutions does not improve neurological outcomes among patients with severe traumatic brain injuries

Table 4 (continued)

Authors	Year	Journal	Study title	Country	Participating centers	Site	Inclusion criteria	Exclusion criteria	Intervention/ comparison	N (intervention/ control)	Primary outcome	Secondary outcomes	Finding	Key message
Bulger EM et al	2010	JAMA	Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial	North America (11 trauma cernters)	Multicenter	Pre-hospital	Patients ≥ 15 years old with a blunt trauma and a GCS ≤ 8	SBP < 70 mmHg, SBP 71–90 mmHg with heart rate ≥ 108 bpm, suspected pregnancy, out of hospital cardiopulmonary resuscitation, administration of > 2000 mL of crystalloid or any amount of colloid/ blood product before enrollment, T° < 28 °C, drowning, asphyxia due to hanging, burns > 20%, isolated penetrating head injury, inability to obtain intravenous access, > 4 h dispatch call and study intervention, prisoner status, interfacility transfer	A single 250 mL bolus of 7,5% saline/6% dextran (SD), 7,5% saline (S7), or 0,9% saline (S0,9)	1331 (359 SD/341S/582)	6 month-GOSE (dichotomized as > 4 or ≤ 4)	GOSE discharge, GOSE 1 month, DRS, 28-day survival, survival to hospital discharge, ICP, interventions required to manage intracranial hypertension, fluid and blood requirements in the first 24 h, physiologic parameters of organ dysfunction, 28 days acute respiratory distress syndrome-free survival, PODS score, nosocomial infection; ventilator-free days in the first 28 days, days alive outside the hospital within 28 days days alive outside the ICU	Primary outcome: Complete analysis GOSE ≤ 4 at 6 months: SD 59.9%, S7 58.4%, S0,9 56.1% ($p = 0.55$) Secondary outcome: Survival: no statistically significant difference	Among patients with severe traumatic brain injuries and no hypovolemic shock resuscitation with hypertonic saline or hypertonic saline with dextran compared with normal saline did not improve neurologic outcomes
Systematic-Review & meta-analysis														
Mc Hugh GS et al	2007	J of neurotrauma	Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study	Not applicable	7 RCTs & 3 observational studies	Pre-hospital & in hospital	7 RCTs & 3 observational studies	None listed	Hypoxia Hypotension Hypothermia (Hypotension defined as SBP < 90 mmHg)	6629	GOSE 6 months (unfavorable = dead, vegetative, severe disability)	Combination of hypoxia and hypotension, computed-tomography signs of raised intracranial pressure	Primary outcome: Hypotension: unfavorable versus favorable outcome OR 2.67 (95% CI 2.18–3.28) Hypotension: dead versus alive OR 2.62 (95% CI 1.99–3.47)	Poorer neurologic outcomes and survival with prehospital or admission hypotension among patients with traumatic brain injuries

Scientific articles were sorted by design: retrospective, prospective observational, randomized controlled trials and systematic-reviews and meta-analyses. Within each category the articles were tabulated in chronological order

AIS, abbreviated injury score; GCS: Glasgow Coma Scale; GOSE, Glasgow outcome scale; HR, hazard ratio; ICU, Intensive Care-Unit; ISS, injury severity score; OR, odds ratio; SBP, systolic blood pressure; UK, United Kingdom; USA, United states of America

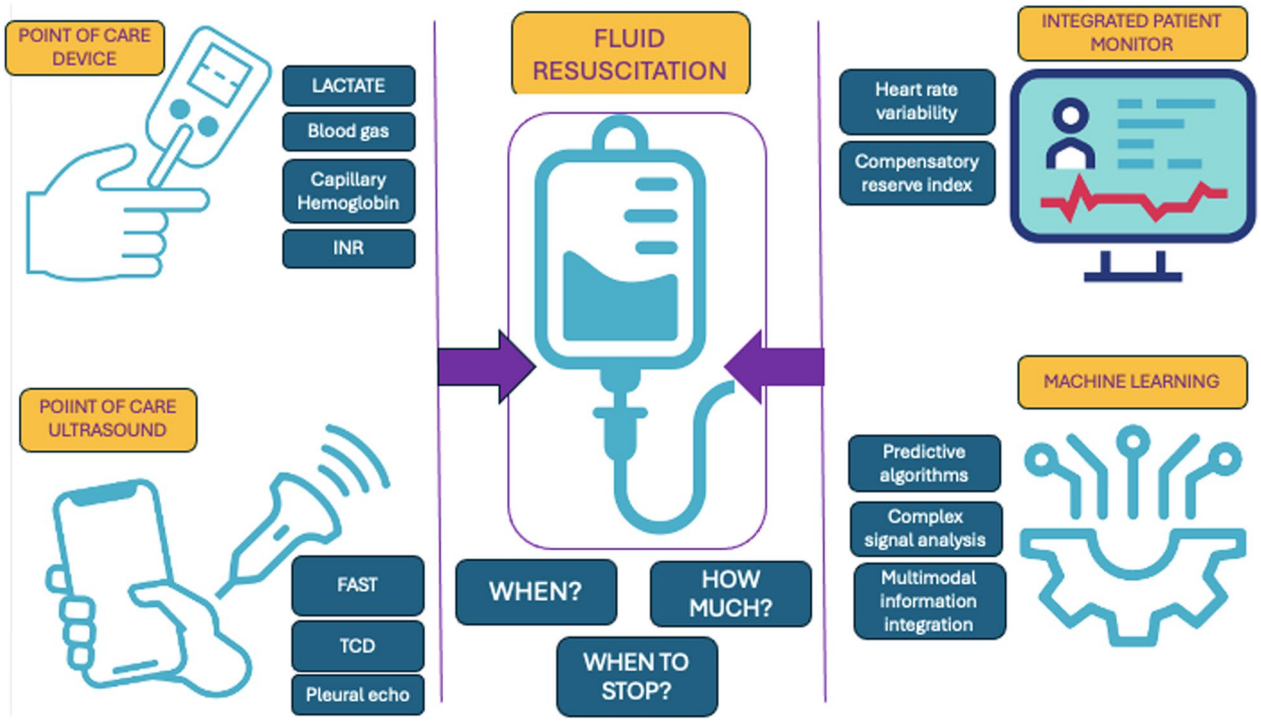

Fig. 1 Crystalloid use in the first hours of trauma induced hemorrhage evidence, uncertainties, and perspectives. Abbreviations: FAST: focused assessment with sonography for trauma, INR: international normalized ratio, TCD: transcranial Doppler

- In which context should crystalloid fluids be administered? In the prehospital setting? Which crystalloids should be used? Should they be continued upon hospital admission?
- How much fluids should be administered? Which sub populations could benefit from higher/lower fluid expansion volumes? Which clinical and/or paraclinical parameters should stop fluid expansion?

Point of care biology and imagery, integrated devices and machine learning models integrated into patients' monitor could help answer such clinical questions (Fig. 1).

Integrated devices

Devices integrated into patients' monitors could help identify patients with the most severe conditions and guide their fluid expansion. Such devices must be easy to interpret for clinicians and reflect spontaneous or treatment induced changes in patients' vitals.

For instance, a dynamic noninvasive index, the compensatory reserve index (CRI), was designed to dynamically assess intravascular volume loss [56]. This device derived from pulse oximetry waveform analysis computes a score between 0 (no intravascular volume loss) and 1 (severe hypovolemia at high risk of decompensation). A low CRI (below 0,6) managed to predict prehospital and admission blood pressure products in an observational study. However, the prognostic value of CRI was lower than that of the shock index and SBP [56].

POC biology

Point of care (POC) biologic assessment could allow rapid identification of patients in need of an advanced prehospital management and assessment of their fluid expansion needs. POC devices measuring hemoglobin, blood gases and lactate and monitoring coagulation have been described in observational studies but lack prospective validation [57–59]. Serum lactate level combined with blood pressure levels could be of particular interest as it is a widely recognized marker of physiologic compromise that could guide initiation and continuation of fluid expansion therapies.

POC ultrasound

Recent research has suggested that prehospital FAST (focus assessment with sonography for trauma) for trauma could allow swift identification of severe internal hemorrhage and consequently hasten transfer to the operating room [60, 61]. Prehospital transcranial Doppler (TCD) in patients with severe brain injury has also been addressed by observational studies suggesting feasibility

and a benefit in the detection of patients with impaired cerebral perfusion [62]. Prehospital FAST/TCD remains limited by the high cost and low availability of ultrasound machines and fully rely on the experience of the operator. Critics of prehospital POC laboratory assessment devices and imagery argue that they risk cognitive overload of prehospital care providers and delays in transport to the hospital.

Machine learning

The heterogeneity of treatment effect [63] on different patient profiles and the dynamic nature of traumatic shock necessitates a tailored approach to treatment. Artificial intelligence (AI) and Machine Learning (ML) solutions could help to personalize patient management. Machine Learning offers the capacity of a standardized analysis of large amount of complex data in a short amount of time [64–66]. AI/ML based algorithms carry the potential for enhanced clinician decision-making in trauma for questions such as: When to start fluids? Which patient requires fluids? When to stop fluids? [67, 68].

For example, machine-learning enhanced analysis of heart variability and complexity predicts patient needs [69, 70]. Such an algorithm could be integrated into a patient monitor and provide automated decision-support such as the so-called compensatory reserve index [71]. Another retrospective study explored ML to guide intraoperative vasopressor support in TBI patients to optimize the cerebral perfusion pressure [72]. Reinforcement learning (RL), a form of machine learning that aims at identifying the optimal set of actions to take in a given environment to maximize the notion of cumulative reward, holds promise for optimizing treatment strategies in sepsis [73] (e.g. optimal timing of vasopressor initiation) and could be implemented in trauma care.

However, currently most AI/ML solutions applied to trauma science correspond to retrospective algorithm development and validation studies. Very few studies attempt prospective validation, work-flow integration or assess impact on patient outcome [74] to prospective validation and proof-of-concept studies are urgently needed to assess and prove feasibility and utility, safety and potential harm of trauma specific AI/ML solutions and are a matter of ongoing research ([75], Clin Trials Shockmatrix, NCT06270615). Numerous challenges remain such as data quality, data granularity and the availability of reliable continuous data [76].

Conclusion

Crystalloid-based resuscitation remains relevant in early trauma care. A delicate balance of fluid resuscitation and vasopressor use is necessary to aim for permissive hypotension in trauma induced circulatory shock. Goal directed therapies must however aim for higher blood pressure goals in the event of severe traumatic brain injury (TBI). Further research is essential to refine fluid resuscitation guidelines, particularly in defining safe fluid volumes and thoroughly investigate the role of vasopressors. Population based approaches by age, comorbidities and injury mechanism could help tailor trauma care and improve survival. Innovations such as integrated and point of care devices as well as machine learning enhanced tools could help clinicians further individualize trauma care.

Abbreviations

AI	Artificial intelligence
AIS	Abbreviated injury score
AVP	Arginine vasopressin
CPP	Cerebral perfusion pressure
CRI	Compensatory reserve index
FAST	Focused assessment with sonography for trauma
MAP	Mean arterial pressure
POC	Point of care
RCT	Randomized controlled trial
RL	Reinforcement learning
TBI	Traumatic brain injury
TCD	Transcranial Doppler
SBP	Systolic blood pressure

Supplementary Information

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Additional file1

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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