

# Perioperative Fluid Therapy for Major Surgery

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The goal of IV fluid administration is to restore and maintain tissue fluid and electrolyte homeostasis and central euolemia, while avoiding salt and water excess. This will in turn facilitate tissue oxygen delivery without causing harm. Achieving optimal IV fluid therapy should improve perioperative outcomes and is a key component in many perioperative guidelines and pathways.<sup>1,2</sup> IV fluids, like other medications, should only be given in well-defined protocols according to individual needs.<sup>3</sup>

There have been numerous studies of fluid and hemodynamic optimization over the past 20 yr. Most of these studies were very small single-center studies, sometimes with conflicting results.<sup>4,5</sup> However, in recent years several large multi-center randomized controlled trials and observational studies using electronic medical records have been published on these topics in major medical journals.<sup>6–12</sup> These efforts have greatly improved the evidence base and are a credit to our specialty.

This article reviews the latest evidence on perioperative IV fluid therapy for major surgery, focusing on the type and volume of fluids, and including suitable criteria to guide such therapy. Although a full review of hemodynamic optimization using advanced monitoring is beyond the scope of this review, it will be briefly covered as the two topics are interrelated.

## Preoperative Fluid Management and Fasting Times

Preoperative fluid management strategies aim to avoid the patient arriving in the operating room in a hypovolemic or dehydrated state. Multiple international guidelines, including those from the American Society of Anesthesiologists, allow unrestricted intake of clear fluids up to 2 h before elective surgery.<sup>13,14</sup> The guidelines are based on a meta-analysis of randomized trials that reports a lower risk of aspiration (gastric volume less than 25 ml and pH greater than 2.5) when clear liquids are given 2 to 4 h before a procedure compared with fasting overnight.<sup>13</sup> We continually produce saliva along with endogenous gastric secretions, and therefore after an 8-hr “fast,” roughly 500 to 1,250 ml of fluid is added naturally to the stomach.<sup>15</sup> This acidic fluid is diluted by whatever we drink. In other words, allowing unrestricted access to clear fluids up to 2 h before surgery is likely to improve

patient comfort and safety as it reduces thirst and hunger, does not increase gastric volumes, and reduces the acidity of gastric contents. The most significant factor determining gastric emptying of fluids is its caloric content.<sup>16</sup>

Some preoperative fasting guidelines have changed the wording from “allow” to “encourage” clear fluids up to 2 h before surgery<sup>14</sup>; this appears to be safe, but requires further scientific validation. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, carbohydrate-rich nutritional drinks, clear tea, and black coffee. Interestingly, some pediatric centers and adult day-case units have removed any restriction on clear fluids before surgery<sup>17,18</sup>—that is, to allow patients to drink clear fluids right up until arrival in the operating suite. This appears to be safe, but it does require further large-scale research before such a practice can be recommended.

Many Enhanced Recovery After Surgery pathways also include the oral intake of a maltodextrin carbohydrate drink 2 h before surgery, which has a probable metabolic benefit of reducing insulin resistance in addition to improving patient satisfaction and reducing thirst, hunger, and postoperative nausea and vomiting.<sup>1</sup> The metabolic benefits center around creating a fed, anabolic state before surgery.<sup>19</sup> This in turn reduces hyperglycemia postoperatively, which is a risk factor for nosocomial infection.

## Assessing Fluid Responsiveness

Preoperative IV fluids are needed for most emergency surgery and sometimes for elective surgery, because of extra fluid losses and typically longer fasting times. Accurate assessment of an individual patient’s fluid status can be difficult, but a careful history and physical examination supported by simple bedside tests should be sufficient to gauge fluid responsiveness in most cases<sup>20</sup>—that is, circumstances when additional IV fluid will increase cardiac output and so improve tissue perfusion.

Additional IV fluids should only be given to patients with a predicted positive fluid response. This is best evaluated by taking advantage of the steep portion of the Frank–Starling curve, whereby small increases in preload will increase stroke volume (SV). The volume needed for a fluid challenge is typically 250 ml of a colloid, but crystalloids

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are probably equally effective and even smaller volumes (100 ml) can be used.<sup>21</sup> Fluid responsiveness is typically defined as a 10% or greater increase in SV. Positive pressure mechanical ventilation induces a cyclic reduction in left ventricular preload mainly through a decrease in venous return, with this effect more pronounced in hypovolemia. Hence, changes in preload during the respiratory cycle will result in variations of SV and pulse pressure.<sup>22</sup> Lung recruitment maneuvers can induce similar effects on preload to predict fluid responsiveness.<sup>23</sup> The resultant SV variations and pulse pressure variations are estimated by analysis of the arterial waveform.

A systematic review of 50 studies (2,260 patients) evaluating techniques to assess adult patients with refractory hypotension or signs of organ hypoperfusion found that half of all the patients studied were fluid-responsive. Findings on physical examination were not predictive of fluid responsiveness, but a low central venous pressure (less than 8 mm Hg) was associated with fluid responsiveness (positive likelihood ratio, 2.6 [95% CI, 1.4 to 4.6]; pooled specificity, 76%). Respiratory variation in vena cava diameter measured by ultrasound (distensibility index greater than 15%) had similar benefits. But perhaps the most compelling, based in part on the simplicity and ready availability, was augmentation of blood pressure or SV *after* passive leg raising, which reliably predicted fluid responsiveness (positive likelihood ratio, 11 [95% CI, 7.6 to 17]; pooled specificity, 92%). Those with a negative passive leg raising test were very unlikely to be fluid-responsive (negative likelihood ratio, 0.13 [95% CI, 0.07 to 0.22]; pooled sensitivity, 88%).<sup>20</sup> Central venous pressure monitoring is unlikely to be helpful in those who are hemodynamically stable.<sup>24</sup> The passive leg raising maneuver transfers about 300 ml of venous blood into the right atrium, mimicking a fluid bolus.<sup>25</sup> Ideally, passive leg raising should be done along with advanced monitoring of fluid responsiveness using a pulse contour device or esophageal Doppler to better reflect changes in SV; if unavailable, the effect on systolic blood pressure can be used. The passive leg raising maneuver can also be used during and after surgery to ascertain intravascular volume status at those times (table 1).

## Intraoperative Fluid Management

Optimal intraoperative IV fluid management is important, with both under- and overresuscitation associated with harm.<sup>26</sup> There are two main bodies of literature providing guidance on this subject: those studies comparing restrictive *versus* liberal fluid regimens, and those studies comparing goal-directed fluid therapy using advanced hemodynamic monitoring *versus* control. We consider each in turn.

### Liberal *versus* Restrictive Fluids

Over the past 20 yr, the “sweet spot” for optimal IV fluid administration has shifted with evolving surgical techniques, patient pathways such as Enhanced Recovery After Surgery, evolving literature, and popular trends. Minimally invasive (and robotic) approaches have reduced evaporative fluid loss and gross anatomic manipulation during many operations. Historically, large amounts of IV fluids were given during and after surgery, particularly for abdominal surgery, because of perceived third space and insensible losses.<sup>27</sup> Approximately 15 yr ago, Brandstrup *et al.*<sup>28</sup> showed that the liberal use of IV fluid in abdominal surgery was associated with a significant increase in complications compared with a restrictive approach. Patients in the liberal group were given just more than 6 l of fluid on the day of surgery, and had a postoperative weight gain (reflecting tissue edema) of close to 4 kg. In contrast, patients in the restrictive group were given just under 4 l of fluid on the day of surgery and had a maximal weight gain of approximately 1 kg.

Over the years, the term “restrictive fluid management” has gained popularity, particularly with the widespread adoption of Enhanced Recovery After Surgery pathways, with recent guidelines advocating a restrictive approach.<sup>2</sup> However, the amount of fluid given with restrictive fluid management has gradually decreased, and the term “zero balance” was introduced to describe a restrictive regimen aiming to avoid postoperative fluid retention (as indicated by weight gain).<sup>5,29</sup>

There has been ongoing concern that an excessively restrictive fluid approach could be associated with an increase in adverse events, particularly acute kidney injury.

**Table 1.** Recommendations for Perioperative Fluid Therapy in Major Surgery

1. Minimize preoperative fasting times. Encourage unrestricted intake of clear fluids until 2 h before elective surgery.<sup>13,14</sup>
2. Passive leg raising followed by measurement of blood pressure or (ideally) stroke volume is a useful test for predicting fluid responsiveness in hemodynamically unstable adults throughout the perioperative period.<sup>20</sup>
3. Aim for a moderately liberal IV fluid regimen with an overall positive fluid balance of 1–2 l at the end of surgery.<sup>30</sup> For major abdominal surgery, an average crystalloid fluid infusion rate of 10–12 ml · kg<sup>-1</sup> · h<sup>-1</sup> during surgery, and 1.5 ml · kg<sup>-1</sup> · h<sup>-1</sup> in the 24-h postoperative period should be used.
4. Ensure that intravascular volume status is optimized before adding vasopressor therapy.
5. Use an advanced hemodynamic monitor to measure fluid responsiveness in higher-risk patients having major surgery.
6. A goal-directed hemodynamic strategy may perform better if a patient's IV fluid status is first optimized, and if needed, introduce a vasopressor or inotrope.<sup>37,38</sup>
7. It is unclear whether crystalloid or colloid should be primarily used for perioperative fluid resuscitation.
8. Aim for early transition from IV to oral fluid therapy after surgery (usually within 24 h).<sup>1,2</sup>

IV, intravenous.

This concern was supported by two large observational studies that showed worse outcomes,<sup>6,7</sup> including acute kidney injury,<sup>7</sup> with patients who had the most restrictive fluid regimen. This background, along with uncertainty as to how best to treat intraoperative hypotension, formed the rationale for the multicenter Restrictive *versus* Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF) trial, which compared a restrictive IV fluid regimen (designed to achieve zero balance during surgery and the 24-hour postoperative period) with a liberal fluid regimen.<sup>8</sup>

One of the key results of RELIEF was that patients in the restrictive fluid group had a significantly higher risk of acute kidney injury than those in the liberal fluid group (8.6% *vs.* 5%,  $P < 0.001$ ). The median duration of surgery was 3.3 h in both groups, and the restrictive regimen led to a median of 1.7 l of fluid administered intraoperatively, compared with 3 l with the liberal regimen. These findings suggest that many perioperative physicians may have become too restrictive if using a zero-balance approach, and that a moderately liberal fluid regimen aiming for an overall positive fluid balance of 1 to 2 l at the end of surgery should be recommended<sup>30</sup>—that is, an overall crystalloid fluid infusion rate of 10 to 12 ml · kg<sup>-1</sup> · h<sup>-1</sup> during major abdominal surgery, and 1.5 ml · kg<sup>-1</sup> · h<sup>-1</sup> in the 24-h postoperative period. Other types of major surgery not associated with such extensive fluid shifts are unlikely to need as much intraoperative IV fluid administration to achieve a moderate positive fluid balance at the end of surgery.

Enhanced Recovery After Surgery guidelines recommend early transition from IV to oral fluid therapy after surgery, and we see no reason to modify this.<sup>1,2</sup> In many patients recovering from major surgery, the transition from IV to oral fluids can occur within 24 h.<sup>2,31</sup> Early transition to oral intake can help preserve gastrointestinal motility, thus limiting ongoing fluid loss into the bowel.<sup>32</sup>

### Advanced Hemodynamic Monitoring *versus* Control

There is a significant body of literature advocating individualized goal-directed fluid or hemodynamic therapy using advanced monitors to optimize SV and/or reduce SV variation.<sup>33</sup> The physiologic rationale for optimizing SV on an individual patient basis is that there is no established definition of normovolemia and that blood pressure is widely accepted as having significant limitations as a monitor of intravascular volume status. In 1928, Jarisch is quoted as saying, “It is a source of regret that the measurement of flow [*i.e.*, SV] is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure.”<sup>34</sup> In reality, organs need both, but a physiologic response to hypovolemia is to maintain pressure at the expense of flow (especially splanchnic flow) to maintain perfusion of vital organs.<sup>35</sup> Thus, measuring blood flow can theoretically alert physicians to hypovolemia earlier than pressure monitoring can.

There have been many small studies showing benefit of fluid administration guided by advanced monitoring (goal-directed therapy) over the last 20 yr.<sup>33</sup> However, within Enhanced Recovery After Surgery pathways, some of this additional benefit seems to have been diminished by overall improvements in patient care, so that the more recent small, single-center studies were unable to show significant reductions in length of stay or complications with implementation of goal-directed therapy pathways.<sup>36</sup>

The first large, multicenter trial of goal-directed therapy, OPTIMISE, reported fewer complications with goal-directed therapy, but this finding did not reach statistical significance ( $P = 0.07$ ).<sup>11</sup> An updated meta-analysis (38 trials) accompanied this publication, showing that goal-directed therapy was associated with a lower risk of complications (31.5% *vs.* 41.6%; relative risk, 0.77 [95% CI, 0.71 to 0.83]) and mortality (8.3% *vs.* 10.3%; relative risk, 0.86 [95% CI, 0.74 to 1.00]). More recently, the multicenter FEDORA trial showed a significant reduction in complications and length of stay with implementation of a goal-directed hemodynamic strategy.<sup>37</sup> The algorithm that was used in the study first optimized fluid status to maximize stroke volume, and then added a vasopressor or inotrope as needed to maintain mean blood pressure greater than 65 mm Hg and cardiac index greater than 2.5 l · min<sup>-2</sup>. There is increasing evidence that even a short duration of hypotension intraoperatively, defined as a mean blood pressure less than 65 mm Hg, is associated with myocardial and kidney injury.<sup>12</sup> The INPRESS trial, recently published in *Journal of the American Medical Association*,<sup>38</sup> was one of the first interventional studies aimed at individualizing perioperative blood pressure management. The study showed a reduction in complications in the intervention group that first had their fluid status optimized, followed by inclusion of a vasopressor to maintain blood pressure within 10% of normal.<sup>38</sup>

### Practical Considerations

How do we reconcile the two different areas of research—determining the optimal infusion rate or volume of IV fluids, and how best to identify an individual patient’s need for extra boluses of IV fluid—into practical considerations for perioperative fluid management? Each patient should have a fluid management plan, in line with local department guidelines and then individualized to the patient.<sup>1</sup> The selection, timing, and doses of IV fluids should be evaluated as carefully as they are for any other medication, with the aim of maximizing efficacy and minimizing iatrogenic toxicity. Institutions without any departmental fluid guidelines have been shown to have tremendous variation in how fluid is administered.<sup>39</sup>

Intraoperative fluid requirements can be considered in two categories: maintenance therapy and volume therapy. Maintenance therapy is needed to cover insensible losses and urine output (from the beginning of preoperative fasting), and current evidence suggests that maintenance fluid

requirements should be met with a basal crystalloid infusion rate of 1 to 1.5 ml · kg<sup>-1</sup> · h<sup>-1</sup>; more is needed for major surgeries associated with large fluid shifts. Volume therapy refers to the administration of boluses of IV fluid (typically 250 ml) to assess volume responsiveness and treat objective evidence of hypovolemia, with the goal of improving intravascular volume and oxygen delivery.<sup>31</sup>

In general terms, based largely on the results of the RELIEF trial,<sup>8</sup> the overall goal of fluid management for major surgery should now be considered to be a moderately liberal approach, with a positive fluid balance at the end of surgery of 1 to 2 l. This can typically be achieved with overall intraoperative fluid requirements of approximately 3 l for a 3- to 4-h procedure, but will obviously vary depending on blood loss and the surgical procedure and duration. Less extensive surgery, such as day-surgery procedures and laparoscopic cholecystectomy, require less IV fluid, with most needing no more than 1 to 2 l of crystalloid in total (*i.e.*, net fluid balance, 0 to 1 l).<sup>40</sup>

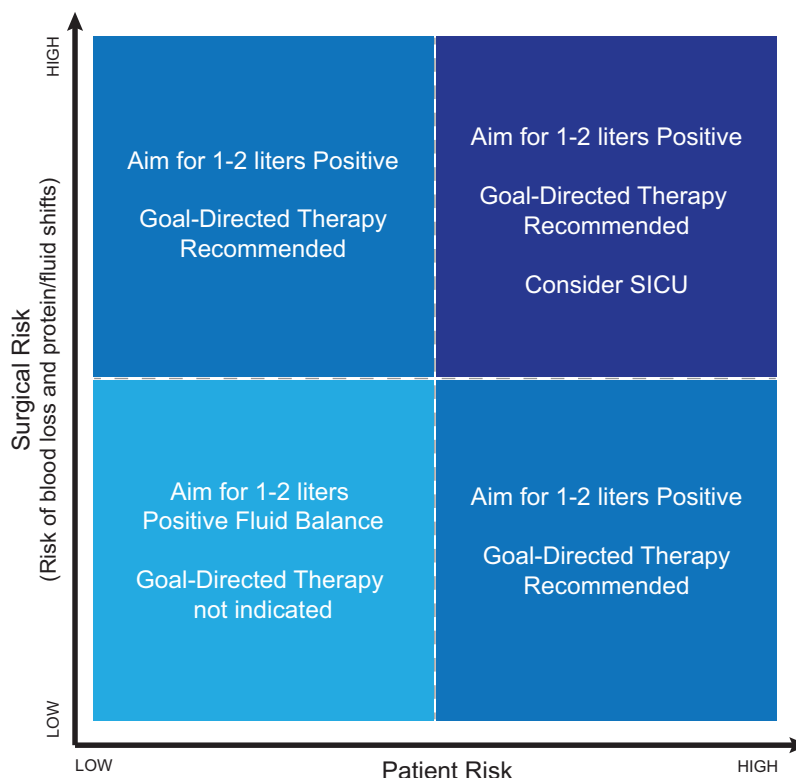
The timing of fluid administration is also important to avoid episodes of hypovolemia and hypotension. There is a significant body of evidence to show that the timing of fluid administration and management of high-risk patients when the “sweet spot” for fluid administration is

harder to be consistently maintained can be aided by using goal-directed therapy with advanced monitoring of SV or SV variation.<sup>33,36,41</sup> We therefore suggest a risk-adapted matrix for fluid and hemodynamic management, an update from previous versions following results of the RELIEF trial (fig. 1). If a patient is volume-optimized (not fluid responsive) and remains hypotensive (mean blood pressure greater than 65 mm Hg and possibly higher in patients with preexisting hypertension), a vasopressor infusion should be considered.

### Postoperative Phase

Early oral intake is encouraged postoperatively in all patients whenever possible (fig. 2).<sup>2</sup> In many Enhanced Recovery After Surgery pathways, this enables IV fluid administration to be discontinued, sometimes even before the patient leaves the postanesthesia care unit. In fact, Enhanced Recovery After Surgery pathways highlight the need to minimize postoperative continuation of intravascular lines (IV and arterial), nasogastric tube, urinary catheter, and drain tubes, which further limit a patient’s ability to ambulate.

However, the results of the RELIEF study suggest that we should be cautious in patients recovering from major abdominal who are not able to obtain adequate oral intake.<sup>8</sup>



**Fig. 1.** A suggested matrix for consideration of goal-directed therapy and postoperative admission to a surgical intensive care unit (SICU) in major surgery.



In RELIEF, the restrictive group were administered a postoperative IV crystalloid infusion at an average rate of  $0.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  (calculated with a maximum weight of 100 kg) or up to 80 ml/h for at least 24 h, and the liberal group were administered a crystalloid infusion of  $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . There was a lower urine output and more oliguria during and after surgery, and a near doubling of the incidence of postoperative acute kidney injury, in the restrictive group. Therefore, although we don't know the overall contribution of the postoperative part of the protocol in RELIEF, it seems prudent to continue titrated IV fluid therapy in patients with impaired oral intake.

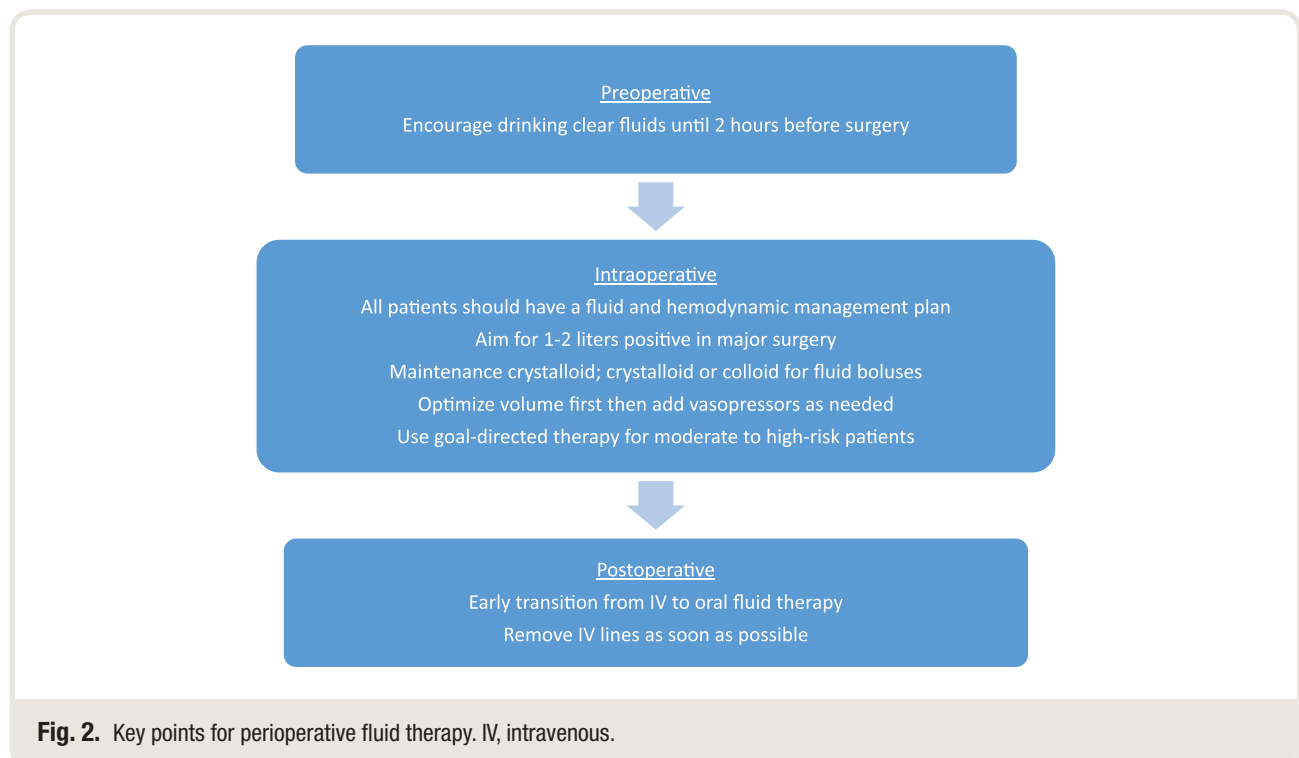
### What IV Fluid Should Be Used?

The primary maintenance IV fluid for all major surgery should be an isotonic, balanced crystalloid.<sup>2,31</sup>—that is, an IV fluid that more closely aligns with plasma electrolytes and acid–base equilibrium (e.g., lactated Ringer's, Hartmann's, PlasmaLyte A [Baxter Healthcare Corp., USA], Normosol [Hospira Inc., USA]). Over the last few years, there has been increasing observational evidence suggesting that 0.9% saline should not be used during major surgery, because it is associated with hyperchloremia, metabolic acidosis, and acute kidney injury.<sup>9,10</sup> This led to the two recent trials comparing the use of balanced crystalloids and 0.9% saline in critically and noncritically ill patients. The studies used a pragmatic, cluster-randomized, multiple-crossover design in which participating emergency departments and intensive care units were

randomly assigned to use either balanced crystalloid or 0.9% saline in all patients for a month for each month of the trial.<sup>42,43</sup> Both trials showed a lower incidence of acute kidney injury with balanced solutions, and in critically ill patients a lower incidence of death and new-onset renal replacement therapy. We therefore suggest that maintenance fluid therapy should be achieved with an isotonic, balanced crystalloid solution at a rate of 1 to  $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ .

The choice of fluid for volume therapy remains controversial. There is a physiologic rationale for using colloids for volume therapy because they tend to remain in the intravascular space longer,<sup>44</sup> and in animal models of hemorrhage, resuscitation with colloids has also been shown to be significantly faster than with crystalloids.<sup>45</sup> Indeed, most goal-directed therapy studies have used colloid boluses for volume therapy.<sup>33</sup> However, there are only a handful of small studies that have compared crystalloids and colloids for volume therapy during major surgery. Although these studies have all demonstrated lower IV fluid volumes with colloid-based resuscitation (ratio around 1.6:1), most have not demonstrated any meaningful difference in clinical outcomes.<sup>46–48</sup> However, a recent study did show a reduction in postoperative complications when using colloids for resuscitation in a closed-loop system.<sup>49</sup> Nevertheless, the crystalloid *versus* colloid debate continues and is one of the unresolved questions in perioperative fluid management.

In major hemorrhage scenarios, there is often a necessity to quickly restore circulating blood volume, and this is probably best accomplished with red cell, plasma, and other



blood product transfusion. Institutions should have a massive transfusion protocol in place.<sup>50</sup>

## Conclusions

One of the most common practices and areas of responsibility for anesthesiologists is perioperative IV fluid therapy. Variations in practice and clinical uncertainty have dogged this seemingly straightforward issue. Thankfully, many high-quality clinical studies have recently been published to guide our practice. Knowledge of these, and thoughtful inclusion of key findings in contemporary practice, should improve the care of patients undergoing major surgery. Perioperative patients with hypotension or evidence of inadequate tissue perfusion should first be fluid-optimized before implementation of vasopressor therapy.

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## Competing Interests

Dr. Miller reports receiving research funding and serving as a consultant for Edwards Lifesciences (Irvine, California) and for Cheetah Medical (Newton Center, Massachusetts). Dr. Myles was the principal investigator of the RELIEF trial.

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