Clinical practice guide for the choice of perioperative volume-restoring fluid in adult patients undergoing non-cardiac surgery

M. Basora\textsuperscript{a,\ast}, M.J. Colomina\textsuperscript{b}, V. Moral\textsuperscript{c}, M.S. Asuero de Lis\textsuperscript{d}, E. Boix\textsuperscript{e}, J.L. Jover\textsuperscript{f}, J.V. Llau\textsuperscript{g}, M.P. Rodrigo\textsuperscript{h}, J. Ripollés\textsuperscript{i}, J.M. Calvo Vecino\textsuperscript{j}

\textsuperscript{a} Anestesiología y Reanimación, Hospital Clinic, Barcelona, Spain
\textsuperscript{b} Anestesiología y Reanimación, Hospital Universitario Vall d’Hebron, Barcelona, Spain
\textsuperscript{c} Anestesiología y Reanimación, Hospital Sant Pau, Barcelona, Spain
\textsuperscript{d} Anestesiología y Reanimación, Hospital Universitario Ramón y Cajal, Madrid, Spain
\textsuperscript{e} Anestesiología y Reanimación, Hospital Universitario del Vinalopó, Elche, Alicante, Spain
\textsuperscript{f} Anestesiología y Reanimación, Hospital Verge dels Llirís, Alcoi, Alicante, Spain
\textsuperscript{g} Anestesiología y Reanimación, Hospital Clínico Universitario, Valencia, Spain
\textsuperscript{h} Anestesiología y Reanimación, Hospital de Basurto, Bilbao, Spain
\textsuperscript{i} Anestesiología y Reanimación, Hospital Universitario Infanta Leonor, Madrid, Spain
\textsuperscript{j} Anestesiología y Reanimación, Hospital Universitario Infanta Leonor, Universidad Complutense, Madrid, Spain

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Abstract The present clinical practice guide responds to the clinical questions about security in the choice of fluid (crystalloid, colloid or hydroxyethyl starch 130) in patients who require volume replacement during perioperative period of non-cardiac surgeries. From the evidence summary, recommendations were made following the GRADE methodology. In this population fluid therapy based on crystalloids is suggested (weak recommendation, low quality evidence). In the events where volume replacement is not reached with crystalloids, the use of synthetic colloids (hydroxyethyl starch 130 or modified fluid gelatin) is suggested instead of 5% albumin (weak recommendation, low quality evidence). The choice and dosage of the colloid should be based in the product characteristics, patient comorbidity and anesthesiologist’s experience.

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\textsuperscript{\ast} Corresponding author.

E-mail address: mbasora@clinic.ub.es (M. Basora).

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Introduction

Fluid management has undergone major changes in clinical practice in recent years. The criteria for volume replacement described in classic anaesthesiology textbooks were based on weak scientific evidence. Since then, perioperative fluid management has undergone a paradigm shift influenced by factors such as the higher mortality rate associated with perioperative fluid overload, evidence proving the inexistence of a non-anatomical third space, and the need to preserve the vascular endothelium and glycocalyx.

Based on this improved scientific understanding, major changes in fluid administration criteria were proposed and accepted at the start of this century, and this led to the adoption of a generally more restrictive approach to fluid management.

Technological developments, meanwhile, in the form of less invasive monitoring systems capable of measuring dynamic changes in volaemia and predicting the response to fluid administration, have given clinicians a far more sophisticated and simple method of guiding intravenous fluid management.

In the context of this improved understanding of fluid management in clinical practice, situations have arisen that have scandalised scientific societies and created confusion among clinicians. First, most of the literature relating to fluid management was found to be fraudulent, and what little scientific evidence remained after journals retracted the articles published by Bolds had to be re-evaluated.

Furthermore, some heterogeneous studies published in recent years have questioned the safety of colloid administration in critical patients. This prompted the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) to recommend suspending the marketing authorisation of medicines containing hydroxyethyl starch (HES) on the grounds that the benefits no longer outweighed the risks. A subsequent evaluation revoked the suspension and the product was authorised subject to strict conditions of use, which excluded critically ill patients.

Following these upheavals, we deemed it necessary to evaluate the existing scientific evidence relating to the safety of perioperative fluid management strategies and divulge our findings in these clinical practices guidelines (CPG). We have developed other guidelines for the intraoperative haemodynamic optimisation of adult patients undergoing non-cardiac surgery, and for this reason fluid management in this context is not discussed in these GPGs.

In drawing up these guidelines, we have excluded all articles published prior to 2000 for two reasons: First, we consider that the new century has ushered in a change in clinical practice, mainly following publication of the study by Rivers et al. in 2001, showing that early, goal-directed fluid management improves outcome in patients with severe sepsis. This study in many ways marks the turning point in fluid management, and was followed by the implementation of laparoscopic and fast track surgery, both of which have considerably reduced the need for perioperative fluid administration.

Secondly, most of the studies published prior to this date discuss products that have been withdrawn from the market, or that have been largely sidelined. Furthermore, they obviously do not include products released in recent years.

In these guidelines, therefore, we will restrict our analysis to articles that discuss the crystalloids and/or colloids most widely used in Spain today. We have included crystalloids, albumin, gelatins and third-generation HES solutions, and have specifically excluded both dextrose and second-generation HES. Studies in cardiac surgery and critically ill patients have also been excluded from our analysis, insofar as fluid management strategies differ considerably in these contexts, and exceed the scope of this CPG.

Perioperative fluid management

The aim of fluid management is to maintain the body’s hydration status and tissue perfusion at optimum levels and...
normalise electrolyte balance by promptly replacing fluids, thus preventing adverse effects, and ultimately, balancing tissue-level oxygen supply and demand.

As with any drugs, indications for fluid and dose regimens must be goal-directed. An understanding of the patient’s clinical situation will guide the clinician in choosing the correct type of fluid and the manner of administration.2,16,17

Indications for fluid management in surgical patients are based on the “5Rs” of the NICE clinical guidelines (Table 1).

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Indication</th>
<th>Recommended fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resuscitation</td>
<td>Urgent administration of fluids to restore circulation to vital organs after bleeding, loss of plasma, excessive loss of fluids and electrolytes (usually through the digestive tract) or internal losses (redistribution secondary to sepsis)</td>
<td>Crystalloid or colloid</td>
</tr>
<tr>
<td>Routine maintenance</td>
<td>Administration of IV fluids in patients who cannot take oral or enteral fluids.</td>
<td>Crystalloids</td>
</tr>
<tr>
<td>Volume replacement</td>
<td>Correct fluid and/or electrolyte deficit due to urinary or gastrointestinal losses, or elevated insensible losses due to fever or burns. Some GI or kidney fluid losses can be high in sodium, chloride and water content.</td>
<td>Crystalloids</td>
</tr>
<tr>
<td>Redistribution</td>
<td>Usually found in septic or critical patients, or following major surgery or in patients with significant comorbidities.</td>
<td>Crystalloids</td>
</tr>
<tr>
<td>Reassess indications</td>
<td>Reassess fluid status daily according to the clinical condition of the patient and/or electrolyte needs.</td>
<td>Crystalloids</td>
</tr>
</tbody>
</table>

Table 1: Indications for fluid management according to clinical situation

Surgical patients may need fluids to correct various clinical situation: to restore volume levels due to blood loss; to maintain fluid levels following surgery; to replace gastrointestinal or urinary tract losses or significant insensible losses due to fever or burns;5 fluid redistribution may cause tissue oedema due to fluid and sodium overload, and fluid may become trapped in the gastrointestinal tract or in the thoracic and/or peritoneal cavity.18

Surgical patients can present haemodynamic changes secondary to anaesthesia, such as vasoparalysis and vasodilation in response to neuraxial blockade.19 Surgery-induced haemodynamic changes can also occur as a result of patient positioning20 or pressure applied to body cavities, such as the pneumoperitoneum induced to facilitate laparoscopic surgery. All these can lead to volume deficit.

A wide range of fluids are available for use in clinical practice, and the choice of one or another is determined by clinical preference, institutional protocols, availability, cost, and marketing strategies.3,15,21,22

Evidence for the choice of fluid is scarce, and of low quality. Besides, the secondary effects associated with fluid management will not only depend on the fluid chosen, but also on the clinical situation of the patient, and this must be taken into account when considering the precautions and contraindications for a particular fluid.14,23

Fluid replacement solutions are typically classified into two groups according to their composition and physical and chemical properties: crystalloids and colloids.

Crystalloids are solutions of ions that are freely permeate semipermeable membranes, but contain concentrations of sodium and chloride that determine the tonicity of the fluid (Table 2). Crystalloids can contain anions—acetate, malate, lactate, gluconate, citrate—which are converted into bicarbonate. Administration of crystalloids does not affect the acid–base balance. Depending on their relative tonicity in relation to plasma, crystalloids can be classified as hypotonic, isotonic and hypertonic. They are also grouped into balanced and unbalanced solutions depending on their properties, physical and chemical composition, and similarity to plasma. Balanced crystalloids are similar to plasma in terms of osmolarity and composition of their main electrolytes, and are recommended due to their small sodium and chloride contents compared to saline solutions. NaCl (0.9%) can be useful in gastrointestinal losses; however, in many cases the fluid lost contains potassium magnesium and calcium, and in this respect balanced crystalloids are preferable to NaCl. This is why balanced solutions are gaining ground in fluid management strategies for surgical patients.24–26

Colloids are suspensions of molecules within a carrier solution that are relatively incapable of crossing the healthy semipermeable capillary membrane, and therefore circulate exclusively in the intravascular compartment.

Medicinal colloids are classified as natural (albumin) and semi-synthetic (gelatins and HES) (Table 3).

The volumetric effect of an isotonic colloid will be determined by the volumetric status of the patient. Therefore, in a hypovolaemic patient, it will expand volume by 100%, while in a normo- or hypervolaemic patient, its expansion capacity will not exceed 40%.14 Albumin is a protein synthesised in the liver, and makes up over 50% of plasmatic protein. It is essential for the transport of endogenous and exogenous substances. It has a role as a weak acid (to maintain the acid-base balance), and has antioxidant and anti-inflammatory properties.27 For medicinal purposes, it is extracted from blood and is processed to prevent transmission of pathogenic viruses. It is sold in a variety of solutions, each with a different concentration. A 5% albumin solution is the most widely used in volume replacement, while 20% and 25% solutions are usually used to treat hypoproteinaemia.
Following IV administration, it has an intravascular half-life of around 16 h or even less in patients with altered capillary permeability.

According to the 2013 revision of the Spanish version of the summary of product characteristics, the therapeutic indications of albumin include the restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is inappropriate. The choice of albumin rather than an artificial colloid will depend on the clinical situation of the individual patient. Albumin is authorised for use in patients on dialysis and in premature infants.

Gelatins are polypeptides obtained from bovine collagen. The transformation of insoluble collagen to soluble gelatin is the key to the industrial production of gelatin. This process can produce different types of gelatin, depending on the breakage of the intramolecular bonds: polygeline gelatins (Hemoclas®), succinylated gelatin (Gelofusine®) and oxygellyatin. Succinylated gelatin (modified gelatin) does not contain calcium, and is therefore compatible with blood products. Due to its low molecular weight, it has less expanding capacity and a shorter half-life (2–3 h) than other colloids.

The latest (2006) version of the summary of product characteristics states that Gelofusine® is a colloidal plasma substitute indicated for the initial management of hypovolaemic shock caused by, for example, haemorrhage, acute trauma or surgery and in situations where volume replacement will improve tissue perfusion. Hydroxyethyl starches (HES) are modified polysaccharides derived from amylopectin obtained from maize or potato starch. HES are classified according to their concentration, molecular weight, degree of molar substitution (hydroxyethyl residues for every 10 glucose molecules) and C2/C6 ratio (hydroxyethyl residues at the C2 atom are more resistant to plasma b-amylase mediated hydroxyethylation than those at C6). Concentration mainly affects initial volume expansion; 6% solutions are iso-oncotic, and 10% solutions are hyper-oncotic. The molecular weight of HES determines their expansion capacity, and this, together with the molar substitution index and C2/C6 ratio, determines their intravascular half-life. Over the years, new HES have been developed with lower molecular weights and molar substitution indexes and a higher C2/C6 ratio, making them less susceptible to degradation, and thus increasing their intravascular half-life.

Table 2 Characteristics of the principle crystalloids used.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Origin</th>
<th>Molecular weight (daltons)</th>
<th>Amylopectin/amylose content (%)</th>
<th>C2/C6</th>
<th>Initial expansion (%)</th>
<th>Elimination</th>
<th>Carrier solution</th>
<th>Price a (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>0.9% saline</td>
<td>135–141</td>
<td>95–105</td>
<td>3.5–4.5</td>
<td>2.2–2.6</td>
<td>2</td>
<td>23–27</td>
<td>289</td>
</tr>
<tr>
<td>Ringer (lactate/acacetate)</td>
<td>154</td>
<td>154</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>28 Lactate/acacetate</td>
<td>308</td>
</tr>
<tr>
<td>Balance, calcium-free solution (Plasmalyte®)</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>–</td>
<td>3</td>
<td>27 Acetate</td>
<td>295</td>
<td>7.4</td>
</tr>
<tr>
<td>Balance solution with calcium (Isofundin®)</td>
<td>145</td>
<td>127</td>
<td>4</td>
<td>2.5</td>
<td>1</td>
<td>24 Acetate</td>
<td>309</td>
<td>5.1–5.9</td>
</tr>
</tbody>
</table>


Table 3 Characteristics of the principle colloids used.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Origin</th>
<th>Molecular weight (daltons)</th>
<th>Amylopectin/amylose content (%)</th>
<th>C2/C6</th>
<th>Initial expansion (%)</th>
<th>Elimination</th>
<th>Carrier solution</th>
<th>Price a (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES 130/0.4</td>
<td>Maize</td>
<td>130,000</td>
<td>99%/&lt;1%</td>
<td>9/1</td>
<td>100</td>
<td>Renal clearance and plasma amylase</td>
<td>CINa 0.9%</td>
<td>12.9</td>
</tr>
<tr>
<td>HES 130/0.42</td>
<td>Potato</td>
<td>130,000</td>
<td>75%/25%</td>
<td>6/1</td>
<td>100</td>
<td>Renal clearance and plasma amylase</td>
<td>CINa 0.9%</td>
<td>12.9</td>
</tr>
<tr>
<td>Succinylated gelatin</td>
<td>Bovine collagen</td>
<td>30,000</td>
<td>–</td>
<td>70–90</td>
<td>Renal clearance and peptidase</td>
<td>CINa 0.9%</td>
<td>5.26</td>
<td></td>
</tr>
<tr>
<td>Polygelines</td>
<td>Bovine collagen</td>
<td>35,000</td>
<td>–</td>
<td>70–80</td>
<td>Renal clearance and peptidase</td>
<td>CINa 0.9%</td>
<td>Not in Spain</td>
<td></td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>Human plasma</td>
<td>67,000</td>
<td>–</td>
<td>80</td>
<td>Reticuloendothelial system</td>
<td>CINa 0.9%</td>
<td>92.26</td>
<td></td>
</tr>
</tbody>
</table>

These guidelines will focus on third generation, 130/0.4/6% (maize-based) or 130/0.042/6% (potato-based) HES. The latter formulation has a slightly higher molar substitution index (0.42 vs 0.4) and a lower C2/C6 hydroxyethyl ratio, and is therefore more resistant to hydrolysis. Potato-derived HES has a lower degree of branching due to the predominance of substantially linear amylose chains, in contrast to the highly-branched anylopectin-rich maize-based formulation.

Most HES are suspended in saline solution, although the latest formulations are based on a balanced solution.25-30

According to the summary of product characteristics, HES are indicated in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. This summary was amended in January 2014 to include indications for administration, recommending that the first 10–20 ml should be infused slowly and under careful monitoring. The maximum daily dose is 30 ml/kg and the lowest possible effective dose should be used.

The most important changes made in the summary involve contraindications for HES, administration in patients with sepsis, burn patients, critically ill patients (typically admitted to the intensive care unit), patients with kidney failure or receiving renal replacement therapy, and patients with intracranial or cerebral haemorrhage. It also recommends restricting the use of HES to the initial phase of volume resuscitation, with a maximum time interval of 24 h.

Scope and objectives

Rationale and objectives
The aim of these CPGs is to clarify concepts, standardise procedures, and provide a series of recommendations or safety suggestions based on the latest scientific evidence that will help clinicians take sound decisions relating to the use of postoperative intravenous fluids for volume resuscitation in non-cardiac surgery. The recommendations in this guideline are aimed at non-cardiac surgical patients with slight to moderate bleeding that require volume resuscitation.

For the purpose of these CPGs, we will use the term perioperative fluid management. Specific treatment of the secondary causes of blood loss will not be addressed. These guidelines do not include children due to the unique characteristics, both general and specific, of the paediatric population.

Cardiac surgery has also been excluded because fluid management in these patients differs significantly from other clinical settings.

Healthcare region
These guidelines are designed for use in the Spanish national health system. The target users are healthcare professionals specialising in anaesthesiology and critical care, surgery, nursing and other fields associated with the perioperative care and treatment of non-cardiac surgery patients.

Methodology
The development of these CPGs has been sponsored by the Spanish Society of Anaesthesiology and Critical Care Medicine (SEDA) and drawn up by the Society’s Haemostasis, Transfusion and Critical Care Medicine division. The aim has been to develop a series of recommendations for perioperative fluid management in surgical patients.

These CPGs have been developed following the recommendations of the Spanish Health System Clinical Practice Guideline Development Manual.40

The guidelines were developed in stages:

Formation of the working group
At this stage, a working group made up of anaesthesiologists, surgeons and surgical nurses involved in perioperative fluid management was formed, together with experts in methodology from the Centro Cochrane Iberoamericano (Barcelona) and the Spanish Society of Anaesthesiology.

Clinical questions

The clinical questions have been formulated according to the PICO (population, intervention, comparison and outcome) format and discussed by the members of the working group. They were prioritised according to the objectives, scope, target population, clinical areas and target users of the recommendations. In order to prioritise outcomes, 4 anaesthesiologists individually and independently rated 24 outcomes on a scale of 1–9, where a score of 1–3 corresponded to an unimportant outcome, 4–6 to an important outcome, and 7–9 to a critical outcome. Table S1 summarises the score for each outcome.

Safety was prioritised according to key outcomes of interest to patients. The main safety outcome was the adverse effects of different interventions.

Literature search

A two-stage bibliographic search of research articles published since 2000 was conducted to address the questions formulated. In the first stage, the MEDLINE bibliographic database accessed through PubMed (including the systematic reviews published in the Cochrane Database of Systematic Reviews) was searched for CPGs, systematic reviews (SR) and other position papers, together with health technology assessment reports. The search strategy is described in Table S2.

In the second stage, the search focussed on retrieving specific studies that added further information to the relevant SRs. Of these, only randomised clinical trials (RCT) were chosen. The search was also performed in MEDLINE, and was not limited by language. However, for the purpose of analysis, only articles written in English and Spanish were chosen. The search was performed in November 2013.

Study selection and evaluation of evidence

The articles retrieved from the bibliographic search were first filtered by title and abstract to determine their relevance to the clinical questions. Fig. 1 shows the article selection process in the form of a flow diagram. Studies
discussing formulations no longer in use in Spain, such as polygelines, dexters, second generation HES and earlier formulations, or those no longer marketed, such as oxy-polygelatin, were excluded from the analysis.

The working group decided to restrict the SRs selected to primary studies published after 2000, on the grounds that surgical and anaesthetic techniques can differ greatly in studies performed before and after this date. Studies published by Joachim Boldt were also excluded because they have been rejected by the scientific community and withdrawn by journals following revelations of research misconduct. Relevant references included on the basis of the title and abstract were then read in their entirety to determine their quality and suitability.

The quality of the evidence was evaluated following the recommendations of the international working group Grading of Recommendations of Assessment Development and Evaluations (GRADE). The quality of the available body of evidence was evaluated for each outcome included in the clinical question. The following factors were taken into consideration: risk of bias, consistency of results across studies, directness of evidence, precision of effect estimates, and publication bias. Following this evaluation process, the quality of the evidence gathered for each outcome was classified into 4 categories: high, moderate, low, or very low.

Use of resources and surgery costs were evaluated by prioritising questions that could provide recommendations on these topics. The questions were prioritised during meetings of the working group, and once the list of priorities had been drawn up, the references retrieved from the above-mentioned bibliographic search were filtered by title and abstract. Structured abstracts were analysed and the text of relevant articles read to evaluate their quality, selecting those that directly addressed the questions of interest. A narrative synthesis was made of the most important outcomes, and a table was created specifically for the kidney disease outcome.

Formulation of recommendations

Following the GRADE methodology, recommendations were formulated on the basis of the summary of findings for each clinical question. To determine the direction (in favour or against an intervention) and the strength of the recommendations (strong or weak), the overall quality of the available evidence, the risk/benefit ratio of each procedure evaluated, patient values and preferences, and if applicable, use of resources and associated costs, were weighed up.

Members of the working group were asked to give their opinion of the summaries of findings and the resulting recommendations on the basis of the comprehensiveness, relevance and outcomes of the articles evaluated. Following this, the recommendations were discussed in a group meeting.

These guidelines have been reviewed independently by a multidisciplinary group of professionals from the Spanish Society of General and Digestive Surgery, the Spanish Society of Anaesthesiology, Intensive Care and Pain Therapy, the Spanish Society of Surgical Nursing, and the Spanish Society of Nursing and Surgery. The guidelines will be updated every 3 years, or whenever specific recommendations need to be amended following the emergence of new scientific evidence.

Results

To find the formulations (colloids or crystalloids) with the best safety profile for perioperative volume replacement in non-cardiac surgery, 3 different comparisons were made of different colloids: (a) albumin vs crystalloids, (b) hydroxyethyl starch (HES) vs crystalloids, and c) gelatins vs crystalloids. The overall quality of the evidence is low due to the risk of bias and the imprecision of the findings.
The characteristics of the studies included are shown in Table 4. The summary of findings and quality of evidence are shown in Tables 5A–5C. The studies on which the evidence and recommendations for this question are based are shown in Table S3. As far as the use of resources and care costs are concerned, the results of an incremental cost-effectiveness ratio calculated in a clinical trial with a small sample size showed that choosing colloids (HES 130/0.4) over crystalloids (Ringer’s Lactate) to prevent complications in patients increased costs by $70.5. In this study, however, more robust cost-effective measures were not calculated. The quality of the studies analysed in the context of the outcomes of interest is shown in Table S4. The impact of the kidney function outcome is detailed separately in Table S5.

**Question 1. Which type of fluid (colloids or crystalloids) has the best safety profile for perioperative volume replacement in non-cardiac surgery?**

**Recommendation**

In patients undergoing non-cardiac surgery, fluid management with crystalloids are recommended over colloids.

**Weak recommendation in favour (Low quality of evidence)**

**Justification**

Available studies have not shown any difference between the use of colloids and crystalloids in terms of critical outcomes such as mortality, impairment of kidney function and coagulopathy, among others. The quality of the evidence is low, and colloids are more expensive than crystalloids. For these reasons, a weak recommendation is given in favour of crystalloids.

**Research recommendations**

Clinical trials of a higher methodological quality with more appropriate sample sizes are needed to investigate critical outcomes. Studies evaluating the cost-effectiveness of treatment strategies are also needed.

To find the colloid solution with the best safety profile for perioperative volume replacement in non-cardiac surgery, 3 different comparisons were made of different colloids: (a) albumin vs HES, (b) modified gelatin vs HES, and (c) HES 130/0.42 vs HES 130/0.4. The overall quality of the evidence is low due to the risk of bias and the imprecision of the findings. The characteristics of the studies included are shown in Table 6. The summary of findings and quality of evidence are shown in Tables 7A–7C. The studies on which the evidence and recommendations for this question are based are shown in Table S6. The quality of the studies analysed in the context of the outcomes of interest is shown in Table S7. The impact of the kidney function outcome is detailed separately in Table S8.

**Question 2. Which colloid solution has the best safety profile for perioperative volume replacement in non-cardiac surgery?**

**Recommendation**

Hydroxyethyl starch (HES 130/0.42 or HES 130/0.4) or modified gelatins are recommended over albumin in non-cardiac surgery patients requiring volume replacement.

**Weak recommendation in favour (Low quality of evidence)**

**Justification**

Available studies have not shown any difference between different types of colloids in terms of critical outcomes such as mortality, impairment of kidney function and coagulopathy, among others. The quality of the evidence is low, and albumin is significantly more expensive than other colloids. For these reasons, a weak recommendation is given in favour of hydroxyethyl starch or modified gelatin.

**Research recommendations**

Clinical trials of a higher methodological quality with more appropriate sample sizes are needed to investigate critical outcomes. Studies evaluating the cost-effectiveness of treatment strategies are also needed.

**Discussion and recommendations**

These guidelines focus on perioperative volume replacement in non-cardiac surgery patients with moderate or severe blood loss who need fluid management strategies to maintain appropriate intravascular volume and tissue perfusion. The onset of massive haemorrhage will require specific treatment that is beyond the scope of these guidelines.

Intravenous fluids are given to all surgical patients. However, the need for this therapy has diminished following the introduction of fast track surgery, less invasive techniques, and shorter preoperative fasting.

Most medical procedures vary greatly in clinical practice. Incorrect fluid administration can be harmful to patients, and most practitioners have a limited understanding of the benefits and risks of fluid management.

Surgical practice in Spain should mirror the results of a study conducted in Catalonia in 2006, in which 22.6% of surgical patients received an average 500 ml of colloids. In a recent meta-analysis, the crystalloid/colloid ratio in surgical patients was 1:5 (750 ml crystalloids for every 500 ml colloids). Since 2000, this ratio has decreased, and now more colloids than crystalloids are administered to these patients. The study found significant variability in the volume of crystalloids administered concurrently.
Table 4  Characteristics of studies used to compare the safety of crystalloids and colloids in volume replacement.

<table>
<thead>
<tr>
<th>Study</th>
<th>Included in systematic review</th>
<th>Type of surgery</th>
<th>Crystalloid</th>
<th>Albumin</th>
<th>Hydroxyethyl starch</th>
<th>Gelatin</th>
<th>Other fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al. 2003</td>
<td>Perel 2013</td>
<td>Hip replacement</td>
<td>0.9% saline (n = 14)</td>
<td>Albumin 20%  (n = 13)</td>
<td>No</td>
<td>Modified gelatin 3% (Gelofusine) (n = 14)</td>
<td>Polygeline (Haemaccel) (n = 14)</td>
</tr>
<tr>
<td>Feldheiser et al. 2013</td>
<td>Study retrieved from supplementary search Perel 2013</td>
<td>Surgical debulking of ovarian cancer Knee arthroplasty</td>
<td>Balanced crystalloid (n = 24)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 24)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fries et al. 2004</td>
<td>Study retrieved from supplementary search Perel 2013</td>
<td>Knee arthroplasty</td>
<td>Ringer’s lactate (n = 20)</td>
<td>No</td>
<td>No</td>
<td>Modified gelatin 4% (Gelofusine) (n = 20)</td>
<td>HES 200/0.5 6% (n = 20)</td>
</tr>
<tr>
<td>Hamaji et al. 2012</td>
<td>Study retrieved from supplementary search Gillies 2013</td>
<td>Hip replacement</td>
<td>Ringer’s lactate (n = 24)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 24)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Hung et al. 2012</td>
<td>Study retrieved from supplementary search Gillies 2013</td>
<td>Abdominal surgery</td>
<td>Ringer’s lactate (n = 39)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 41)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Innerhofer et al. 2002</td>
<td>Groeneveld 2011</td>
<td>Knee arthroplasty</td>
<td>Ringer’s lactate (n = 20)</td>
<td>No</td>
<td>No</td>
<td>Modified gelatin 4% + Ringer’s lactate (Gelofusine) (n = 20)</td>
<td>HES 200/0.5 6% (n = 20)</td>
</tr>
<tr>
<td>Jin et al. 2013</td>
<td>Van der Linden and Hartog 2011</td>
<td>Cancer-related gastrectomy</td>
<td>Ringer’s lactate (n = 12)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 12)</td>
<td>Modified gelatin 4% (Gelofusine) (n = 12)</td>
<td>No</td>
</tr>
<tr>
<td>Parker et al. 2004</td>
<td>Saw 2012</td>
<td>Hip replacement</td>
<td>0.9% saline (n = 198)</td>
<td>No</td>
<td>No</td>
<td>Modified gelatin 4% (Gelofusine) (n = 198)</td>
<td>No</td>
</tr>
<tr>
<td>Rasmussen et al. 2013</td>
<td>Study retrieved from supplementary search Mutter 2013</td>
<td>Cystectomy</td>
<td>Ringer’s lactate (n = 16)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 17)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yang et al. 2011</td>
<td>Study retrieved from supplementary search Mutter 2013</td>
<td>Hepatectomy</td>
<td>Ringer’s lactate (n = 25)</td>
<td>Albumin 20%  (n = 30)</td>
<td>HES 130/0.4, 6% (Voluven) (n = 26)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yates et al. 2013</td>
<td>Study retrieved from supplementary search Mutter 2013</td>
<td>Colectomy</td>
<td>Balanced crystalloid (n = 100)</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 106)</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

GRADE summary of findings and quality of evidence tables.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.
### Table 5A  Summary of findings and quality of evidence: albumin vs crystalloids (question 1).

<table>
<thead>
<tr>
<th>Outcome assessment</th>
<th>Patients, n</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (2):50,60</td>
<td>0/43 Albumin, 0/39 Crystalloids</td>
<td>Relative (CI 95%)</td>
<td>Absolute&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney failure (defined by author) (1):50</td>
<td>0/30 Albumin, 0/25 Crystalloids</td>
<td>Not assessable</td>
<td>Not assessable due to no events in at least one group&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>Very low</td>
</tr>
<tr>
<td>Coagulopathy: intraoperative blood loss (ml) (1):50</td>
<td>30/25 Albumin, 25/25 Crystalloids</td>
<td>14 ml more (from 119.24 less to 147.24 more)&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>Not assessable due to no events in at least one group&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>Critical</td>
</tr>
<tr>
<td>Clinical haemorrhage (1):50</td>
<td>0/30 Albumin, 0/25 Crystalloids</td>
<td>Not assessable</td>
<td>Not assessable due to no events in at least one group&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Very low</td>
</tr>
<tr>
<td>Venous thrombosis (1):50</td>
<td>9/30 Albumin, 5/25 Crystalloids</td>
<td>RR 1.50 (0.58–3.90)</td>
<td>100 cases more per 1000 (from 84 less to 580 more)&lt;sup&gt;b,d,f&lt;/sup&gt;</td>
<td>Important</td>
</tr>
<tr>
<td>Length of ICU stay (days) (1):50</td>
<td>30/25 Albumin, 25/25 Crystalloids</td>
<td>–</td>
<td>0.1 day less (from 0.52 less to 0.32 more)&lt;sup&gt;d,f,g&lt;/sup&gt;</td>
<td>Important</td>
</tr>
<tr>
<td>Length of hospital stay (days) (1):50</td>
<td>30/25 Albumin, 25/25 Crystalloids</td>
<td>–</td>
<td>(from 0.40 less to 0.40 more)&lt;sup&gt;b,d,f,g&lt;/sup&gt;</td>
<td>Important</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: risk ratio.

<sup>+</sup> Assumed risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).

<sup>a</sup> Generation of randomisation sequence and allocation unclear.

<sup>b</sup> Few events. The 95% confidence interval includes zero.

<sup>c</sup> No events presented. RR not assessable.

<sup>d</sup> Important losses to follow-up.

<sup>e</sup> Only one study with events.

<sup>f</sup> Major heterogeneity I² 75% p = 0.003.

<sup>g</sup> The 95% confidence interval includes zero.
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Outcome (number of clinical trials)</th>
<th>Patients, n</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (5):50–53,63</td>
<td>(HES MP 130) 7/221</td>
<td>Crystalloids 2/209</td>
<td>Relative (CI 95%) RR 2.57 (0.7–9.49)</td>
<td>Absolute* 15 more per 1000 (from 3 less to 81 more)</td>
<td>⊕⊕</td>
</tr>
<tr>
<td>Kidney failure (defined by author) (4):50–53</td>
<td>5/180</td>
<td>0/173</td>
<td>RR 5.79 (0.7–47.67)</td>
<td>–</td>
<td>⊕</td>
</tr>
<tr>
<td>RIFLE at risk or very serious (1):50</td>
<td>0/26</td>
<td>1/25</td>
<td>RR 0.32 (0.01–7.53)</td>
<td>27 less per 1000 (from 40 less to 261 more)</td>
<td>⊕⊕</td>
</tr>
<tr>
<td>Acute pulmonary oedema (1):52</td>
<td>5/106</td>
<td>2/100</td>
<td>RR 2.36 (0.47–11.88)</td>
<td>27 more per 1000 (from 11 less to 218 more)</td>
<td>⊕</td>
</tr>
<tr>
<td>Coagulopathy: intraoperative blood loss (ml) (3):50,63,66</td>
<td>79</td>
<td>76</td>
<td>–</td>
<td>33.73 ml less (from 180.18 less to 112.73 more)</td>
<td>⊕</td>
</tr>
<tr>
<td>Coagulopathy: Blood loss up to 1st POP day (accumulative, ml) (3):42,51,52</td>
<td>147</td>
<td>140</td>
<td>–</td>
<td>329.6 ml more (from 69.48 less to 728.67 more)</td>
<td>⊕</td>
</tr>
<tr>
<td>Myocardial Infarction (1):52</td>
<td>11/106</td>
<td>4/100</td>
<td>RR 2.59 (0.85–7.88)</td>
<td>64 more per 1000 (from 6 less to 275 more)</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>Sepsis (1):52</td>
<td>13/106</td>
<td>8/100</td>
<td>RR 1.53 (0.66–3.54)</td>
<td>42 more per 1000 (from 27 less to 203 more)</td>
<td>⊕</td>
</tr>
<tr>
<td>Length of ICU stay (days) (1):50</td>
<td>26</td>
<td>25</td>
<td>–</td>
<td>0.1 less (0.51 less to 0.31 more)</td>
<td>⊕</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: risk ratio.
*Estimated risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).

a Randomisation sequence unclear, or no randomisation.
b Few events. The 95% confidence interval includes zero.
c Only one study.
d Major heterogeneity I² 77% p = 0.01.
e The 95% confidence interval includes zero.
f Major heterogeneity I² 79% p = 0.009.
### Table 5C  Summary of findings and quality of evidence: modified gelatin vs crystalloids (question 1).

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Patients, n</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinical trials</td>
<td>Modified gelatin</td>
<td>Crystalloids</td>
<td>Relative (CI 95%)</td>
<td>Absolute</td>
</tr>
<tr>
<td>Mortality (3):60,62,67</td>
<td>19/232</td>
<td>9/232</td>
<td>RR 2.11 (0.98 to 4.55)</td>
<td>43 more per 1000 (from 1 less to 138 more)&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Coagulopathy: intraoperative blood loss (ml) (2):65–66</td>
<td>32</td>
<td>32</td>
<td>–</td>
<td>0.33 ml more (from 50.14 less to 50.8 more)&lt;sup&gt;a,c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Coagulopathy: blood loss up to 1st day POP (ml) (1):62</td>
<td>20</td>
<td>20</td>
<td>–</td>
<td>34 ml more (from 120.88 less to 188.88 more)&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart failure (1):67</td>
<td>13/198</td>
<td>8/198</td>
<td>RR 1.62 (0.69–3.83)</td>
<td>25 more per 1000 (from 13 less to 114 more)&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial infarction (1):67</td>
<td>1/198</td>
<td>0/198</td>
<td>RR 3 (0.12–73.2)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Venous thrombosis (1):67</td>
<td>5/198</td>
<td>5/198</td>
<td>RR 1 (0.29–3.4)</td>
<td>0 less per 1000 (from 18 less to 61 more)&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: risk ratio.

* Estimated risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).

<sup>a</sup> Generation of randomisation sequence and allocation unclear. Some non-blinded studies.

<sup>b</sup> Only one study with events.

<sup>c</sup> The 95% CI includes zero.

<sup>d</sup> Only one study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Included in systematic review</th>
<th>Type of surgery</th>
<th>Albumin</th>
<th>Hydroxyethyl starch</th>
<th>Gelatin</th>
<th>Other fluid</th>
<th>Other fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godet54 2008</td>
<td>Bunn31 2012, Mutter69 2013 and Toomtong70 2010</td>
<td>Vascular surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 32)</td>
<td>Modified gelatin 3% (Plasmion) (n = 33)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Jin66 2010</td>
<td>Bunn31 2012, Hartog30 2011 and Van der Linden38 2013</td>
<td>Gastrectomy</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 12)</td>
<td>Modified gelatin 4% (Gelofusine) (n = 12)</td>
<td>No</td>
<td>Ringer’s lactate (n = 12)</td>
</tr>
<tr>
<td>Kim71 2009</td>
<td>Van der Linden38 2013</td>
<td>Major non-cardiac surgery</td>
<td>Albumin20% (n = 19)</td>
<td>HES 6% 130/0.4 (Voluven) (n = 41)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Liang72 2006</td>
<td>Hartog30 2011 and Saw64 2012</td>
<td>Large bowel resection</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 20)</td>
<td>Gelatin (succinyl gelatin) 4% (Gelofusine) (n = 20)</td>
<td>No</td>
<td>Ringer’s lactate (n = 12)</td>
</tr>
<tr>
<td>Mahmood55 2007</td>
<td>Bunn31 2012 and Toomtong39 2010, Mutter69 2013</td>
<td>Aortic surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 21)</td>
<td>Gelatin 4% (Gelofusine) (n = 21)</td>
<td>No</td>
<td>Ringer’s lactate (n = 21)</td>
</tr>
<tr>
<td>Mittermayr71 2007</td>
<td>Bunn31 2012, Groeneveld55 2011 and Hartog30 2011</td>
<td>Orthopaedic surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 19)</td>
<td>Gelatin 4% (Gelofusine) (n = 21)</td>
<td>No</td>
<td>Ringer’s lactate (n = 21)</td>
</tr>
<tr>
<td>Mukhtar26 2009</td>
<td>Bunn31 2012 and Mutter69 2013</td>
<td>Liver transplant recipients</td>
<td>Albumin5% (n = 20)</td>
<td>HES 6% 130/0.4 (Voluven) (n = 20)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Staikou74 2012</td>
<td>Study retrieved from supplementary search</td>
<td>Abdominal surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 25 vs HES 6% 130/0.42 (n = 24) (Venofundin)</td>
<td>Gelatin 4% (succinyl gelatin) (n = 25)</td>
<td>No</td>
<td>Ringer’s lactate (n = 25)</td>
</tr>
<tr>
<td>Topcu75 2012</td>
<td>Study retrieved from supplementary search</td>
<td>Major orthopaedic surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 25)</td>
<td>Gelatin 4% (succinyl gelatin) (n = 25)</td>
<td>No</td>
<td>Ringer’s lactate (n = 25)</td>
</tr>
<tr>
<td>Volta76 2007</td>
<td>Bunn31 2012 and Hartog30 2011</td>
<td>Major cancer-related abdominal surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 12)</td>
<td>No</td>
<td>Polygeline 4% (n = 12)</td>
<td>Ringer’s lactate (n = 12)</td>
</tr>
<tr>
<td>Wu57 2010</td>
<td>Gattas77 2013</td>
<td>Kidney transplant</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) (n = 38)</td>
<td>Gelatin 4% (succinyl gelatin) (n = 39)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Yang9 2011</td>
<td>Bunn31 2012 and Mutter69 2013</td>
<td>Hepatectomy</td>
<td>Albumin20% (n = 30)</td>
<td>HES 6% 130/0.4 (Voluven) (n = 26)</td>
<td>No</td>
<td>No</td>
<td>Ringer’s lactate (n = 25)</td>
</tr>
<tr>
<td>Yassen et al.58 2011</td>
<td>Bunn31 2012 and Mutter69 2013</td>
<td>Liver transplant recipients</td>
<td>Albumin4% (n = 15)</td>
<td>HES 6% 130/0.4 (Voluven) (n = 30)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Zdolsek78 2011</td>
<td>Gattas77 2013</td>
<td>Orthopaedic surgery</td>
<td>No</td>
<td>HES 6% 130/0.4 (Voluven) vs HES 6% 130/0.4 (Venofundin)</td>
<td>No</td>
<td>Dextran 70</td>
<td>No</td>
</tr>
</tbody>
</table>
Clinical practice guide for the choice of perioperative volume-restoring fluid

Table 7A  Summary of findings and quality of evidence table: albumin vs hydroxyethyl starch (HES) (question 2).

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Patients, n</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinical trials</td>
<td>Albumin</td>
<td>HES</td>
<td>Relative (CI 95%)</td>
<td>Absolute&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortality (up to hospital discharge)</td>
<td>1/50</td>
<td>1/46</td>
<td>RR 1 (0.07-14.9)</td>
<td>0 less per 1000 (from 20 less to 302 more)</td>
</tr>
<tr>
<td>(2):50-56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment of kidney function (RIFLE risk)</td>
<td>2/45</td>
<td>2/56</td>
<td>RR 2 (0.31-12.84)</td>
<td>36 more per 1000 (from 25 less to 423 more)</td>
</tr>
<tr>
<td>(2):50,58</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy (1):56</td>
<td>1/20</td>
<td>1/20</td>
<td>RR 1 (0.07-14.9)</td>
<td>0 less per 1000 (from 47 less to 695 more)</td>
</tr>
<tr>
<td>Intraoperative blood loss (1):50</td>
<td>30</td>
<td>26</td>
<td>-</td>
<td>47 more (from 92.75 less to 186.75 more)</td>
</tr>
<tr>
<td>Blood loss at 24 hours POP (ml) (1):71</td>
<td>19</td>
<td>41</td>
<td>-</td>
<td>203 more (from 7.97 to 398.03 more)</td>
</tr>
<tr>
<td>Blood loss at 72 hours POP (ml) (1):71</td>
<td>19</td>
<td>41</td>
<td>-</td>
<td>228 more (from 49.08 less to 505.08 more)</td>
</tr>
<tr>
<td>Time on ventilation (days) (2):56,71</td>
<td>39</td>
<td>61</td>
<td>-</td>
<td>0.18 less (from 1.42 less to 1.06 more)</td>
</tr>
</tbody>
</table>

Cl: confidence interval; RR: risk ratio.
<sup>*</sup> Assumed risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).
<sup>a</sup> Very wide CI that includes zero.
<sup>b</sup> Incomplete follow-up data.
<sup>c</sup> Blinding unclear.
<sup>d</sup> Very wide CI.

Table 7B  Summary of findings and quality of evidence: modified gelatin vs hydroxyethyl starch (HES) (question 2).

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No. patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinical trials</td>
<td>Modified gelatin</td>
<td>HES</td>
<td>Relative (CI 95%)</td>
<td>Absolute&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortality (at 28 or 30 days) (2):54,55</td>
<td>8/54</td>
<td>3/54</td>
<td>RR 2.39 (0.37-15.28)</td>
<td>77 more per 1000 (from 35 less to 793 more)</td>
</tr>
<tr>
<td>Renal replacement therapy (1):55</td>
<td>1/21</td>
<td>1/21</td>
<td>RR 1 (0.07-14.95)</td>
<td>0 less per 1000 (from 44 less to 664 more)</td>
</tr>
<tr>
<td>Blood loss at 24 hours POP (ml) (4):55,66,72,73</td>
<td>72</td>
<td>71</td>
<td>-</td>
<td>21.47 less (from 68.35 less to 25.41 more)</td>
</tr>
</tbody>
</table>

Cl: confidence interval; RR: risk ratio.
<sup>*</sup> Assumed risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).
<sup>a</sup> Very wide CI that includes zero.
<sup>b</sup> Small sample size, few events.
<sup>c</sup> Blinding unclear.
with colloids, above all in terms of study population heterogeneity.

Improved understanding among clinicians with regard to which fluids should be used and how they should be administered will improve management of hypovolaemia and standardise the indication for and management of fluids.

This review has enabled us to make strong recommendations for some solutions over others in respect of the critical perioperative outcomes of interest (Table S1). The overall quality of the evidence is low due to the high to moderate risk of bias and the imprecision of the findings. The low grade of scientific evidence and the absence of data relating to certain outcomes in these guidelines are due to the scant number of RCTs conducted in surgical patients. In the few studies published, the sample size is small and the results largely inconsistent, in contrast to studies in critically ill patients, which are usually multicentre RCTs with large cohorts.

Only 5 of the 11 studies reviewed evaluated kidney function as an outcome of interest in the comparison of crystalloids with colloids (Table S5). With the exception of Yates et al. with 200 patients, all these studies involved a small sample size. The fluids compared were mainly Ringer’s Lactate, in the case of crystalloids, and HES in the case of colloids. Follow-up was limited to the hospital stay, and serum creatinine levels were used to monitor impairment of kidney function in all studies. Taken together, the studies reviewed found that perioperative kidney function was not significantly impaired, irrespective of the type of fluid administered.

Only 6 of the 16 studies reviewed (246 patients) evaluated kidney function following administration of the different colloids evaluated in these guidelines. Serum creatinine was measured to monitor kidney function, except in Yassen et al., where it was measured on the RIFLE scale. Sample size was small in all studies (<100 patients), and follow-up was limited to the hospital stay. None of the studies reported significant changes in kidney functions among the different colloids evaluated.

As crystalloids are a more cost-effective therapy and have not been shown to be inferior to colloids, they would seem to be the best option for most patients, and are also recommended in fast-track, minimally invasive surgery.

These guidelines have not evaluated the haemodynamic effectiveness of colloid therapy. The expansion capacity of these solutions is well-documented (Table S3), and the correct indication for crystalloids or concurrent crystalloid-colloid therapy will depend on the dose given, the duration of treatment, the speed with which volume must be replaced, and the haemodynamic status and clinical context of the patient. In all events, it is important to note that colloids restore the fluid balance faster, at a lower dosage, and with less risk of tissue oedema than crystalloids. They are indicated for fast volume replacement. However, in perioperative non-cardiac patients they should only be used under the circumstances and at the dose recommended in the summary of characteristics of each product.

Colloids are usually indicated when rapid volume replacement is needed to treat hypovolaemia secondary to haemorrhage, trauma or sepsis, and in patients in whom volume replacement will improve tissue perfusion when crystalloids alone are not sufficient. Clinical parameters and/or goal-directed fluid management monitoring parameters will help quantify replacement. In addition, indications and/or limitations are specific to each type of colloid, and the recommendations given in the summary of product characteristics should be followed.

In the absence of evidence for or against, when colloids are considered necessary or advisable, we suggest choosing a fluid on the basis of its expansion capacity, intravascular half life, the characteristics of the carrier solution, the availability of the product, and the experience of the anaesthesiologist. For the purpose of these guidelines, however, synthetic colloids are recommended over albumin due to the lack of scientific evidence and the expense of albumin therapy. Fig. 2 shows a fluid management algorithm for surgical patients.

In addition to the recommendations given in these guidelines in respect of the questions formulated, the NICE guidelines recommend a number of strategies to improve fluid administration. Among these, they suggest that hospitals should provide the resources needed to facilitate monitoring fluid administration, provide professionals with

<table>
<thead>
<tr>
<th>Table 7C Summary of findings and quality of evidence table: comparison 3: HES 130/0.42 vs HES 130/0.4 (question 2).</th>
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</thead>
<tbody>
<tr>
<td>Quality assessment</td>
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<td>Intraoperative blood loss</td>
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CI: confidence interval.

* Assumed risk is based on the median risk for all control group studies. The corresponding risk (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).

+ Blinding unclear.

- Very wide CI that includes zero.
Hypovolaemic surgical patient

NO

Maintenance fluid management with 102 mL/Kg/h balanced crystalloids
+ volume replacement depending on estimated losses. (a)

YES

Haemodynamically stable patient? (b)

YES

Start volume replacement with balanced crystalloids: 250-500 mL, depending on response.
If not effective, add goal-directed colloids (c) until haemodynamically stable:
• 3rd generation HESa (d): 2-3 mL/Kg bolus
• Modified gelatin: 2-3 mL/Kg bolus
Take measures to control bleeding.

NO

Is patient haemodynamically stable?

YES

Continue crystalloid administration

NO

Consider:
• Repeating colloid dose
• Administering vasopressive drugs
• Administering red blood cells to ensure good O₂ transport

Figure 2  Volume replacement algorithm in non-cardiac surgery.

the training they need in this regard, and audit and review fluid prescribing protocols and patient outcomes. All healthcare professionals involved in the prescription and administration of fluids should understand the physiology of fluids and electrolytes.

Some guidelines accepted by the scientific community²⁵ include recommendations that cannot easily be implemented in clinical practice in Spain. These include reducing preoperative fasting, preoperative administration of carbohydrate-rich liquids to reduce thirst, anxiety and postoperative nausea and vomiting,¹ and reconsidering postoperative fluid management in patients capable of resuming oral intake of liquids.³ The use of mechanical flow regulators (Dosi-Flow®) or electronic devices such as infusion pumps facilitates IV fluid administration in surgical patients.
Conclusion

One of the most important contributions made by these guidelines lies in separating surgical patients from critically ill or septic patients, in whom HES is ruled out. We have also focussed on studies on crystalloids and/or colloids published in Spain over the past 15 years. To simplify decision-making and streamline our recommendations, we have expressly excluded from our analysis any products that are not longer marketed or that have been replaced by more recent formulations, such as dextran, first and second generation HES and polygeline gelatins, which are now only rarely used. Finally, we have adopted the GRADE methodology, which is now considered the gold standard for CPGs.

The main limitations of these guidelines are, firstly, the paucity of evidence available from studies on the critical outcomes of interest in the perioperative context. Secondly, uncertainties persist with regard to dosage, duration of treatment and adverse effects relating to the use of crystalloids and/or colloids in surgical patients. Thirdly, the studies reviewed did not evaluate the clinical condition of the patients, such as heart, respiratory, kidney, and liver failure and neurological dysfunction; these are important factors to be considered in fluid management.

These recommendations can be adopted at no additional expense, and this, coupled with the widespread practice of administering fluids to surgical patients, is a facilitating factor for the implementation of these guidelines.

However, implementation could be hindered by the limited range of fluids available in some hospitals, the lack of solid evidence to justify the introduction of changes in intraoperative fluid management strategies, and the resistance of some clinicians, who attach little importance to the choice of one fluid over another.

Implementation of most of these recommendations will not increase costs, although colloids are more expensive than crystalloids. The guidelines were drafted over a period of 12 months, and should therefore be updated within 4 years of their publication. Meanwhile, if evidence comes to light that significantly modifies the approach to volume replacement in our patients, SEDAR and the working group will issue an alert notice.

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CPG working group

Pablo Alonso, Instituto de Investigación Biomédica Sant Pau. Barcelona. INPECS (Instituto para la Excelencia Clínica y Sanitaria).

Dimelza Osorio, Instituto de Investigación Biomédica Sant Pau. Barcelona. INPECS (Instituto para la Excelencia Clínica y Sanitaria).

Montserrat Ortega Urbanjea, Registered Nurse Hospital Universitario Infanta Leonor, Madrid.

José Manuel Ramírez, Head of General and Digestive Surgery Hospital Clínico Lozano Blesa. Associate professor, University of Zaragoza.

Melchor Javier Ripolles, Specialist in Anaesthesiology and Critical Care Medicine Hospital Universitario Infanta Leonor, Madrid.

Conflict of interests

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.redare.2015.11.001.

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Clinical practice guide for the choice of perioperative volume-restoring fluid

