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Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations

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Abstract

Objective: To report the ESICM consensus and clinical practice recommendations on fluid therapy in neurointensive care patients.

Design: A consensus committee comprising 22 international experts met in October 2016 during ESICM LIVES2016. Teleconferences and electronic-based discussions between the members of the committee subsequently served to discuss and develop the consensus process.

Methods: Population, intervention, comparison, and outcomes (PICO) questions were reviewed and updated as needed, and evidence profiles generated. The consensus focused on three main topics: (1) general fluid resuscitation and maintenance in neurointensive care patients, (2) hyperosmolar fluids for intracranial pressure control, (3) fluid management in delayed cerebral ischemia after subarachnoid haemorrhage. After an extensive literature search, the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were applied to assess the quality of evidence (from high to very low), to formulate treatment recommendations as strong or weak, and to issue best practice statements when applicable. A modified Delphi process based on the integration of evidence provided by the literature and expert opinions—using a sequential approach to avoid biases and misinterpretations—was used to generate the final consensus statement.

Results: The final consensus comprises a total of 32 statements, including 13 strong recommendations and 17 weak recommendations. No recommendations were provided for two statements.

Conclusions: We present a consensus statement and clinical practice recommendations on fluid therapy for neurointensive care patients.

Keywords: Evidence-based medicine, Guidelines, Fluid therapy, Traumatic brain injury, Subarachnoid haemorrhage, Intracerebral haemorrhage, Stroke, Mannitol, Hypertonic, Neurointensive care

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Introduction

Fluid therapy is a fundamental component of neurointensive care (NIC), with general (volume resuscitation and maintenance) and "neurospecific" indications [intracranial pressure (ICP) control, management of delayed cerebral ischemia (DCI)]. Questions about fluid therapy in NIC patients—such as optimal composition and volume, and choice and dose of hyperosmolar fluids to control ICP—remain and there is limited high quality evidence to guide fluid management and define physiologic triggers and monitoring endpoints of fluid therapy.

Our objective in developing this consensus was to provide guidance to clinicians caring for NIC patients. We addressed three issues: (1) general fluid management in NIC, (2) hyperosmolar fluids for ICP control and (3) fluid therapy for the management of DCI. In view of the low levels of evidence identified, treatment recommendations do not represent standard of care but rather are the summary of current best clinical practice.

Methodology

Definitions

NIC patients were adult critically ill comatose (GCS < 9) patients following severe traumatic brain injury (TBI), high-grade aneurysmal subarachnoid haemorrhage (SAH), severe arterial ischemic stroke (AIS) or intracerebral haemorrhage (ICH).

Registration

The methodological plan for this systematic review was registered on PROSPERO (ID 42016052123 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=52123).

Sponsorship

No funding was provided. The European Society of Intensive Care Medicine (ESICM) provided logistical support for the first meeting.

Conflict-of-interest policy

There was no industry input into guideline development, and no consensus panel member received honoraria.

Selection of committee members

Participants were members of ESICM, Neurocritical Care Society (NCS) and Latin America Brain Injury Consortium (LABIC). Chairs and co-chairs were selected by ESICM NIC section. An external member (DP) provided methodological expertise for the GRADE process.

Question development

We did not follow the standard Delphi model, but generated the initial ideas and developed the main questions in a face-to-face meeting, during which methodology for literature search, grading of evidence, and the process for reaching the consensus were illustrated.

The focus was the management of NIC patients during the critical care episode, but aspects of pre-hospital management were included when considered important. The guideline panel was divided into three sections, according to the questions addressed:

1. General fluid management (volume resuscitation and maintenance)
2. Hyperosmolar fluids for ICP control
3. Fluid therapy for the management of DCI

Topic selection was the responsibility of consensus chairs (MO, GC) and co-chairs (GM, NS, RH), with input from panel members from each group. All questions were structured in the PICO (population, intervention, comparison and outcomes) format.

Search strategy, data analysis and grading of the evidence

The search strategies and grading of the evidence, including advanced statistical approach such as meta-analyses and meta-regression, are described in detail in the electronic supplementary material (ESM) (ESM_Methodology).

Consensus methodology

The consensus was developed using a modified Delphi process based on the integration of evidence from the literature review and expert opinions. The results of the GRADE assessment of the evidence were made available to the panel through web-based files. The chairs integrated the initial questions with literature revision and grading, and formulated four mutually exclusive questions and 35 questions (clustered in five different sections) requiring a score ranging from 1 (strongly disagree) to 10 (strongly agree). These questions were submitted to each panel member through a web-based system. In addition to providing an overall score (1–10) for each question or cluster of questions, the experts were also invited to provide comments to clarify their answers. The responses were analysed by a non-voting member of the panel (DP). Answers providing scores were analysed as medians and 20th and 80th percentiles. Further, scores were clustered into low (1–3), intermediate (4–7) and high (8–10), and analysed with correspondence analysis. Both approaches were used to identify answers that provided clear-cut responses from the experts, particularly those polarized on agreement or disagreement. Correspondence analysis was used to assess if individual panel members provided specific response patterns, particularly when intermediate positions were taken. The results

of the analyses were returned to the panel anonymously for information (the name of each member was replaced with a numeric code), and the same list of questions was then resubmitted to the panel in a second round of voting.

Based on the analysis of the second round of questions, consensus statements were formulated by the chairs, selecting questions with higher degrees of agreement, and then resubmitted to the panel for review. Answers were analysed with correspondence analysis to identify heterogeneity among panel members. In order to minimize the risk of misinterpretations of some questions and statements, individual panel members who had provided heterogeneous answer patterns were invited to review their responses and confirm or correct their vote.

After the final round of voting, the consensus was finalised as follows:

- A *strong* recommendation (*in favour* or *against*) was made when more than 80% of voting members supported this position for a particular question.
- When votes *in favour* or *against* (a mix of *strong* and *weak* options) reached the 80% threshold, a *weak* recommendation was made.
- When the 80% threshold was not reached a "no recommendation" option was adopted.

If panel members had *minor concerns* about one question, they could declare *reservation*. No blocking option was permitted in the case of *major concerns*, but a stand aside position was adopted with the reasons for any concerns reported.

Finally, a total of 32 treatment recommendations were formulated, which represent the balance between desirable and unwanted effects, resource implications and quality of evidence [1]. Quality of evidence influenced the strength and direction of recommendations, but in the presence of low or very low scientific evidence, we considered the possibility of providing not only *weak* but also *strong* recommendations based on expert opinions.

Additional considerations

The consensus focused on human studies only and did not include animal data. Regarding clinical practice, this consensus selected specific questions and conditions, but was not intended to cover generic issues related to sodium/osmolarity management or specific disorders (diabetes insipidus, SIADH, cerebral salt wasting syndrome), for which the reader may refer to separate reviews [2, 3]. For laboratory safety limits and precise timing of electrolyte/osmolarity follow-up, the reader must follow clinical judgment and general good clinical practices.

This consensus addressed fluid therapy in stable NIC patients, i.e. without circulatory shock, acute bleeding, or poly-trauma, and was restricted to the early ICU phase but did not apply to later ICU care. Additional acute cerebral conditions (infectious encephalitis, hypoxic-ischemic brain injury after cardiac arrest) were not addressed. Because cerebral perfusion pressure (CPP) depends on invasive ICP monitoring (which may not be available everywhere), only arterial blood pressure/mean arterial pressure (MAP) and ICP were considered, but we did not treat CPP separately.

Results

Each section is organized as follows. For every question, the *analysis of available evidence* based on the GRADE process is reported: when studies were too heterogeneous to be combined in an overall body of evidence, the individual GRADE is reported (GRADE details for each question can be found in ESM_GRADE).

At the end of each section, *treatment recommendations* are reported.

A summary of all treatment recommendations is shown in Table 1.

Randomized controlled trials (RCTs) with report of specific outcomes tested are summarized in Table 2.

Fluids for the general management of NIC patients

Analysis of available evidence

Question 1: Is there evidence to prefer albumin to crystalloids? (ESM, SG1 Q1 GRADE)

One multicentre RCT in AIS patients found comparable 90-day outcome for high-dose (25%) albumin ($n = 422$) vs. normal saline (NS) ($n = 419$) [4]. One single-centre observational study in AIS patients ($n = 82$) found that high-dose albumin was associated with better outcome [OR 1.81 (95% CI 1.11–2.94)] [5].

GRADE for both studies: high quality evidence (against).

A subgroup analysis of the SAFE trial found higher mortality (33.2% vs. 20.4%) for low-dose (4%; osmolality 260 mOsm/l) albumin ($n = 214$) vs. NS ($n = 206$) after TBI [6]. Excess mortality was higher in severe TBI patients [41.8% vs. 22.2%; RR 1.88 (95% CI 1.31–2.70)], with no significant difference in moderate TBI patients.

GRADE: low quality evidence (against).

One multicentre propensity score study ($n = 5400$) [7] and one retrospective single-centre study ($n = 42$) [8] in SAH patients found that high-dose albumin vs. crystalloids was associated with better neurological outcome.

GRADE for both studies: very low quality evidence (in favour).

Table 1 Summary of recommendations for fluid therapy in neurointensive care (NIC) patients (see "Methodology" for details)

	Recommendations
Fluids for the general management of NIC patients	1. We *recommend* the use of crystalloids as preferred maintenance fluids in NIC patients (Strong recommendation) 2. We *recommend against* the use of colloids, glucose-containing hypotonic solutions and other hypotonic solutions[a], or albumin as maintenance fluids in NIC patients (Strong recommendation) 3. We *recommend against* the use of high-dose (20–25%) albumin in acute ischemic stroke patients (Strong recommendation) 4. We *suggest* using crystalloids as first-line resuscitation fluids in NIC patients with low blood pressure (Weak recommendation) 5. We *suggest against* the use of synthetic colloids as resuscitation fluids in NIC patients with low blood pressure (Weak recommendation) 6. We *recommend against* the use of glucose-containing hypotonic solutions and other hypotonic solutions[a] as resuscitation fluids in NIC patients with low blood pressure (Strong recommendation) 7. We *recommend against* the use of low-dose (4%) albumin as resuscitation fluid in NIC patients with low blood pressure (Strong recommendation) 8. We *suggest against* the use of high-dose (20–25%) albumin as resuscitation fluid in NIC patients with low blood pressure (Weak recommendation) 9. We *suggest against* the use of hypertonic saline solutions as resuscitation fluids in NIC patients with low blood pressure (Weak recommendation) 10. We *suggest* that clinicians consider targeting normovolaemia during fluid replacement in NIC patients (Weak recommendation) 11. We *recommend* the use of a multimodal approach, guided by the integration of more than a single haemodynamic variable, to optimize fluid therapy in NIC patients (Strong recommendation) 12. We *recommend* considering using arterial blood pressure and fluid balance as the main endpoints to optimize fluid therapy in NIC patients (Strong recommendation) 13. We *suggest* integrating other variables (such as cardiac output, SvO_2, blood lactate, urinary output) to optimize fluid therapy in NIC patients (Weak recommendation) 14. We *recommend against* the use of central venous pressure alone as an endpoint for guiding fluid therapy in NIC patients (Strong recommendation) 15. We *suggest against* the use of restrictive fluid strategies (aiming for an overall negative fluid balance) in NIC patients (Weak recommendation) 16. We *suggest* using fluid balance as a safety endpoint for fluid therapy in NIC patients (Weak recommendation) 17. We *suggest* monitoring electrolytes (Na^+, Cl^-) as a safety endpoint for fluid therapy in NIC patients (Weak recommendation) 18. We *suggest* monitoring measured osmolarity as a safety endpoint for fluid therapy in NIC patients (Weak recommendation) 19. We *recommend against* the use of central venous pressure monitoring as safety endpoint for fluid therapy in NIC patients (Strong recommendation)
Hyperosmolar fluids for the management of elevated ICP	1. We *suggest* the use of mannitol or hypertonic saline solutions for reducing increased ICP (Weak recommendation) 2. We *are unable to provide* any recommendations on the use of hypertonic lactate as first-line osmotic solution for reducing increased ICP (No recommendation) 3. We *suggest* using a predefined trigger for starting osmotherapy to treat elevated ICP (Weak recommendation) 4. We *recommend* using a combination of clinical and neuromonitoring variables for starting osmotherapy to treat elevated ICP (Strong recommendation) 5. We *recommend* a combination of neurological worsening (defined as a decrease of 2 points of the GCS motor score, or loss of pupillary reactivity or asymmetry, or deterioration of head CT findings) and ICP > 25 mmHg as a trigger for starting osmotherapy to treat elevated ICP (Strong recommendation) 6. We *suggest* using an ICP threshold > 25 mmHg, independent of other variables, as a trigger for starting osmotherapy to reduce ICP (Weak recommendation) 7. We are unable to provide any recommendations about whether an ICP threshold of 20–22 mmHg independent of other variables should be used as a trigger for starting osmotherapy to reduce ICP (No recommendation) 8. We *recommend against* the use of an ICP threshold of 15 mmHg independent of other variables as a trigger for starting osmotherapy to reduce ICP (Strong recommendation) 9. We *suggest* monitoring measured serum osmolarity and electrolytes to limit the side effects of osmotherapy (Weak recommendation) 10. We *suggest* monitoring ICP response to hyperosmolar fluids to limit the side effects of osmotherapy (Weak recommendation) 11. We *suggest* monitoring the effects of hyperosmolar fluids on arterial blood pressure and fluid balance as secondary variables to limit the side effects of osmotherapy (Weak recommendation)
Fluids for the management of cerebral ischemia	1. We *recommend* assessing the efficacy of fluid infusion in SAH patients with delayed cerebral ischemia using a multimodal approach that includes arterial blood pressure and reversal of neurological deficit as the main endpoints (Strong recommendation) 2. We *suggest* that reduction in transcranial Doppler cerebral blood flow velocities, improvements of cerebral perfusion and reduction of mean transit time on CT perfusion should be used as secondary endpoints when assessing the efficacy of fluids for reversal of delayed cerebral ischemia in SAH patients (Weak recommendation)

Using a modified Delphi process, we integrated the evidence provided by the literature review with expert opinions. Some recommendations are based only on expert opinion and should be considered as best practice

[a] Hypotonic solutions = osmolality < 260 mOsm/l

Question 2: Is there evidence to prefer colloids to crystalloids? (ESM SG1 Q2 [Q6 Q7] GRADE)

One propensity score study ($n = 123$) in SAH patients found that colloids (plasma, dextran, starch and/or albumin) had no impact on DCI/cerebral infarcts, but were associated with worse NIH Stroke Scale at 6 weeks [9].

GRADE: low quality evidence (against).

Another study on SAH patients recruited in two RCTs ($n = 160$) found that cumulative daily colloid dose (4% gelatin or 6% pentastarch) was associated with worse 6-month Glasgow Outcome Score (GOS) [adjusted OR 2.53 (95% CI 1.13–5.68)] while crystalloids (L/day) were associated with better GOS [adjusted OR 0.27 (95% CI 0.11–0.67)] [10].

GRADE: very low quality evidence (against).

In *severe TBI patients*, Cox proportional hazard modeling of single-centre data ($n = 171$) found no association between cumulative pentastarch dose and mortality [11].

GRADE: very low quality evidence (against).

Question 3: Is there evidence to prefer buffered crystalloids to standard crystalloids? (ESM SG1 Q3 [Q8] GRADE)

Two small single-centre RCTs, one in SAH patients ($n = 36$) [12] and another in TBI patients ($n = 41$) [13], found that, compared to NS, buffered crystalloids reduced hyperchloraemia rate (a secondary outcome in our revision design). The studies had a sufficiently homogenous design to allow a meta-analysis (RR 0.57, 95% CI 0.37–0.75, $p < 0.001$). The body of evidence was downgraded because of the high degree of imprecision due to small sample size and the risk of inflated effect [14].

GRADE: low quality evidence (in favour).

In addition, one RCT in TBI patients ($n = 34$, two centres) found that Ringer's lactate (RL) reduced serum sodium and osmolarity compared to hypertonic saline (HTS) [15].

GRADE: very low quality evidence (in favour).

No study considered robust outcomes such as survival or neurological outcome therefore no recommendation regarding the choice of one specific crystalloid solution (e.g. normal saline vs. buffered solutions) was given.

Question 4: Is there evidence to prefer infusion of hypertonic fluids (given as resuscitation solutions) to infusion of isotonic fluids? (ESM SG1 Q4 GRADE)

All studies were performed in TBI patients.

One RCT comparing a bolus infusion (250 mL) of 7.5% HTS vs. RL ($n = 113$ patients in each group) in the prehospital setting reported no differences in 6-month mortality and GOS [16].

GRADE: high quality evidence (against).

In an RCT ($n = 64$) comparing 7.5% HTS/6% dextran solutions with NS (given as a single 250-mL resuscitation dose), Baker et al. found no significant difference in 30-day mortality and GOS [17].

GRADE: low quality evidence (against).

In a small RCT ($n = 34$, two centres), Shackford et al. compared 1.6% HTS to RL for resuscitation and found no significant difference in GOS at hospital discharge [15].

GRADE: very low quality evidence (against).

Treatment recommendations

- We *recommend* crystalloids as preferred maintenance fluids in NIC patients (Strong recommendation).
- We *recommend against* the use of colloids, glucose-containing hypotonic solutions and other hypotonic solutions, or albumin as maintenance fluids in NIC patients (Strong recommendation).
- We *recommend against* the use of high-dose (20–25%) albumin in acute ischemic stroke patients (Strong recommendation).
- We *suggest* using crystalloids as first-line resuscitation fluids in NIC patients with low blood pressure (Weak recommendation).
- We *suggest against* the use of synthetic colloids as resuscitation fluids in NIC patients with low blood pressure (Weak recommendation).
- We *recommend against* the use of glucose-containing hypotonic solutions and other hypotonic solutions as resuscitation fluids in NIC patients with low blood pressure (Strong recommendation).
- We *recommend against* the use of low-dose (4%) albumin as resuscitation fluid in NIC patients with low blood pressure (Strong recommendation).
- We *suggest against* the use of high-dose (20–25%) albumin as resuscitation fluid in NIC patients with low blood pressure (Weak recommendation).
- We *suggest against* the use of hypertonic saline solutions as resuscitation fluids in NIC patients with low blood pressure (Weak recommendation).
- We *suggest* targeting normovolaemia during fluid replacement in NIC patients (Weak recommendation).
- We *recommend* the use of a multimodal approach, guided by the integration of more than a single haemodynamic variable, to optimize fluid therapy in NIC patients (Strong recommendation).
- We *recommend* considering using arterial blood pressure and fluid balance as the main endpoints to optimize fluid therapy in NIC patients (Strong recommendation).
- We *suggest* integrating other variables (such as cardiac output, SvO_2, blood lactate, urinary output) to

Table 2 Summary of randomized controlled trials on fluid therapy in neurointensive care patients

References	Population	Patients	Intervention	Control	Outcomes
Fluids for the general management (resuscitation and maintenance)					
Ginsberg [4]	AIS	$N = 841$	25% albumin	N-saline	Comparable 3-month mRS score
Myburgh [6]	TBI	$N = 420$	4% albumin	N-saline	4% albumin group had higher mortality (33.2% vs. 20.4% in the N-saline group)
Lehmann [12]	SAH	$N = 36$	Balanced crystalloids/colloids	N-saline/HES	Balanced solutions reduced the rate of hyperchloraemia
Roquilly [13]	TBI	$N = 41$	Balanced crystalloids/HES	N-saline/HES	Balanced solutions reduced the rate of hyperchloraemia
Shackford [15]	TBI	$N = 34$	1.6% HTS	R-lactate	Comparable GOS at hospital discharge
Cooper [16]	TBI	$N = 226$	7.5% HTS	R-lactate	Comparable 6-month mortality and GOS-E
Baker [17]	TBI	$N = 64$	7.5% HTS/6% dextran	N-saline	Comparable 1-month mortality and GOS
Hyperosmolar fluids for the management of elevated ICP					
Ichai [18]	TBI	$N = 60$	1/2-molar H-lactate	N-saline	H-lactate vs. N-saline had greater efficacy in preventing ICP elevations and improved 6-month GOS (60% vs. 50%)
Battison [51]	TBI + SAH	$N = 18$	7.5% HTS/6% dextran	20% MAN	HTS vs. MAN yielded a greater ICP reduction
Francony [23]	TBI	$N = 20$	7.5% HTS	20% MAN	Comparable effectiveness in reducing ICP
Cottenceau [20]	TBI	$N = 47$	7.5% HTS	20% MAN	Comparable effectiveness in reducing ICP and mortality
Ichai [47]	TBI	$N = 34$	1/2-molar H-lactate	20% MAN	H-lactate vs. MAN was more effective in reducing elevated ICP and improved 1-year GOS (69% vs. 35%)
Vialet [50]	TBI	$N = 20$	7.5% HTS	20% MAN	HTS vs. MAN was more effective in reducing elevated ICP
Harutjunyan [52]	TBI + SAH	$N = 32$	7.2% HTS/HES 200/0.5	15% MAN	Comparable effectiveness in reducing ICP
Jagannatha [48]	TBI	$N = 38$	3% HTS	20% MAN	Comparable effectiveness in reducing ICP
Sakellaridis [49]	TBI	$N = 29$	15% HTS	20% MAN	Comparable effectiveness in reducing ICP
Schwarz [42]	AIS	$N = 9$	7.5% HTS/6% dextran	20% MAN	Comparable effectiveness in reducing ICP
Misra [54]	ICH	$N = 24$	20% MAN	N-saline	Comparable effectiveness in reducing MRI-measured brain shift
Diringer [55]	AIS	$N = 9$	23.4% HTS	20% MAN	Comparable effectiveness in increasing CBF
Fluids for the management of cerebral ischemia					
Egge [68]	SAH	$N = 32$	Triple H therapy (4 L crystalloids/colloids)	Normovolaemia (2 L crystalloids)	Comparable regional CBF, rate of vasospasm and 1-year GOS
Lennihan [69]	SAH	$N = 82$	Triple H therapy (crystalloids/colloid)	Normovolaemia (crystalloids/colloids)	Comparable regional and global CBF, rate of vasospasm and cerebral infarcts
IASS Group [78]	AIS	$N = 1267$	Haemodilution (venesection/dextran)	N-saline	Comparable proportion of dead and severely disabled patients at 6 months
Mutoh [87]	SAH	$N = 160$	Fluid therapy targeted to transpulmonary thermodilution	Standard management	Comparable rate of delayed cerebral ischemia and 3-month mRS

AIS acute ischemic stroke, *CBF* cerebral blood flow, *GOS* Glasgow Outcome Score, *HES* hydroxyethyl starch, *H-lactate* hypertonic sodium lactate, *HTS* hypertonic saline, *IASS* Italian Acute Stroke Study, *ICH* intracerebral haemorrhage, *ICP* intracranial pressure, *MAN* mannitol, *MRI* magnetic resonance imaging, *mRS* modified Rankin scale, *N-saline* normal saline, *SAH* subarachnoid haemorrhage, *TBI* traumatic brain injury

optimize fluid therapy in NIC patients (Weak recommendation).

- We *recommend against* the use of central venous pressure (CVP) alone as an endpoint for guiding fluid therapy in NIC patients (Strong recommendation).
- We *suggest against* the use of restrictive fluid strategies (aiming for an overall negative fluid balance) in NIC patients (Weak recommendation).
- We *suggest* using fluid balance as a safety endpoint for fluid therapy in NIC patients (Weak recommendation).
- We *suggest* monitoring electrolytes (Na^+, Cl^-) as a safety endpoint for fluid therapy in NIC patients (Weak recommendation).

- We *suggest* monitoring measured osmolarity as a safety endpoint for fluid therapy in NIC patients (Weak recommendation).
- We *recommend against* the use of CVP as safety endpoint for fluid therapy in NIC patients (Strong recommendation).

Hyperosmolar fluids for the management of elevated ICP

Analysis of available evidence

Question 1: Are hyperosmolar fluids effective in reducing ICP? (ESM SG2 Q1 GRADE)

RCTs One RCT (60 patients, 2 centres) in severe TBI patients showed that 48-h continuous prophylactic infusion of half-molar hypertonic lactate (HTL) vs. NS was more effective in preventing elevated ICP (> 20 mmHg) [% ICP reduction 30% (95% CI − 50.4 to − 4.8%); number needed to treat 3 (95% CI 2–21)] [18].

Observational studies Despite limitations (small sample size, no adjustments for confounders), a high number of before–after observational studies investigating the effectiveness of mannitol (MAN) and HTS in reducing ICP were identified [19–45], allowing a meta-analysis to examine whether a common trend could be found. PubMed search code, selection criteria, meta-analysis and meta-regression are reported in detail in the ESM (ESM_Hyperosmolar Fluids).

Mannitol By meta-analysis, MAN was associated with a 10.9 mmHg ICP reduction (95% CI 8.2–13.5 mmHg, $p < 0.001$, Fig. 1). Heterogeneity was high ($I^2 = 69\%$; 95% CI 45–90%, $p < 0.001$), but sensitivity analysis using high correlation between before and after measurements was consistent with these findings (ESM_Hyperosmolar Fluids, Fig. 3).

By meta-regression, for every 1 mmHg increase in baseline ICP, MAN bolus yielded an additional 0.53 mmHg ICP reduction ($p < 0.001$, Fig. 2). The heterogeneity estimate dropped to 20% ($p = 0.255$). However, the degree of imprecision was high and this finding should be interpreted with caution. The meta-regression assuming high correlation provided similar results, but heterogeneity was highly significant ($p < 0.001$), (ESM_Hyperosmolar Fluids, Fig. 4).

Mannitol dose By meta-regression, the extent of ICP reduction did not correlate with MAN dose (0.42 mmHg per 100 mg/kg, $p = 0.478$, Table 3). However, by multivariable analysis after adjusting for initial ICP, the relationship of MAN dose with ICP became statistically significant (0.78 mmHg for every 100 mg/kg increase, $p = 0.003$, Table 3); this was confirmed by the less conservative sensitivity analysis (data not shown).

These results should be treated with great caution because the low numbers of studies included in the analysis may generate spurious results although the use of random effects methods limits this risk [46].

Hypertonic saline By meta-analysis, HTS was associated with an average 8.8 mmHg ICP reduction (95% CI 6.5–11.1 mmHg, $p < 0.001$, ESM_Hyperosmolar Fluids, Fig. 1), but heterogeneity was high ($I^2 = 77\%$, 95% CI 45–94, $p < 0.001$). The meta-regression using baseline ICP with post-HTS ICP reduction produced a statistically significant result (slope 0.343, $p = 0.040$), despite heterogeneity ($I^2 = 56\%$, CI 0–91%, ESM_Hyperosmolar Fluids, Fig. 2) and two studies with Cook distances of 3.4 and 1.8 that strongly influenced the slope.

Hypertonic saline dose Dose was not a predictor of ICP reduction: however, the inclusion of dose and initial ICP in a multivariate meta-regression approach generated statistically significant slopes (Table 3). As for mannitol, the same caution in interpreting these results should be applied.

In summary, there is evidence to suggest that HTL, MAN and HTS are associated with a reduction in ICP.

GRADE: low quality evidence (in favour).

Question 2: Is there evidence that hyperosmolar fluids have different efficacy (more or less effective) in reducing ICP? (ESM SG2 Q2 GRADE)

A total of nine RCTs were identified, comparing different hyperosmolar fluids administered as infusion boluses to treat elevated ICP: six were performed in TBI patients [20, 23, 47–50], two in a heterogeneous population of TBI and SAH patients [51, 52], and one in AIS patients [42]. Four studies compared MAN to HTS [20, 23, 42, 48], and one MAN vs. HTL [47].

One small observational study provided very low evidence in favour of the superiority of HTS over MAN [53], but did not give information on osmotic doses, precluding comparisons on their effectiveness.

With the exception of one observational study [42] that was graded *very low*, evidence from all these RCTs was equally graded as *low*.

RCTs comparing hypertonic fluids given in equiosmolar doses (7 studies, N = 186 patients) One study ($n = 9$, crossover design, single-centre) found that 7.5% HTS/6% dextran vs. 20% MAN produced a greater ICP reduction at 60 min [− 5 mmHg (95% CI − 10.8 to − 3), p 0.014] [51], while four studies ($n = 20$ [23], $n = 47$ [20], $n = 38$

[48], $n = 29$ [49]) found that 7.5%, 3%, 15% HTS and 20% MAN, respectively, were equally effective in reducing ICP. One study ($n = 9$) investigating ICP reduction using 7.5% HTS/6% dextran and 20% MAN did not compare the two groups with formal statistical tests and received a *very low* evidence grading [42].

Ichai et al. ($n = 34$, single-centre) found that half-molar HTL was more effective than 20% MAN in reducing elevated ICP, but, although the difference in ICP decrease at 4 h in favour of HTL was statistically significant, it was of limited clinical relevance (2.7 mmHg) [47].

RCTs comparing hypertonic fluids given in non-equiosmolar doses (2 studies, n = 52 patients) In these studies, osmotic load was higher for HTS than for MAN, therefore favouring HTS. Vialet et al. ($n = 20$, single-centre) found that 7.5% HTS was more effective than half the osmotic dose of 20% MAN in reducing the daily number of episodes of elevated ICP > 25 mmHg (6 vs. 13) [50]. The other study ($n = 32$) found a statistically significant ICP percentage reduction with HTS/HES 200/0.5 vs. 15% MAN [52].

GRADE for all these studies: low quality evidence (in favour or against according to specific study findings).

Question 3: Is there evidence for using hyperosmolar fluids without ICP monitoring? (ESM SG2 Q3 GRADE)

One RCT performed in ICH patients ($n = 24$) found that MAN and HTS had comparable effects on midline shift reduction assessed by magnetic resonance imaging [54]. A second RCT in patients with severe AIS ($n = 9$) found that MAN and HTS had comparable effects on cerebral blood flow (CBF) increase measured by positron emission tomography (PET) [55].

GRADE: very low quality evidence (against).

Several observational studies investigated the effects of MAN or HTS in patients monitored with transcranial Doppler (TCD) [26, 44, 56], PET [21, 40], xenon-CT [44, 57, 58], CT scan (to measure brain volume and shift, water content) [29, 59–62] or EEG [63].

GRADE: very low quality evidence (in favour or against according to specific study findings).

Question 4: Is there evidence that hyperosmolar fluids improve outcome? (ESM SG2 Q4 GRADE)

RCTs RCTs were heterogeneous and could not be combined into a meta-analysis.

One multicentre RCT performed in TBI patients ($n = 226$) found that pre-hospital resuscitation with HTS or NS had similar 6-month outcome assessed by GOS-E [16].

GRADE: high quality evidence (against).

There were three additional RCTs. One was performed in TBI patients ($n = 60$; two centres) and found that prophylactic half-molar HTL did not improve 6-month GOS compared to NS despite significantly reducing episodes of ICP increase greater than 20 mmHg [18]. In a further study in TBI patients, HTL for treatment of elevated ICP was associated with better 12-month GOS compared to MAN (69% vs. 35%), although this difference was not statistically significant ($p = 0.055$) [47]. A third RCT in TBI patients found no mortality difference between 20% MAN and 7.5% HTS [20].

These three RCTs were downgraded for methodological limitations.

GRADE: low quality evidence (against).

Observational studies One propensity score matched study in ICH patients included in the INTERACT-2 trial found no significant outcome difference between MAN-treated ($n = 1533$) and non-MAN treated ($n = 993$) patients [64].

GRADE: low quality evidence.

One study reported that MAN negatively affected neurological outcome in AIS or ICH patients [65], while in another HTS/dextran improved survival of hypotensive TBI patients [66].

GRADE: very low quality evidence.

Asehnoune et al. found increased survival in TBI treated with continuous infusion of HTS [67]: this study was published after closing the consensus process and therefore could not be included.

Treatment recommendations

- We *suggest* the use of mannitol or hypertonic saline for reducing increased ICP (Weak recommendation).
- *We are unable to provide any recommendation* on the use of hypertonic lactate as first-line osmotic solution for reducing increased ICP (No recommendation).
- We *suggest* considering a predefined trigger for starting osmotherapy to treat elevated ICP (Weak recommendation).
- We *recommend* a combination of clinical and neuromonitoring variables for starting osmotherapy to treat elevated ICP (Strong recommendation).
- We *recommend* a combination of neurological worsening (defined as a decrease of 2 points of the GCS motor score, or loss of pupillary reactivity or asymmetry, or deterioration of head CT findings) and ICP > 25 mmHg as a trigger for starting osmotherapy to treat elevated ICP (Strong recommendation).
- We *suggest* using an ICP threshold > 25 mmHg independent of other variables as a trigger for starting osmotherapy to reduce ICP (Weak recommendation).

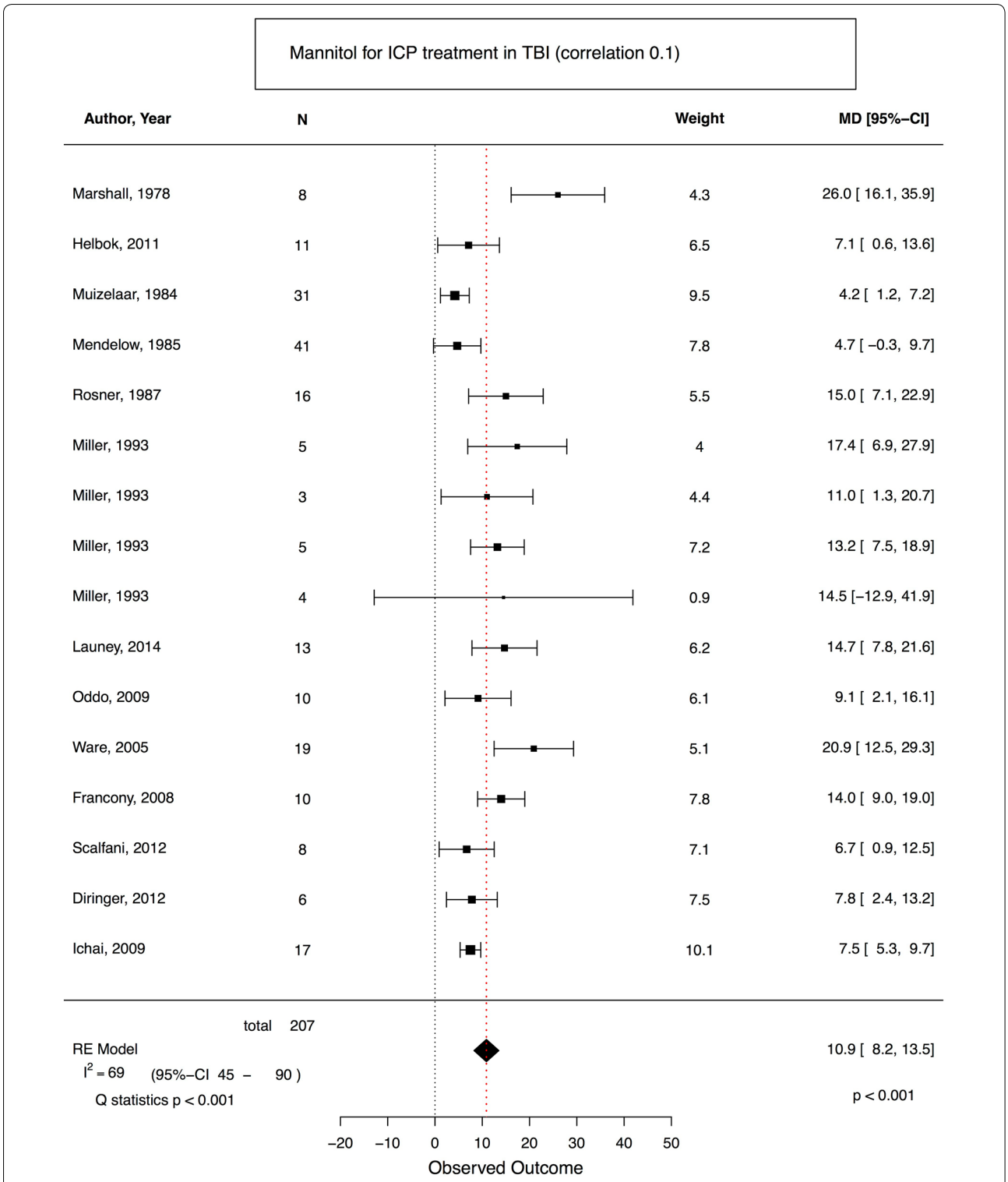

Fig. 1 Meta-analysis, examining the efficacy of mannitol in reducing ICP, assuming low correlation between before and after ICP measurements. Observed outcome = ICP reduction (mmHg) by mannitol

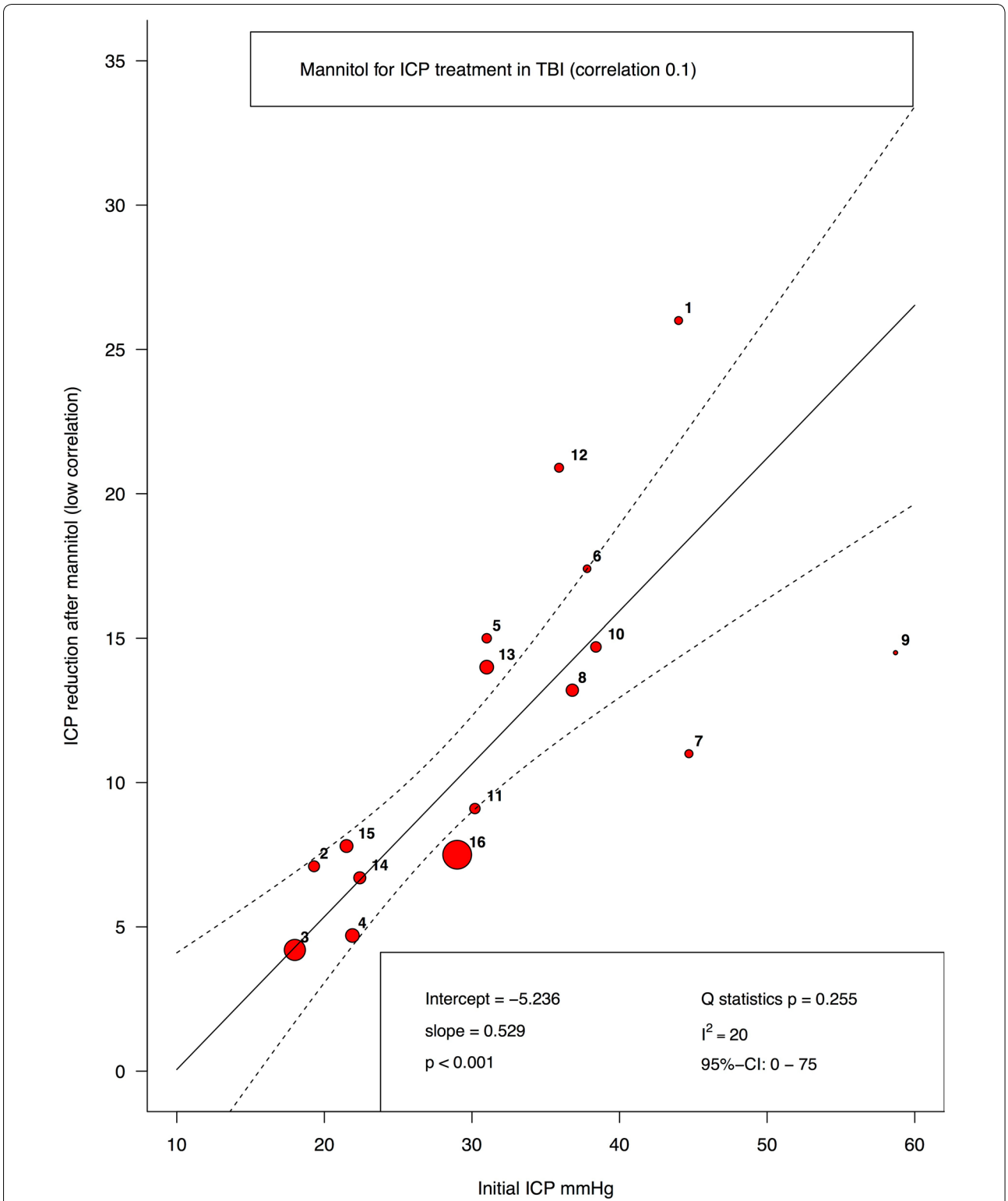

Fig. 2 Meta-regression, showing the magnitude of mannitol effect on ICP reduction, according to initial pretreatment ICP, and assuming a low correlation between before and after ICP measurements. Studies included in the meta-regression are (1) Marshall [31]; (2) Helbok [25]; (3) Muizelaar [34]; (4) Mendelow [32]; (5) Rosner [38]; (6–9) Miller [33], (10) Launey [28]; (11) Oddo [35]; (12) Ware [45]; (13) Francony [23]; (14) Scalfani [40]; (15) Diringer [21]; (16) Ichai [47]

Table 3 Meta-regression analysis, using ICP reduction as dependent variable

		Mannitol		Hypertonic Saline	
		Estimate	*P value*	Estimate	*P value*
Only dose	**Intercept**	8.2	0.059	6.4	0.003
	Dose	0.42	0.478	0.50	0.182
Only initial ICP	**Intercept**	-5.24	0.088	0.35	0.932
	Initial ICP	0.53	<0.001	0.34	0.039
Dose and initial ICP	**Intercept**	-11.7	<0.001	-8.5	<0.001
	Dose	0.78	0.003	0.87	<0.001
	Initial ICP	0.59	<0.001	0.58	<0.001

Model including only hyperosmolar fluid dose (above), only initial ICP (middle), dose and initial ICP (below). Unitary measures for dose are 100 mg/kg and 100 mOsm for mannitol and hypertonic saline, respectively. The unitary measure for ICP is mmHg

- We are unable to provide any recommendations about whether an ICP threshold of 20–22 mmHg, independent of other variables, should be used as a trigger to start osmotherapy to reduce ICP (No recommendation).
- We *recommend against* the use of an ICP threshold of 15 mmHg independent of other variables as a trigger for starting osmotherapy to reduce ICP (Strong recommendation).
- We *suggest* monitoring measured serum osmolarity and electrolytes to limit side effects of osmotherapy (Weak recommendation).
- We *suggest* monitoring ICP response to hyperosmolar fluids to limit the side effects of osmotherapy (Weak recommendation).
- We *suggest* monitoring the effects of hyperosmolar fluids on arterial blood pressure and fluid balance as secondary variables to limit the side effects of osmotherapy (Weak recommendation).

Fluids for the management of cerebral ischemia

Analysis of available evidence

Question 1: Is there enough evidence to prefer specific fluids (crystalloids/colloids) in the prevention of cerebral ischemia (CBF or clinical) improve outcome? (ESM SG3 Q1 GRADE)

Only studies focused on the prevention of vasospasm and delayed cerebral ischemia (DCI) and its consequences on the outcome of SAH patients were considered.

RCTs Triple H therapy (4 L/day hypervolaemic hypertensive haemodilution fluid therapy, including colloids and crystalloids) vs. normovolaemia (2 L/day crystalloids) did not affect the proportion of patients with TCD evidence of vasospasm, regional CBF, or 1-year GOS ($n = 32$ patients, two centres) [68]. However, in the context of triple H therapy, the net impact of colloids could not be measured. Lennihan et al. ($n = 82$ patients, single-centre) similarly found that prophylactic hypervolaemic therapy (including colloids and crystalloids) vs. normovolaemia had no impact on CBF, vasospasm and cerebral infarction [69].

GRADE: very low quality evidence (against).

Observational studies Because studies ($n = 12$) were limited by single-centre design, small sample size, heterogeneous treatment protocols and diverse outcomes, it was not possible to combine them into a single body of evidence. Detailed reporting of grading process was made for six studies, after adjustment for confounding factors. Several studies found that higher fluid volumes and positive fluid balance were associated with worse morbidity and neurological outcomes [7, 70, 71]; however, only one specified that colloids were used to achieve hypervolaemia [4].

When specifically addressing DCI therapy, Ibrahim and Macdonald ($n = 123$ patients) found that colloid administration and positive fluid balance were associated with worse outcome [9]. Another study ($n = 288$ patients) also found that positive fluid balance was associated with worse functional outcome [72]; however, there was no mention about whether colloids were used to reach a positive balance, and it was of limited use for evidence provision.

Among studies not performing statistical adjustment for confounders, six examined the effect of fluids on CBF and CBF surrogates. In one, hypervolaemia (colloids and crystalloids) modestly increased regional CBF but without improving brain tissue oxymetry ($PbtO_2$) [73], whereas in others volume expansion with HTS was associated with better $PbtO_2$ as well as CBF [57, 74, 75]. Volume expansion with albumin correlated with CBF decrease [76], while NS had no effect on CBF [77].

GRADE for studies: very low quality evidence (in favour or against according to the study findings).

Question 2: Does fluid therapy in the management of cerebral ischemia influence outcome? (ESM SG3 Q2 GRADE and ESM_SG3_AllQs GRADE ischemia)

Although the main focus was on SAH patients, studies on severe ischemic stroke patients were also included when relevant for the topic of cerebral ischemia.

A multicentre RCT in AIS patients ($n = 1267$) found that haemodilution (by venesection followed by dextran replacement) did not change 6-month outcome compared to standard treatment [78].

GRADE: moderate quality evidence (against).

In AIS patients (observational study, $N = 193$) daily fluid intake greater than 1650 mL was associated with malignant brain oedema [OR 13.86 (95% CI 5.11–37.60)] [79].

GRADE: very low quality evidence (against).

Additional observational studies (not performing any statistical adjustment for confounders, including small sample sizes and heterogeneous design, to be assessed with a meta-analytical approach) are listed below for, at best, hypotheses-generating purposes:

- *CBF* In patients with SAH and vasospasm, boluses of NS ($n = 6$) [80] or HTS ($n = 35$) [44] significantly improved CBF, whilst hypervolaemia (albumin, dextran and 10% glycerol) normalized CBF in the cerebral hemisphere where perfusion was reduced because of vasospasm [81]. In contrast, volume expansion with colloids and albumin [82] and isovolaemic haemodilution obtained by venisection and infusion of albumin and dextran [83] did not increase CBF.
- *Clinical endpoints* Two studies found that hypervolaemia (albumin, glycerol, dextran or plasma) targeted to haemodynamic monitoring endpoints (Swan-Ganz catheter) led to neurologic improvement and absence of progression to infarction in most patients [84, 85]. Several limitations (small sample size, absence of an instrumental diagnosis of vasospasm, no specific definition of treatment, and lack of adjustment for confounding factors) preclude any definitive conclusions.

Question 3: Is there enough evidence to prefer colloids to crystalloids in the management of cerebral ischemia? (ESM SG3 Q3 GRADE)

One observational study ($n = 160$ SAH patients) found that higher colloid dose (L/day) was associated with unfavourable 6-month GOS [OR 2.53 (95% CI 1.13–5.68)] [10].

GRADE: very low quality evidence (against).

Question 4: Is brain monitoring useful as a trigger or endpoint to guide fluid therapy in the management of cerebral ischemia? (ESM SG3 Q4 GRADE)

One study in *SAH patients* ($n = 10$) found that albumin (250 mL fluid bolus) increased cardiac index and improved $PbtO_2$ [86], but the limited sample size raises internal and external validity issues despite use of a multivariable approach to account for multiple measurements.

GRADE: very low quality evidence (in favour).

Question 5: Should a change in neurological status trigger a modification in fluid management away from normovolaemia? (ESM SG3 Q5 GRADE)

Two studies investigated treatment of new neurological symptoms in SAH patients with hypervolaemia (albumin, glycerol, dextran or plasma); in a subset of patients treatment was guided by pulmonary artery catheter. Neurologic improvement and absence of progression to infarction led the authors to conclude that hypervolaemic therapy was effective [84, 85]. However, these two studies have serious limitations (small sample size, vasospasm diagnosed by means of clinical symptoms, no specific definition of treatment, lack of adjustment for confounding factors).

GRADE for both studies: very low quality evidence (in favour).

Question 6: Is there a place for early goal-directed fluid therapy in the management of cerebral ischemia? (ESM SG3 Q6 GRADE)

One RCT in SAH patients ($n = 160$), comparing fluid management targeted to maintain high global end-diastolic volume index (GEDI), measured by transpulmonary thermodilution, with standard management found no effect on DCI and poor 3-month outcome rates [87]. However, a predefined analysis of high-grade SAH patients that were stratified at randomization demonstrated a statistically significant reduction in both outcomes. A recalculation (DP) during preparation of this consensus, using the same statistical methods as the authors (see ESM), found that neither result was statistically significant ($p = 0.101$ for DCI and $p = 0.054$ for 3-month poor outcome).

GRADE: moderate quality evidence (against).

Three observational studies using logistic regression model found that transpulmonary thermodilution (with the use of Cardiac Function Index [88] and GEDI [89, 90]) were associated with improved outcome.

GRADE: very low quality evidence (in favour).

Treatment recommendations

- We *recommend* assessing the efficacy of fluid infusion in SAH patients with delayed cerebral ischemia using a multimodal approach that includes arterial blood pressure and reversal of neurological deficit as main endpoints (Strong recommendation).
- We *suggest* that reduction in transcranial Doppler CBF velocities, improvements of cerebral perfusion and reduction of mean transit time on CT perfusion should be used as secondary endpoints when assessing the efficacy of fluids for reversal of delayed cerebral ischemia in SAH patients (Weak recommendation).

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5086-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest for this manuscript.

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References

1. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S et al (2013) GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 66(7):726–735
2. Rabinstein AA, Bruder N (2011) Management of hyponatremia and volume contraction. Neurocrit Care 15(2):354–360
3. Tisdall M, Crocker M, Watkiss J, Smith M (2006) Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol 18(1):57–63
4. Ginsberg MD, Palesch YY, Hill MD, Martin RH, Moy CS, Barsan WG, Waldman BD, Tamariz D, Ryckborst KJ, Alias et al (2013) High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: a randomised, double-blind, phase 3, placebo-controlled trial. Lancet Neurol 12(11):1049–1058
5. Palesch YY, Hill MD, Ryckborst KJ, Tamariz D, Ginsberg MD (2006) The ALIAS Pilot Trial: a dose-escalation and safety study of albumin therapy for acute ischemic stroke–II: neurologic outcome and efficacy analysis. Stroke 37(8):2107–2114
6. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R et al (2007) Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 357(9):874–884
7. Kuwabara K, Fushimi K, Matsuda S, Ishikawa KB, Horiguchi H, Fujimori K (2013) Association of early post-procedure hemodynamic management with the outcomes of subarachnoid hemorrhage patients. J Neurol 260(3):820–831
8. Suarez JI, Shannon L, Zaidat OO, Suri MF, Singh G, Lynch G, Selman WR (2004) Effect of human albumin administration on clinical outcome and hospital cost in patients with subarachnoid hemorrhage. J Neurosurg 100(4):585–590
9. Ibrahim GM, Macdonald RL (2013) The effects of fluid balance and colloid administration on outcomes in patients with aneurysmal subarachnoid hemorrhage: a propensity score-matched analysis. Neurocrit Care 19(2):140–149
10. Tseng MY, Hutchinson PJ, Kirkpatrick PJ (2008) Effects of fluid therapy following aneurysmal subarachnoid haemorrhage: a prospective clinical study. Br J Neurosurg 22(2):257–268
11. Sekhon MS, Dhingra VK, Sekhon IS, Henderson WR, McLean N, Griesdale DE (2011) The safety of synthetic colloid in critically ill patients with severe traumatic brain injuries. J Crit Care 26(4):357–362
12. Lehmann L, Bendel S, Uehlinger DE, Takala J, Schafer M, Reinert M, Jakob SM (2013) Randomized, double-blind trial of the effect of fluid composition on electrolyte, acid-base, and fluid homeostasis in patients early after subarachnoid hemorrhage. Neurocrit Care 18(1):5–12
13. Roquilly A, Loutrel O, Cinotti R, Rosenczweig E, Flet L, Mahe PJ, Dumont R, Marie Chupin A, Peneau C, Lejus C et al (2013) Balanced versus chloride-rich solutions for fluid resuscitation in brain-injured patients: a randomised double-blind pilot study. Crit Care 17(2):R77
14. Ioannidis JP (2008) Why most discovered true associations are inflated. Epidemiology 19(5):640–648
15. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE (1998) Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J Trauma 44(1):50–58
16. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, HTS Study Investigators (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA 291(11):1350–1357
17. Baker AJ, Rhind SG, Morrison LJ, Black S, Crnko NT, Shek PN, Rizoli SB (2009) Resuscitation with hypertonic saline-dextran reduces serum biomarker levels and correlates with outcome in severe traumatic brain injury patients. J Neurotrauma 26(8):1227–1240
18. Ichai C, Payen JF, Orban JC, Quintard H, Roth H, Legrand R, Francony G, Leverve XM (2013) Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med 39(8):1413–1422
19. Bentsen G, Breivik H, Lundar T, Stubhaug A (2006) Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage. Crit Care Med 34(12):2912–2917
20. Cottenceau V, Masson F, Mahamid E, Petit L, Shik V, Sztark F, Zaaroor M, Soustiel JF (2011) Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma 28(10):2003–2012
21. Diringer MN, Scalfani MT, Zazulia AR, Videen TO, Dhar R, Powers WJ (2012) Effect of mannitol on cerebral blood volume in patients with head injury. Neurosurgery 70(5):1215–1218 (discussion 1219)
22. Eskandari R, Filtz MR, Davis GE, Hoesch RE (2013) Effective treatment of refractory intracranial hypertension after traumatic brain injury with repeated boluses of 14.6% hypertonic saline. J Neurosurg 119(2):338–346
23. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, Jacquot C, Payen JF (2008) Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 36(3):795–800
24. Hartl R, Ghajar J, Hochleuthner H, Mauritz W (1997) Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. Acta Neurochir Suppl 70:126–129
25. Helbok R, Kurtz P, Schmidt JM, Stuart RM, Fernandez L, Malhotra R, Presciutti M, Ostapkovich ND, Connolly ES, Lee K et al (2011) Effect of mannitol on brain metabolism and tissue oxygenation in severe haemorrhagic stroke. J Neurol Neurosurg Psychiatry 82(4):378–383
26. Huang SJ, Chang L, Han YY, Lee YC, Tu YK (2006) Efficacy and safety of hypertonic saline solutions in the treatment of severe head injury. Surg Neurol 65(6):539–546 (discussion 546)

27. Kerwin AJ, Schinco MA, Tepas JJ 3rd, Renfro WH, Vitarbo EA, Muehlberger M (2009) The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma 67(2):277–282
28. Launey Y, Nesseler N, Le Maguet P, Malledant Y, Seguin P (2014) Effect of osmotherapy on optic nerve sheath diameter in patients with increased intracranial pressure. J Neurotrauma 31(10):984–988
29. Lescot T, Degos V, Zouaoui A, Preteux F, Coriat P, Puybasset L (2006) Opposed effects of hypertonic saline on contusions and noncontused brain tissue in patients with severe traumatic brain injury. Crit Care Med 34(12):3029–3033
30. Major EH, O'Connor P, Mullan B (2015) Single bolus 30% hypertonic saline for refractory intracranial hypertension. Ir J Med Sci 184(1):159–165
31. Marshall LF, Smith RW, Rauscher LA, Shapiro HM (1978) Mannitol dose requirements in brain-injured patients. J Neurosurg 48(2):169–172
32. Mendelow AD, Teasdale GM, Russell T, Flood J, Patterson J, Murray GD (1985) Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J Neurosurg 63(1):43–48
33. Miller JD, Piper IR, Dearden NM (1993) Management of intracranial hypertension in head injury: matching treatment with cause. Acta Neurochir Suppl (Wien) 57:152–159
34. Muizelaar JP, Lutz HA 3rd, Becker DP (1984) Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg 61(4):700–706
35. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, Kofke WA, Mayer SA, LeRoux PD (2009) Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry 80(8):916–920
36. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR (2009) Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery 65(6):1035–1041 (discussion 1041–1032)
37. Roquilly A, Mahe PJ, Latte DD, Loutrel O, Champin P, Di Falco C, Courbe A, Buffenoir K, Hamel O, Lejus C et al (2011) Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study. Crit Care 15(5):R260
38. Rosner MJ, Coley I (1987) Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the postmannitol hemogram. Neurosurgery 21(2):147–156
39. Sakowitz OW, Stover JF, Sarrafzadeh AS, Unterberg AW, Kiening KL (2007) Effects of mannitol bolus administration on intracranial pressure, cerebral extracellular metabolites, and tissue oxygenation in severely head-injured patients. J Trauma 62(2):292–298
40. Scalfani MT, Dhar R, Zazulia AR, Videen TO, Diringer MN (2012) Effect of osmotic agents on regional cerebral blood flow in traumatic brain injury. J Crit Care 27(5):526 (e527–e512)
41. Schwarz S, Georgiadis D, Aschoff A, Schwab S (2002) Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke 33(1):136–140
42. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W (1998) Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. Stroke 29(8):1550–1555
43. Soustiel JF, Mahamid E, Chistyakov A, Shik V, Benenson R, Zaaroor M (2006) Comparison of moderate hyperventilation and mannitol for control of intracranial pressure control in patients with severe traumatic brain injury—a study of cerebral blood flow and metabolism. Acta Neurochir (Wien) 148(8):845–851 (discussion 851)
44. Tseng MY, Al-Rawi PG, Czosnyka M, Hutchinson PJ, Richards H, Pickard JD, Kirkpatrick PJ (2007) Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. J Neurosurg 107(2):274–282
45. Ware ML, Nemani VM, Meeker M, Lee C, Morabito DJ, Manley GT (2005) Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. Neurosurgery 57(4):727–736 (discussion 727–736)
46. Higgins JP, Thompson SG (2004) Controlling the risk of spurious findings from meta-regression. Stat Med 23(11):1663–1682
47. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, Grimaud D, Leverve X (2009) Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med 35(3):471–479
48. Jagannatha AT, Sriganesh K, Devi BI, Rao GS (2016) An equiosmolar study on early intracranial physiology and long term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline. J Clin Neurosci 27:68–73
49. Sakellaridis N, Pavlou E, Karatzas S, Chroni D, Vlachos K, Chatzopoulos K, Dimopoulou E, Kelesis C, Karaouli V (2011) Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries. J Neurosurg 114(2):545–548
50. Vialet R, Albanese J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin C (2003) Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 31(6):1683–1687
51. Battison C, Andrews PJ, Graham C, Petty T (2005) Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med 33(1):196–202 (discussion 257–198)
52. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J (2005) Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients—a randomized clinical trial [ISRCTN62699180]. Crit Care 9(5):R530–R540
53. Mangat HS, Chiu YL, Gerber LM, Alimi M, Ghajar J, Hartl R (2015) Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. J Neurosurg 122(1):202–210
54. Misra UK, Kalita J, Vajpayee A, Phadke RV, Hadique A, Savlani V (2007) Effect of single mannitol bolus in intracerebral hemorrhage. Eur J Neurol 14(10):1118–1123
55. Diringer MN, Scalfani MT, Zazulia AR, Videen TO, Dhar R (2011) Cerebral hemodynamic and metabolic effects of equi-osmolar doses mannitol and 23.4% saline in patients with edema following large ischemic stroke. Neurocrit Care 14(1):11–17
56. Ye H, Su Y (2013) Hemodynamic effects of mannitol infusion in patients with acute intracerebral hemorrhage. Acta Cir Bras 28(2):106–111
57. Al-Rawi PG, Tseng MY, Richards HK, Nortje J, Timofeev I, Matta BF, Hutchinson PJ, Kirkpatrick PJ (2010) Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. Stroke 41(1):122–128
58. Jafar JJ, Johns LM, Mullan SF (1986) The effect of mannitol on cerebral blood flow. J Neurosurg 64(5):754–759
59. Manno EM, Adams RE, Derdeyn CP, Powers WJ, Diringer MN (1999) The effects of mannitol on cerebral edema after large hemispheric cerebral infarct. Neurology 52(3):583–587
60. Nath F, Galbraith S (1986) The effect of mannitol on cerebral white matter water content. J Neurosurg 65(1):41–43
61. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, Ulatowski JA (1998) Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. Crit Care Med 26(3):440–446
62. Videen TO, Zazulia AR, Manno EM, Derdeyn CP, Adams RE, Diringer MN, Powers WJ (2001) Mannitol bolus preferentially shrinks non-infarcted brain in patients with ischemic stroke. Neurology 57(11):2120–2122
63. Huang Z, Dong W, Yan Y, Xiao Q, Man Y (2002) Effects of intravenous mannitol on EEG recordings in stroke patients. Clin Neurophysiol 113(3):446–453
64. Wang X, Arima H, Yang J, Zhang S, Wu G, Woodward M, Munoz-Venturelli P, Lavados PM, Stapf C, Robinson T et al (2015) Mannitol and outcome in intracerebral hemorrhage: propensity score and multivariable intensive blood pressure reduction in acute cerebral hemorrhage trial 2 results. Stroke 46(10):2762–2767
65. Bereczki D, Mihalka L, Szatmari S, Fekete K, Di Cesar D, Fulesdi B, Csiba L, Fekete I (2003) Mannitol use in acute stroke: case fatality at 30 days and 1 year. Stroke 34(7):1730–1735
66. Wade CE, Grady JJ, Kramer GC, Younes RN, Gehlsen K, Holcroft JW (1997) Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. J Trauma 42(5 Suppl):S61–S65
67. Asehnoune K, Lasocki S, Seguin P, Geeraerts T, Perrigault PF, Dahyot-Fizelier C, Paugam Burtz C, Cook F, Demeure Dit Latte D, Cinotti R et al

(2017) Association between continuous hyperosmolar therapy and survival in patients with traumatic brain injury—a multicentre prospective cohort study and systematic review. Crit Care 21(1):328
68. Egge A, Waterloo K, Sjoholm H, Solberg T, Ingebrigtsen T, Romner B (2001) Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. Neurosurgery 49(3):593–605 (discussion 605–596)
69. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA (2000) Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. Stroke 31(2):383–391
70. Martini RP, Deem S, Brown M, Souter MJ, Yanez ND, Daniel S, Treggiari MM (2012) The association between fluid balance and outcomes after subarachnoid hemorrhage. Neurocrit Care 17(2):191–198
71. Tagami T, Kuwamoto K, Watanabe A, Unemoto K, Yokobori S, Matsumoto G, Igarashi Y, Yokota H (2014) Group SAHPS: effect of triple-h prophylaxis on global end-diastolic volume and clinical outcomes in patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care 21(3):462–469
72. Kissoon NR, Mandrekar JN, Fugate JE, Lanzino G, Wijdicks EF, Rabinstein AA (2015) Positive fluid balance is associated with poor outcomes in subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 24(10):2245–2251
73. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, Quintel M, Schmiedek P, Vajkoczy P (2007) Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. Crit Care Med 35(8):1844–1851 (quiz 1852)
74. Al-Rawi PG, Zygun D, Tseng MY, Hutchinson PJ, Matta BF, Kirkpatrick PJ (2005) Cerebral blood flow augmentation in patients with severe subarachnoid haemorrhage. Acta Neurochir Suppl 95:123–127
75. Tseng MY, Al-Rawi PG, Pickard JD, Rasulo FA, Kirkpatrick PJ (2003) Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. Stroke 34(6):1389–1396
76. Yamakami I, Isobe K, Yamaura A (1987) Effects of intravascular volume expansion on cerebral blood flow in patients with ruptured cerebral aneurysms. Neurosurgery 21(3):303–309
77. Dhar R, Scalfani MT, Zazulia AR, Videen TO, Derdeyn CP, Diringer MN (2012) Comparison of induced hypertension, fluid bolus, and blood transfusion to augment cerebral oxygen delivery after subarachnoid hemorrhage. J Neurosurg 116(3):648–656
78. Italian Acute Stroke Study Group (1988) Haemodilution in acute stroke: results of the Italian haemodilution trial. Lancet 1(8581):318–321
79. Dharmasaroja PA (2016) Fluid intake related to brain edema in acute middle cerebral artery infarction. Transl Stroke Res 7(1):49–53
80. Jost SC, Diringer MN, Zazulia AR, Videen TO, Aiyagari V, Grubb RL, Powers WJ (2005) Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. J Neurosurg 103(1):25–30
81. Mori K, Arai H, Nakajima K, Tajima A, Maeda M (1995) Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 26(9):1620–1626
82. Kim CY, Paek SH, Seo BG, Kim JH, Han DH (2003) Changes in vascular responses of the basilar artery to acetylcholine and endothelin-1 in an experimental rabbit vasospasm model. Acta Neurochir (Wien) 145(7):571–577
83. Ekelund A, Reinstrup P, Ryding E, Andersson AM, Molund T, Kristiansson KA, Romner B, Brandt L, Saveland H (2002) Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 144(7):703–712 (discussion 712–703)
84. Shimoda M, Oda S, Tsugane R, Sato O (1993) Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. J Neurosurg 78(3):423–429
85. Tanabe T, Saitoh T, Tachibana S, Takagi H, Yada K (1982) Effect of hyperdynamic therapy on cerebral ischaemia caused by vasospasm associated with subarachnoid haemorrhage. Acta Neurochir (Wien) 63(1–4):291–296
86. Kurtz P, Helbok R, Ko SB, Claassen J, Schmidt JM, Fernandez L, Stuart RM, Connolly ES, Badjatia N, Mayer SA et al (2014) Fluid responsiveness and brain tissue oxygen augmentation after subarachnoid hemorrhage. Neurocrit Care 20(2):247–254
87. Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T (2014) Early intensive versus minimally invasive approach to postoperative hemodynamic management after subarachnoid hemorrhage. Stroke 45(5):1280–1284
88. Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T (2014) Impact of transpulmonary thermodilution-based cardiac contractility and extravascular lung water measurements on clinical outcome of patients with Takotsubo cardiomyopathy after subarachnoid hemorrhage: a retrospective observational study. Crit Care 18(4):482
89. Tagami T, Kuwamoto K, Watanabe A, Unemoto K, Yokobori S, Matsumoto G, Yokota H (2014) Group SAHPS: optimal range of global end-diastolic volume for fluid management after aneurysmal subarachnoid hemorrhage: a multicenter prospective cohort study. Crit Care Med 42(6):1348–1356
90. Yoneda H, Nakamura T, Shirao S, Tanaka N, Ishihara H, Suehiro E, Koizumi H, Isotani E, Suzuki M (2013) Group SAHPS: multicenter prospective cohort study on volume management after subarachnoid hemorrhage: hemodynamic changes according to severity of subarachnoid hemorrhage and cerebral vasospasm. Stroke 44(8):2155–2161