

FORMAL EXPERT RECOMMENDATIONS



## Guidelines for perioperative haemodynamic optimization<sup>☆</sup>

### Stratégie du remplissage vasculaire périopératoire

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##### Bibliography

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#### I. SUMMARY

The objective of these recommendations is to review perioperative fluid management (FM) practices, which demonstrated benefits for patients, in order to transfer them to daily practice. In surgical patients considered at “high risk”, it is recommended to titrate the intraoperative FM by measuring

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stroke volume (SV), in order to reduce postoperative morbidity, hospital stay, and recovery time of oral feeding for patients undergoing digestive surgery. It is recommended to regularly reassess SV and its increase (or not) in response to a fluid challenge, especially during hemodynamic instability episodes, to ensure that the treatment is appropriate.

During “minor” surgery, it is probably advisable to administer at least 15 mL/kg of crystalloids for shorter procedures and 20 to 30 mL/kg for one to two hour-procedures, in order to reduce the incidence of nausea, vomiting, and the use of antiemetics and postoperative morphine. In children and neonates without associated comorbidity, it is recommended to ensure a supply of hydro-electrolyte and carbohydrate base respecting the “4-2-1” rule, with isotonic saline with 1% glucose in children and infants, and 10% glucose in the newborns. Beyond an age of 10 years and/or a weight of 30–40 kg, paediatric physiological characteristics become less prominent; adult recommendations should then be applied.

## 2. SIMPLIFIED SUMMARY

The administration of fluid through the veins during surgery can change the postoperative outcome of the patient, that is to say the length of hospital stay, and recovery time of oral feeding when the patient undergoes digestive surgery.

In a so-called “high-risk” surgery, it is recommended to guide fluid administration by following the response of the patient’s heart through continuous measurement. During “minor” surgery, the continuous measurement is not necessary, but sufficient volume, however, should be administered.

In the newborn, the focus is on minimum sugar intake. Beyond an age of 10, adult recommendations should be implemented.

## 3. PREAMBLE

### 3.1. Considerations for recommendations

#### 3.1.1. Current knowledge

The administration of intravenous fluids, commonly referred to as “fluid management” (FM), is a daily therapeutic practice in the perioperative setting. The fact that this treatment is regularly indispensable for all patients undergoing a surgical procedure is not disputed by anyone. However, the realization of FM needs to be defined, not only through the nature and quantity of fluids to administer, but also through the ways to achieve it.

Physiologically, FM consists in increasing the “constrained” volume (therefore the mean systemic pressure) and in reducing the resistance to venous return [1]. These two actions have the effect of increasing venous return and thus cardiac output, provided that the cardiovascular system is able to “pump” this increase in volume, that is to say that the two ventricles’ stroke volume is dependent upon filling or “preload”. The ventricles are then called “preload-dependent”. If the main effect of FM is

to increase venous return and thus cardiac output, it is surprising that the flow is rarely monitored in practice by anaesthetists. This has been explained to date partly by the technical difficulties of measuring cardiac output in the operating room.

In the absence of cardiac output measurement, anaesthesiologists have learned to guide FM on other parameters: blood pressure (BP), heart rate (HR), urine output, central venous pressure (CVP), with many limitations repeatedly described and outlined below. Anaesthesiologists have associated to these unreliable parameters their own experience that led to stereotyped patterns of FM. For example, patients with a femoral neck fracture were often considered with a potential heart failure and, therefore, not given fluid. In contrast, patients undergoing abdominal surgery were supposed to have significant losses and received large amounts of fluid. Questioning this “a priori” approach, studies have compared “traditional” fluid management to a fluid management strategy guided on quantitative criteria: stroke volume measurement (SV) or quantification of SV decreases. These studies have demonstrated that “optimizing” SV in patients with femoral neck fracture [2,3] or “reducing” fluid given to high-risk abdominal surgery patients [4,5] could improve their prognosis.

This work confirmed that fluid management can have a measurable impact on patient outcome since it is possible to reduce morbidity by changing practices. These studies also reveal that an empirical approach based on normal hemodynamic parameters measurement (BP, HR) and our own experience, is less efficient than a dynamic approach based on the SV response to a fluid challenge.

HR and BP (systolic [SBP], diastolic [DBP] and mean [MAP]), measured non-invasively, and diuresis (if justified) constitute the “basis” of hemodynamic monitoring in anaesthetized patients. This basis often shows limitations.

The limitations of these hemodynamic variables are well established: changes in BP are multifactorial and do not reflect changes in cardiac output. BP may continue to show “normal” values, even though cardiac output may not allow optimal tissue perfusion. HR can increase without indicating a drop in ventricular preload (due to the patient awakening, or to the increased level of noxious stimulation compared to the level of analgesia). HR can show no increase whereas preload is decreasing (due to the use of a beta-blockers treatment or in a sudden and significant drop in venous return: Bezold-Jarisch reflex). A decrease in urine output may result from opposing hemodynamic mechanisms, from the antidiuretic effect of stress hormones and opioids. Relatively low intraoperative urine output values are not necessarily associated with renal hypoperfusion.

Monitoring CVP (described as a “static” preload parameter) to predict cardiac output dependence to preload (and thus to guide hemodynamic treatment) is a notoriously inadequate invasive approach in adults [6] and in children [7].

Therefore, monitoring conventional hemodynamic variables, especially in high-risk surgery, does not ensure an adequate systemic perfusion (“occult hypovolemia” risk) and

may lead to inappropriate treatment decisions, including excessive and unjustified fluid administration.

Two approaches, less empirical than the former, are currently proposed to guide perioperative fluid management. The first approach is based on volume titration according to stroke volume (SV) measurement. The objective of this strategy is to maximize SV to limit the hypoperfusion risk. The absence of SV increase in response to a fluid challenge shows that the plateau of the cardiovascular function curve has been reached, and fluid administration should be stopped to prevent venous congestion (systemic or pulmonary).

Nearly a dozen controlled clinical trials in different patient populations evaluated the strategy involving SV monitoring (in particular via esophageal Doppler) and fluid challenges (approximately 250 mL of colloid) from the beginning of the anaesthesia, with fluid boluses repeated in case of SV increase, but stopped as soon as SV does not increase. The administration of a new bolus was only possible if SV declined compared to the initial titration maximum value. Compared to a standard fluid management approach, this strategy has helped reduce the incidence of postoperative complications (including at the surgical site), accelerate the recovery of gastrointestinal function in abdominal surgery, and reduce the duration of hospital stay [8].

The second approach uses dynamic indicators of preload dependence to predict the effectiveness of fluid administration: in this case, SV respiratory variations resulting from changes in intrathoracic pressure in ventilated patients. As SV is a determinant of pulse pressure ( $PP = SBP - DBP$ ) or SBP, SV respiratory variations result in changes in PP or SBP. The main conditions for obtaining valid measurements are the invasive blood pressure monitoring, a regular heartbeat and mechanical ventilation with a closed chest and a tidal volume of at least 7 mL/kg. Pulse pressure variation (PPV) above 12–13% during the respiratory cycle predicts an increase in cardiac output in response to fluid (state of “preload responsiveness”), as has been demonstrated in several studies [6]. It was equally demonstrated that SV respiratory variations (SVV) predicted a positive response to fluid, both perioperatively and postoperatively. Values of PPV or SVV below 9% show almost certainly no “preload-responsiveness”. For intermediate PPV values between 9 and 13%, dynamic parameters can be combined with a fluid challenge and SV measurements [9]. Non-invasive preload-responsiveness monitoring can also be obtained by observing the pulse wave measured by photoplethysmography. An automated parameter with demonstrated reliability, the Pleth Variability Index (PVI), is now available [10,11]. It could enable the generalization of preload-responsiveness monitoring in patients under general anaesthesia and mechanical ventilation in minor and moderate risk surgery.

Many monitors, from invasive to non-invasive, are currently available for clinicians and provide “new” parameters (for example SVV or PPV), or new methods of obtaining “traditional” hemodynamic variables (such as cardiac output). Measurement methods may differ from one monitor to another, as well as algorithms for obtaining variables. Results

obtained with the method or parameter of a given manufacturer can not be accepted for all monitors. What has been shown with esophageal Doppler cardiac output measurement can not necessarily be taken for granted with other methods cardiac output monitoring. Similarly, validation of automated PPV or SVV should be specific to each monitor.

In front of any hemodynamic variable, the question of medical relevance must be raised. This last point relates to the basis of the assessment of hemodynamic monitoring relevance: it can be useful if (and only if) it is associated with treatment decisions. The concept of hemodynamic optimization results directly from this principle: it consists in setting hemodynamic goals to implement an individualized hemodynamic therapy (or “goal-directed hemodynamic therapy”), as opposed to a predefined management and a predetermined SV value for a given type of surgery (see introduction). Only rapid-implementation, operator-independent, little to non-invasive, and low cost strategies can be generalized in the future.

From a diagnostic and therapeutic standpoint, systemic hemodynamics and tissue oxygenation are not opposed, but are instead fully complementary. However, questions can arise in clinical practice when tissue oxygenation monitoring (venous oxygen saturation in pulmonary artery catheter [ $SvO_2$ ] or central venous catheter [ $ScvO_2$ ]) coupled with hemodynamic monitoring involve additional costs in terms of time for implementation, monitors, consumables and, potentially, iatrogenic complications. Studies [12] have shown the benefit of perioperative optimization strategies based only on hemodynamic monitoring systems on the one hand, and on the monitoring of tissue oxygenation associated with hemodynamic monitoring on the other hand. But no study compared these two types of strategies together to evaluate the benefit of getting the entire picture. While optimizing blood volume seems reliable only on systemic hemodynamic variables, the use of inotropic agents (unusual in the operating room) or vasopressors (more regularly used) could support an assessment of the adequacy to tissue oxygen demand (blood lactate,  $SvO_2$ ,  $ScvO_2$ ). These decisions are to be taken case by case, for patients and/or interventions at higher risk, with a need to extend monitoring, and therefore this fluid optimization, postoperatively.

### 3.1.2. Recommendations' rationale

References available today and dealing with “Perioperative fluid management strategy” are old (fluid management in the relative or absolute hypovolaemia – Recommendations for clinical practice – SRLF-Sfar; juin 1996 <http://www.sfar.org/article/65/remplissage-vasculaire-au-cours-des-hypovolemies-relatives-ou-absolues-rpc-1997>) while data from recent, important and new studies are now available. Moreover, the application of new monitoring techniques for perioperative fluid management, and the apparent opposition between concepts of “restrictive” versus “liberal” fluid management, make it necessary to revisit this theme in order to propose new formal expert recommendations.

### 3.1.3. Recommendations' objectives

The objective of these recommendations is to review perioperative fluid management practices, which demonstrated benefits for patients, in order to transfer them to daily practice. Implementing a parallel professional practices evaluation (PPE) programme will enable clinicians to use and evaluate these recommendations in their daily practice, in accordance with the French Society of Anaesthesia and Intensive Care (Sfar) and the French College of Anaesthetists (Cfar) common policy to structure and facilitate quality management and integration into continuing professional development (CPD).

### 3.2. Methodology preamble

The methodology used to develop recommendations is the GRADE<sup>®</sup> method. After a quantitative analysis of literature, this method helps determine the quality of evidence individually, and thus provides a confidence level for the quantitative analysis and a recommendation level. The quality of evidence is divided into four categories [13]:

- 1 - high: further research is very unlikely to change confidence in the estimated effect;
- 2 - moderate: further research is likely to change confidence in the estimated effect and may alter the estimated effect itself;
- 3 - low: further research will most likely have an impact on confidence in the estimated effect and will likely alter the estimated effect itself;
- 4 - very low: the estimated effect is very uncertain.

The analysis of evidence quality is performed for each endpoint, then an overall level of evidence is defined based on the quality of evidence for key criteria. The final formulation of recommendations is always binary: either positive or negative and strong or weak:

- strong: “Must do” or “Must not do” (GRADE 1+ or 1–);
- weak: “It is possible to do” or “not to do” (GRADE 2+ and 2–).

The strength of the recommendation is determined by four key factors and validated by experts after a vote, using the Delphi method:

- 1 - estimated effect;
- 2 - the overall level of evidence: in case of high overall level, the recommendation is more likely to be strong;
- 3 - the balance between desirable and undesirable effects: in case of favourable balance, the recommendation is more likely to be strong;
- 4 - values and preferences: in case of uncertainty or variability, the recommendation is more likely to be weak. These values and preferences must be obtained directly with people involved (patient, physician, decision-maker);
- 5 - costs: in case of higher costs or resources utilization, the recommendation is more likely to be weak. In case of significant net savings, the recommendation is more likely to be strong.

In the absence of quantified assessment of the effect, an expert review is proposed based on the grading “GRADE method<sup>®</sup>”.

## 4. RECOMMENDATIONS

### 4.1. Recommendation I

#### 4.1.1. Question

Does fluid management guided by Stroke Volume measurement reduce postoperative morbidity and length of stay?

#### 4.1.2. Recommendations and rationale

- In surgical patients considered at “high risk”, it is recommended to titrate intraoperative volume administration by measuring stroke volume (SV) in order to reduce postoperative morbidity, length of hospital stay and the recovery time of oral feeding for patients undergoing digestive surgery. GRADE 1 +.

Patients at “high risk” means patients who, because of their history or the nature of the procedure, are exposed to increased risk of postoperative complications. Currently, the patient is considered to be “at risk” or not, based on the individual assessment by the anaesthesiologist in charge. The POSSUM score ([http://www.sfar.org/scores/p\\_possum.php](http://www.sfar.org/scores/p_possum.php)) is a tool for quantifying surgical risk [14], but it is not certain that using such a score is necessary to start monitoring SV intraoperatively. “Titration” of the intraoperative volume administration means splitting into  $200 \pm 50$  mL boluses (Fig. 1). The higher the intolerance risk (poor cardiac function, fluid overload already present, poor lung function. . .), the smaller the bolus. In children, SV is titrated with boluses of 10 to 20 mL/kg, depending on the patient and the hemodynamic status.

SV can only increase if the venous return increases. In cases of bleeding (decrease in absolute blood volume) or vasodilation (decrease in effective blood volume, such as during anaesthesia induction) the decrease in blood volume may conflict with increased fluid administration, and as a result no increase in SV is observed. Fluid administration must of course be continued if bleeding is active and threatening, or fluid challenges repeated once the situation stabilizes and could be continued after anaesthesia induction time, when vascular tone is more stable.

There is no study evaluating this strategy (based on increased SV) in case of surgery with haemorrhage. It could increase bleeding at the surgical site. It is up to the anaesthesiologist to assess the individual benefit/risk balance between bleeding and hypoperfusion.

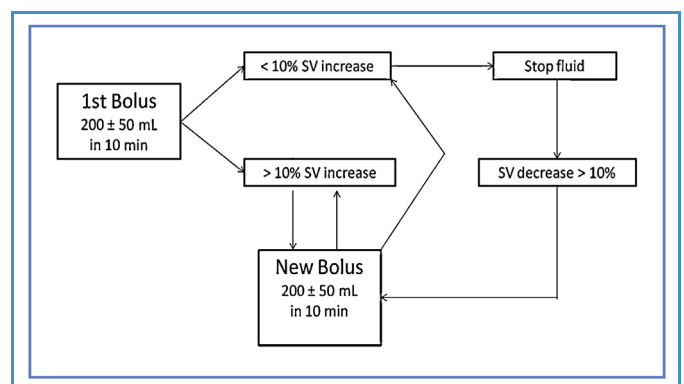


Fig. 1. Guiding Fluid Management with changes in Stroke Volume (SV).

## 4.2. Recommendation 2

### 4.2.1. Question

Should fluid administration be stopped in the absence of an increase in SV?

### 4.2.2. Recommendations and rationale

- It is recommended to stop fluid administration in the absence of increase in SV. GRADE I +. The absence of increase in SV after a fluid challenge indicates that more fluid would be unnecessary or harmful. Stopping fluid administration when SV does not increase avoids congestive complications (systemic/pulmonary). This applies of course if there is no situation of simultaneous decrease in venous return, which would conflict with the effect of fluid administration on SV, not reaching the plateau of the cardiovascular function curve (see recommendation 1).

## 4.3. Recommendation 3

### 4.3.1. Question

Should SV be reassessed regularly?

### 4.3.2. Recommendations and rationale

- It is recommended to regularly reassess SV and its increase (or not) in response to a fluid challenge, especially during hemodynamic instability episodes, to ensure that the treatment is appropriate. GRADE I +

These recommendations are based on studies in which (mostly) fluid administration titration was guided by intraoperative SV measurement obtained by esophageal Doppler [8]. Other monitors for SV, other dynamic parameters of preload-responsiveness and SV variation (PPV, SVV, PVI), have been the subject of several studies, with results also suggesting a benefit in favour of an SV or SV variations-driven optimization, as opposed to an “empirical” approach. The continued use of dynamic parameters (PPV, SVV, PVI) contributes to detecting a “low probability of fluid responsiveness” as the value remains low (< 9%), eliminating the need to test regularly and systematically the response to a fluid challenge.

Although the level of evidence of these other monitors is lower than with esophageal Doppler, there is little doubt that the principle of fluid titration guided with SV is beneficial compared to an empirical approach (sometimes insufficient and sometimes excessive) and improves the prognosis of patients. The other monitors available today should confirm their ability to measure reliably and quickly changes in SV (decrease or increase) or to detect the absence of increase in SV (criterion for stopping fluid administration).

Furthermore, the results have been obtained with decision algorithms (Fig. 1) in which the increase in SV was obtained with colloid boluses (hydroxyethyl starch [HES] or modified fluid gelatine [MFG], between 100 and 250 mL depending on the patient). This fluid optimization was performed most often at the beginning of the procedure. At any time during surgery, a decrease in SV would justify a new titration. The benefits of this

strategy could be related to an improvement of capillary tissue perfusion.

Some older studies using monitoring by pulmonary artery catheter demonstrated benefits of optimizing arterial oxygen delivery in high-risk surgical patients. These studies used more complex algorithms, based on the addition of inotropes and packed red blood cells to fluid, to optimize oxygen delivery.

It is not clear if this more complex and more invasive approach is better than the simple SV optimization described above. If the anaesthesiologist believes that monitoring by pulmonary artery catheter is justified, then it could be used to optimize oxygen delivery and to assess its adequacy to the patient's needs. One could also use a central venous access (catheter equipped with optical fibres in the superior vena cava) to monitor ScvO<sub>2</sub>, which reflects the adequacy of oxygen delivery and oxygen consumption (target ScvO<sub>2</sub> > 73%) and/or lactate (lactate < 2 mmol/L).

## 4.4. Recommendation 4

### 4.4.1. Question

Does the additional administration of crystalloid reduce postoperative nausea and vomiting in patients undergoing minor surgery?

### 4.4.2. Recommendations and rationale

- It is probably advisable to administer 15 to 30 mL/kg of crystalloid in “minor” surgery patients to reduce the incidence of nausea, vomiting and the use of antiemetics. GRADE 2 +

“Minor” surgery means procedures, which last less than two hours and rarely expose patients to post-operative complications that may prolong their hospital stay. Ambulatory surgery falls into this category. This recommendation is the result of studies carried out mostly in women undergoing gynecological surgery or laparoscopic cholecystectomy, for whom the period of fasting was generally greater than or equal to eight hours. Ingestion of clear liquids up to two hours before the procedure was sometimes allowed. Fluid administration was started before induction of anaesthesia or during surgery, reducing by around 35% postoperative nausea and vomiting and the use of anti-emetics.

## 4.5. Recommendation 5

### 4.5.1. Question

Does systematic fluid administration drop the risk of hypotension when installing epidural analgesia in labour patients?

### 4.5.2. Recommendations and rationale

- It is not recommended to use a systematic intravenous fluid administration to reduce the risk of hypotension when installing epidural analgesia in labour patients. GRADE I –

The incidence of hypotension when installing epidural analgesia was 30% in the 1990s. This incidence decreased (about 10%) with the use of lower concentrations of local

anaesthetic combined with fat-soluble opioids, and the use of split initial doses. In addition, the intensity of hypotension is modest with these diluted epidural analgesia solutions. Fluid administration is not effective to prevent or treat hypotension. In addition, low doses of ephedrine (< 15–20 mg) are usually sufficient and significantly improve the utero-placental flow through its betamimetic effect. At these low doses, ephedrine does not generate any significant risk of neonatal acidosis. As a result, ephedrine remains the basic treatment of this complication during labour, in combination with a left lateral decubitus position to reduce aortocaval compression.

#### 4.6. Recommendation 6

##### 4.6.1. Question

Does a systematic crystalloid preloading decrease the risk of hypotension when installing spinal anaesthesia for caesarian section?

##### 4.6.2. Recommendations and rationale

- It is not recommended to perform a crystalloid pre-administration for spinal anaesthesia for caesarian section. GRADE I –

Spinal anaesthesia for caesarian section induces an almost systematic maternal hypotension due to sympathetic upper-body sympathetic block and aortocaval compression caused by the gravid uterus. This hypotension generates maternal nausea and vomiting (or even more serious complications) and above all is potentially harmful to the newborn, because it is associated with a decrease in utero-placental perfusion: it should be prevented and/or treated actively. Numerous studies have clearly demonstrated that prophylactic crystalloid administration or “preloading” (before installing spinal anaesthesia) had no effect on the incidence of hypotension, the amounts of vasoconstrictor necessary to prevent or treat hypotension, and the maintenance of neonatal well-being assessed by the umbilical arterial pH. At high volumes, this strategy can even have a counterproductive effect, in particular by promoting the release of atrial natriuretic peptide, which reduces vascular tone and initiates a maternal natriuresis.

#### 4.7. Recommendation 7

##### 4.7.1. Question

Does a combined administration of fluid and vasoconstrictor reduce the risk of maternal hypotension when installing spinal anaesthesia for caesarian section?

##### 4.7.2. Recommendations and rationale

- To avoid or minimize maternal and foetal risks of very frequent episodes of maternal hypotension after spinal anaesthesia, it is recommended to use a combined administration of crystalloid and vasoconstrictor (phenylephrine may be associated with ephedrine). GRADE I +

Rapid combined administration (fluid management started at the same time as the intrathecal anaesthetic injection) with 1–2 L of crystalloid, is also effective. Sufficient volume must be

infused, especially during the first 5 to 10 min after spinal anaesthesia, during onset of the sympathetic block. There is a correlation between the volume infused during this period and the amount of phenylephrine required to maintain blood pressure. It is an inexpensive, simple practice, it avoids waiting time of “preloading”, and can be offered to the vast majority of patients. “Preloading” with HES is effective. This well documented efficacy consists in reducing the incidence of hypotension, but also its severity. This strategy is widely used in the United States and some European countries. But HES do not yet have authorization in this indication in France and are therefore not yet recommended routinely. However, the summary of product characteristics (SPC) for third generation HES in France allows their targeted use in parturients.

High required ephedrine doses ( $\geq 20$ –30 mg or 50–80 mg) during spinal anaesthesia for caesarian section have an inferior and delayed effect, side effects (arrhythmia, tachycardia, extrasystoles) and their transplacental passage induces foetal acidemia that should be avoided. Phenylephrine has found a prominent place in recent years, with a faster effect over ephedrine, without tachyphylaxis and with a low transplacental passage. It can be used in continuous IV syringe pump (50  $\mu\text{g}/\text{min}$  to be adapted to maintain BP close to baseline, without exceeding 100  $\mu\text{g}/\text{min}$ ) and/or direct intravenous (bolus) injection (50 to 150  $\mu\text{g}$ ). The most severe reflex bradycardia induced by phenylephrine can be controlled by combining small doses of ephedrine ( $\leq 15$  mg).

#### 4.8. Recommendation 8

##### 4.8.1. Question

Does HES administration bring a benefit in preeclampsia?

##### 4.8.2. Recommendations and rationale

- It is not recommended to use a colloid (HES) in a patient with preeclampsia outside of hypovolemic or hemorrhagic shock.

##### Expert review

Fluid management never demonstrated any value in modifying the patient's history of preeclampsia or in limiting the occurrence of complications. In the only randomized study available, fluid was administered daily with a fixed colloid dose, with no hemodynamic response monitoring. In this study, using HES was even associated with an increased rate of caesarian section and a more frequent use of oxygen therapy in newborns. Finally, there is no data promoting the use of albumin in this context.

#### 4.9. Recommendation 9

##### 4.9.1. Question

Is colloid administration an option for patients allergic to a substance other than colloids?

##### 4.9.2. Recommendations and rationale

- It is not recommended to exclude colloids in a patient allergic to a substance other than the colloid itself. *Expert review*

## 4.10. Recommendation 10

### 4.10.1. Question

Is the administration of a different class colloid an option in patients allergic to a given colloid?

### 4.10.2. Recommendations and rationale

- In surgical patients who experienced actual or suspected anaphylaxis due to a colloid (HES or MFG), it is recommended to use a colloid of a different class if necessary. *Expert review*

## 4.11. Recommendation 11

### 4.11.1. Question

Is the administration of HES an option in patients with impaired renal function?

### 4.11.2. Recommendations and rationale

- In the presence of impaired renal function (including septic origin), it is probably advisable to avoid HES. GRADE 2 +

Two studies have demonstrated that perioperative administration of hyperoncotic HES 200/0.5 [15] and 200/0.6 [16] presented a risk for renal function after cardiac surgery, with a threshold dose of 16 mL/kg in the first study. In contrast, several studies have shown no difference in the impact on renal function between the different types of solutions (latest generation HES 130/0.4 versus MFG versus diluted albumin), for volumes inferior to 33 mL/kg used in intraoperative and immediate postoperative period (first day). In a randomized study [17] performed in aortic aneurysm surgery, the average renal function, which was normal preoperatively, was less altered with the use of HES 200/0.6 or HES 130/0.4 than with gelatin. Two randomized, yet smaller studies ( $n = 40$  and  $65$ ), evaluated the effect of HES 130/0.4 (versus albumin [18] or gelatin [19]) on renal function in patients with impaired preoperative renal function, and showed that there was no worsening versus the comparator [18,19].

In another randomized trial, controlled hypotension associated with normovolemic hemodilution performed with a crystalloid altered renal function parameters more than when using HES 130/0.4 [20]. In addition, in a renal transplantation study, in which the donor and recipient were administered HES 130/0.4 or gelatin [21], the recovery of renal function was satisfactory in both groups, and faster with HES.

The recommendation is based primarily on intensive care studies showing the negative effects of HES (including HES 130/0.4) on renal function in patients who presented impaired renal function before treatment and often sepsis. These studies are summarized in several meta-analyses, demonstrating a statistical link between HES and impaired renal function [22–24]. Caution therefore invites to use HES for perioperative fluid management in surgical patients with normal renal function in the limits of the recommended dose of 33 mL/kg. Current data favours only HES 130/0.4 when HES must be used. HES with high molecular weight, high degree of substitution and hyperoncotic HES should be avoided.

## 4.12. Recommendation 12

### 4.12.1. Question

Which kind of fluids should be administered in brain-dead patients in case of kidney transplant?

### 4.12.2. Recommendations and rationale

- It is probably advisable to use crystalloids for Fluid Management in brain-dead kidneys donor. *Expert review*

## 4.13. Recommendation 13

### 4.13.1. Question

Which precautions should be taken with HES administration in case of coagulopathy?

### 4.13.2. Recommendations and rationale

- All volume expansion solutions, including crystalloids, can generate a dilution coagulopathy. In addition, HES have specific effects on hemostasis. It is recommended to comply with the maximum HES doses (33 mL/kg/24 h the first day and 20 mL/kg/24 h the two following days), and not to use in patients with hemostasis disorders. GRADE I +

HES can cause a decrease in factor VIII and von Willebrand, alter fibrinogen and polymerization of the fibrin clot, and reduce the expression of the glycoprotein IIb/IIIa on the surface of activated platelets, thus causing an alteration in their function [25]. These in vitro changes in hemostasis are not found in clinical practice with HES 130/0.4, which have been shown to be associated with a lower transfusion risk than previous generations.

The maximum doses, given in the summary of product characteristics, are justified by the dose-dependent nature of the effects on hemostasis.

Pre-existing hemostasis disorders are a contra-indication of HES as stated in the summary of product characteristics.

## 4.14. Recommendation 14

### 4.14.1. Question

Which solution should be used in patients with brain injury?

### 4.14.2. Recommendations and rationale

- It is recommended not to use hypotonic fluids in brain-injured patients. *Expert review*

## 4.15. Recommendation 15

### 4.15.1. Question

Which fluid management strategy should be used in paediatric patients?

### 4.15.2. Recommendations and rationale

- In children and neonates without associated co-morbidity, it is recommended to ensure a supply of electrolyte and carbohydrate base respecting the “4-2-1” rule, through

isotonic saline with 1% glucose in children and infants, and 10% glucose in the newborns. *Expert review*

The infusion rate should follow the 4-2-1 rule: 4 mL/kg/hour for the first 10 kilos of body weight, adding 2 mL/kg/hour for the following 10 kg, adding 1 mL/kg/hour for the following 10 kg: for example 65 mL/h for a 25 kg child [26]. Losses related to preoperative fasting are added to this base. These losses are calculated as a number of fasting hours and adjusted at 50% during the first hour of surgery and 50% over the following 2 h [27].

In children, it is necessary to monitor natremia and glucose levels during prolonged fasting. In the newborn, glucose levels should be monitored regardless of the duration of fasting. Stopping unnecessary infusions after minor surgery is required.

In paediatrics, it is recommended to use a medical device to control the infusion rate (pump or syringe pump...); otherwise a precision infusion set "metriset" may be used. Flow regulators based on reducing the size of the infusion line (for example Dial-a-Flow<sup>TM</sup>...) should be avoided since they are unreliable in young children.

In the newborn, the choice of solutions for fluid management is not documented. In children and infants, invasive monitoring of static indicators such as PVC or pulmonary artery occlusion pressure do not predict fluid responsiveness and their use is not recommended to titrate fluid management.

In children and infants, only variations of aortic peak velocity (measured by transthoracic echocardiography) can predict fluid responsiveness. Other methods of stroke volume variation measurement (PPV, including PVI) have not shown any value so far. Beyond an age of 10 years and/or a weight of 30–40 kg, paediatric physiological characteristics become less prominent; adult's recommendations should then be applied.

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