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What's new in volume therapy in the intensive care unit?

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The administration of intravenous fluid to critically ill patients is one of the most common but also one of the most fiercely debated interventions in intensive care medicine. During the past decade, a number of important studies have been published which provide clinicians with improved knowledge regarding the timing, the type and the amount of fluid they should give to their critically ill patients. However, despite the fact that many thousands of patients have been enrolled in these trials of alternative fluid strategies, consensus remains elusive and practice is widely variable.

Early adequate resuscitation of patients in shock followed by a restrictive strategy may be associated with better outcomes. Colloids such as modern hydroxyethyl starch are more effective than crystalloids in early resuscitation of patients in shock, and are safe when administered during surgery. However, these colloids may not be beneficial later in the course of intensive care treatment and should best be avoided in intensive care patients who have a high risk of developing acute kidney injury. Albumin has no clear benefit over saline and is associated with increased mortality in neurotrauma patients. Balanced fluids reduce the risk of hyperchloraemic acidosis and possibly kidney injury. The use of hypertonic fluids in patients with sepsis and acute lung injury warrants further investigation and should be considered experimental at this stage.

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Fluid therapy impacts relevant patient-related outcomes. Clinicians should adopt an individualized strategy based on the clinical scenario and best available evidence. One size does not fit all.

Introduction

The administration of intravenous fluids is one of the most common interventions in the intensive care environment. There is ongoing discussion regarding the benefits and disadvantages of infusion therapy. While the application of fluid during shock leads to circulatory stabilization and can therefore be life-saving, fluid overload is associated with oedema development and worse outcomes. This single measure, which may be vital in the early phase of shock, also has the potential to harm the patient. Interestingly, despite the worldwide use of various infusion solutions, no concrete evidence has been provided that infusion therapy per se leads to a lower mortality among seriously ill patients. This may be related to the complexity of treatment in an intrinsically heterogeneous group of critically ill patients, as well as to considerable differences that exist in the clinical use of infusion therapy.

In the past 10 years, an impressive amount of new research has been conducted and published in the field of fluid resuscitation in critically ill patients. To put this statement into context, combining the search terms fluid resuscitation and intensive care in PubMed, and limiting the search to papers published between 2003 and 2013, an impressive number of 1238 publications can be identified. The results of some of the largest and most rigorously conducted studies in the history of intensive care medicine have provided clinicians with useful answers but also with many more questions and, as a result, a significant level of debate and controversy still remains. In the following review, an attempt will be made to put some of these new data into clinical context. Some of the more specific topics (e.g., balanced solutions, fluids in trauma and fluids in anaesthesia) will be discussed elsewhere in this edition of Best Practice and Research, Clinical Anaesthesiology, and readers will be referred to other sections where appropriate.

Timing of fluid administration

It is important to differentiate between fluid substitution and volume substitution in intensive care patients [1]. Different indications warrant different strategies and fluid choices, a distinction that has not always been appreciated sufficiently in the design of fluid studies.

The now generally accepted concept based on some interventional but mostly on observational studies and expert opinion is that resuscitation of patients in shock needs to be timely and adequate. Often, this part of the resuscitation will have occurred in the pre-intensive care unit (ICU) setting, for example, in the emergency department.

Early goal-directed treatment (EGDT) of septic shock has been incorporated into the surviving sepsis guidelines [2,3]. However, the findings of the original Rivers et al. study were not replicated in the recently published randomized trial of Protocol-based Care for Early Septic Shock (ProCESS) [4]. In this study, 1341 patients with septic shock were randomly assigned to protocol-based EGDT, protocol-based standard therapy or to usual care. Resuscitation strategies differed significantly with respect to the monitoring of central venous pressure and oxygen and the use of intravenous fluids, vasopressors, inotropes and blood transfusions. No differences in 90 day mortality, 1-year mortality or the need for organ support were observed.

Other large studies including the Australasian Resuscitation in Sepsis Evaluation randomized controlled trial (ARISE) and the Protocolised Management in Sepsis trial (ProMISe) are currently under way and should provide us with more definitive data in this specific area of fluid resuscitation [5]. An important challenge the investigators of these three important trials face is the likelihood that the

baseline (the control group or the current standard care) has significantly changed since Rivers' study and the subsequent publication of the Surviving Sepsis guidelines.

In the next phase of their treatment, once patients have been stabilized, it has been shown that a restrictive fluid resuscitation strategy may improve outcome. Fluid-overloading our patients or causing hypervolaemia in the post-resuscitation phase indeed is likely to be harmful. For example, in septic shock patients, a positive fluid balance and elevated central venous pressure are associated with an increased mortality [6]. Patients with a less positive fluid balance tend to have a better outcome, but this may simply be because these patients are less severely ill and therefore tolerate this strategy, rather than this being a direct effect of an intervention targeted at a negative fluid balance. For example, both early adequate resuscitation and restrictive ongoing resuscitation independently improved outcome in a retrospective cohort of patients with septic shock and acute lung injury [7].

Rather alarmingly, we as clinicians do not appear to be particularly good at determining whether a patient will benefit from the administration of a fluid bolus, especially when basing this decision on clinical examination and static haemodynamic indices such as central venous pressure. In studies summarized in a review by Michard et al., in 2002, around 50% of patients who received a fluid bolus based on clinical signs and static haemodynamic measurements turned out to be not fluid responsive [8]. In other words, the decision-making process to administer a fluid bolus was not much better than tossing a coin. Another important conclusion based on that observation is that we may be causing harm in about 50% of our patients who are given a fluid bolus in error.

Fluid resuscitation therefore should ideally be based on dynamic indices of fluid responsiveness, such as stroke volume or pulse pressure variation, but the presence of arrhythmias and spontaneous breathing activity and the use of lung protective ventilation may preclude these indices from being used [9]. The easy-to-perform passive leg-raising test has been well validated in situations where these dynamic indices cannot be used reliably in the intensive care environment [10].

Type of fluid

Currently, there is no evidence from randomized controlled trials that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma or burns or following surgery [11]. The same statement applies to patients with sepsis [12]. However, it is important to emphasize that ‘colloid’ is not a homogeneous group of fluids. Significant differences exist between different colloids with regard to haemodynamic effects, side effects and pharmacokinetics. It is also important to note that in intensive care studies, significant heterogeneity exists regarding the primary diagnoses, patients' responses to the underlying illness and its treatment in a context of complex ICU management. Because of this heterogeneity, a treatment may be beneficial to one subgroup of patients while being harmful to another subgroup [13]. This effect may not become apparent in a study, regardless of the sample size, unless these subgroups have been well recognized and defined a priori. This is a common but only recently fully appreciated problem, which complicates intensive care research in many more ways than previously realized.

Great regional variation exists regarding the use of resuscitation fluids in intensive care patients [14]. In this observational study, colloids were administered to more patients and during more resuscitation episodes than were crystalloids. The country in which the patient was being treated was a major determinant of fluid choice even after adjusting for patient and prescriber characteristics. Some of these variations may be explained by pharmaco-economic considerations rather than proven clinical benefits. For example, the use of human albumin in Australia is significantly higher than in many other parts of the world, despite the fact that a large trial conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), comparing albumin with normal saline in intensive care patients, showed no benefit of albumin over saline [15]. Albumin is delivered free of charge to Australian hospitals, whereas prescribing albumin in most Western European countries is relatively costly and in the latter situation probably not justified from a pharmaco-economic perspective given the lack of relevant clinical benefit.

As mentioned before, it is also pertinent to differentiate the indications for fluid administration into volume therapy and fluid therapy. In the first occasion, fast and efficient volume replacement is paramount and solutions that can reach predefined targets in less time may improve outcome, in the same way that earlier administration of antibiotics improves outcome in patients with septic shock [16]. Resuscitation with modern starch solutions has been shown to provide more effective results in the golden hours of resuscitation (also see the contribution by James (this issue), principles of resuscitation in trauma and neurotrauma) [17,18]. The colloid controversy will be discussed in more detail later.

Hypertonic fluids

Small-volume hypertonic fluid resuscitation can provide effective and rapid intravascular volume resuscitation. Recent data suggest that hypertonic fluid administration in sepsis may have beneficial effects on the global circulation and the cardiac function that exceed simple intravascular volume expansion. In addition, hypertonic resuscitation may exert specific effects on inflammatory pathways and endothelial function that may be beneficial in patients with septic shock and acute lung injury [19,20]. Whether these observations translate into improved clinical outcomes has not yet been established, and much more work is required before this experimental approach is to be implemented into clinical practice [21].

Albumin

The use of albumin showed a worldwide decline following the publication of the much-debated meta-analysis in the late 1990s suggesting possible but substantial harm associated with the use of albumin in intensive care patients [22]. Since then and as mentioned earlier, the large Saline versus Albumin Fluid Evaluation (SAFE) study conducted in almost 7000 patients showed no benefit of albumin over saline, but also no harm [15]. Some relevant subgroup analyses deserve to be mentioned. In the a priori defined subgroup of septic patients, albumin administration was associated with a non-significant trend towards improved survival [23]. This finding was not consistent with results from a large observational study, where albumin use in septic patients was associated with an increase in mortality [24]. Based on the observations from SAFE, a number of prospective randomized trials have been conducted to shed more light on this topic. A large Italian multicentre study compared the outcomes of 1818 patients in severe sepsis or septic shock who were randomized to open-label albumin and crystalloid solution versus crystalloid solution alone [25]. No differences were found between the two groups with respect to mortality after 28 or 90 days. French investigators conducted a multicentre study in 794 patients with septic shock and reported similar findings, with no differences in relevant outcome parameters including mortality and sequential organ failure assessment scores (NCT00327704, personal communication).

The SAFE study also suggested that patients with traumatic brain injury resuscitated with albumin had a higher mortality rate than those resuscitated with saline. This was confirmed in a post hoc study of critically ill patients with traumatic brain injury, showing indeed that fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline, and therefore should better be avoided in this group of patients [26].

Hydroxyethyl starch

Hydroxyethyl starches (HESs) are the most widely used artificial colloid solutions in the world [14]. It is important to emphasize that HES is not a homogeneous group of fluids [27]. Significant differences exist between different HES formulations, not only regarding molecular weight and the degree of molar substitution with hydroxyl–ethyl groups but also with respect to the source material (corn or potato) and the carrier solution. These differences may translate into different haemodynamic effects, side effects, pharmacokinetics and thus clinical outcomes.

There have been concerns that colloids may increase the risk of acute kidney injury (AKI) in sepsis patients. However, studies that showed this possible increase in AKI had confounding factors including the use of older HES products and hyperoncotic solutions, dehydration, excessive HES dose (overdosing) and baseline imbalances [28,29]. In a large European prospective observational study, no association was found between HES administration and adverse renal events [30]. Because of this controversy, a number of large-scale trials were undertaken to evaluate the efficacy and safety of commonly used HES preparations.

In a Scandinavian multicentre study (6S study) with a blinded, parallel group study design, 804 patients with severe sepsis were randomized to fluid resuscitation with potato-derived 6% HES 130/0.42 (Tetraspan 6%, B. Braun) or Ringer's acetate in a dosage of up to 33 ml/kg ideal body weight/day [31]. Patients assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal replacement therapy, as compared with those receiving Ringer's acetate. There was no difference in the rate of end-stage kidney failure (dialysis dependence) at 90 days. Intriguingly, based on reported values of central venous pressure, central venous oxygen saturation and lactate concentration, it appears that most patients were haemodynamically stable at the time of inclusion in the study. Trial fluid was used when ICU clinicians judged that volume expansion was needed in the ICU and was not based on protocolled assessment of the haemodynamic situation. The criteria for renal replacement therapy were also not included in the protocol. Of note, both arms of the study received different fluid volumes before randomization was carried out. The HES group was infused with more volume and, on average, one additional blood product than the Ringer's acetate group.

In the largest intensive care trial to date, the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), 7000 ICU patients were randomly assigned to receive either 6% maize-based 130/0.4HES (Voluven, Fresenius Kabi) in 0.9% sodium chloride or 0.9% sodium chloride (saline, Fresenius Kabi) for all fluid resuscitation until ICU discharge, death or 90 days after randomization [32]. There was no significant difference in 90 day mortality (primary outcome) between the two groups. There was also no difference in mortality between treatment arms in any of the predefined subgroups including the subgroup of patients with sepsis. Of note, this sepsis subgroup consisted of almost 2000 patients, which is significantly more than the total number of patients in the 6S study. There are several possible explanations why CHEST did not find an increase in mortality in patients with sepsis when treated with HES as opposed to 6S. These include the fact that the mortality of patients with sepsis was lower in CHEST compared with 6S, and the use of a different HES product with possibly different biological and pharmacokinetic effects [27].

CHEST also showed that renal replacement therapy was used more frequently in the HES group (7%) than in the saline group (6%) ($p = 0.04$; $p = 0.05$ after adjustment for covariates). The duration of treatment with kidney replacement therapy was comparable in both groups (HES 5.6 days vs. saline 5.5 days, $p = 0.86$). Interestingly, renal risk (RIFLE-R) and renal injury (RIFLE–I) were observed more frequently in the saline group than in the HES group. There was no statistical difference in kidney failure (RIFLE-F) between the groups and there was no loss of kidney function or end-stage renal disease (RIFLE-L and RIFLE-E).

Meybohm et al. re-evaluated 11 available colloid versus crystalloid studies conducted between 2008 and 2013 including CHEST and 6S, using six criteria to construct a definition of 'presumably correct indication': short time interval from shock to randomization (<6 h), restricted use for initial volume resuscitation, use of any consistent algorithm for haemodynamic stabilization, reproducible indicators of hypovolaemia, maximum dose of HES and exclusion of patients with pre-existing renal failure or renal replacement therapy [33]. They concluded that the studies showed significant heterogeneity with regard to these criteria. Therefore, the studies do not answer the question whether or not HES may be beneficial or harmful when it is limited to immediate haemodynamic stabilization.

The only study to compare colloids and crystalloids in patients who required resuscitation for shock was the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) study [34]. CRISTAL was a pragmatic trial comparing crystalloids with colloids for adults in acute hypovolemic shock at 57 ICUs across three continents. The study was terminated based on a predefined stopping rule after 2857 of the planned 3010 patients had been enrolled. Patients treated with

colloids received significantly less fluid than those treated with crystalloids. Mortality did not differ at 28 days (359 deaths (25.4%) among 1414 colloid-treated patients vs. 390 deaths (27.0%) among 1443 crystalloid-treated patients); however, the colloid group had more days free of vasopressor therapy and mechanical ventilation at 7 and 28 days and had significantly lower mortality at 90 days (30.7% of colloid group vs. 34.2% of crystalloids group). Other secondary outcomes, including measures of renal function, did not differ and there were no significant treatments by strata effects. Some possible study limitations need to be mentioned. The study only compared the two classes (colloid or crystalloid) of fluids, and not any specific agent. Lack of blinding leaves the study open to potential bias, although during the entire period of ICU fluid management was nicely separated into crystalloids or colloids.

This study shows that colloids have a possible advantage over crystalloids when used for initial haemodynamic stabilization of critically ill patients. This advantage has also been shown in patients with penetrating trauma [17]. Resuscitation of trauma patients will be discussed in more detail elsewhere in this edition of Best Practice and Research, Clinical Anaesthesiology by M. James.

Finally, it is essential to emphasize that the results of the aforementioned intensive care studies comparing colloids and crystalloids should not be extrapolated to other clinical scenarios. Importantly, the safety of tetrastarches during surgery has been confirmed in a recent meta-analysis of 59 studies that randomly allocated 4529 patients with 2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator [35]. There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy, increased blood loss, allogeneic erythrocyte transfusion or increased mortality (odds ratio for HES mortality = 0.51 (0.24–1.05), $p = 0.079$). In another meta-analysis of 1230 patients in 17 studies, the effect of maize-derived HES 130/0.4 on renal function in surgical patients was investigated [36]. No differences were found regarding peak creatinine levels or need for renal replacement therapy.

Balanced fluids

Balanced fluids are crystalloid and colloid solutions with a more physiologically balanced electrolyte formulation, such as Hartmann's solution, PlasmaLyte and Hextend. The use of these fluids for volume resuscitation can prevent the development of hyperchloraemic acidosis, an electrolyte abnormality often encountered with the use of 'normal' saline even after relatively low-volume application [37]. In experimental sepsis models, balanced fluids are associated with a better short-term survival [38]. In a prospective, open-label, sequential period pilot study of 1533 critically ill patients, the implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and the use of renal replacement therapy [39]. Magder discusses this topic in more detail elsewhere in this edition of Best Practice and Research, Clinical Anaesthesiology.

Conclusions

Fluid resuscitation is one of the cornerstones of intensive care treatment. The past decade has provided exciting new research findings to help clinicians decide when, what and how much fluid they should give to their critically ill patients. Early adequate resuscitation followed by a restrictive strategy may be associated with better outcomes. Although much controversy remains regarding the type of fluid that should be used, clinicians should adopt an individualized strategy based on the clinical scenario. Colloids such as modern hydroxyethyl starch are more effective than crystalloids in the early resuscitation of patients in shock and are safe when administered during surgery. However, these colloids may not be beneficial later in the course of intensive care treatment. Albumin has no clear benefit over saline and is associated with increased mortality in neurotrauma patients. The use of hypertonic fluids in patients with sepsis warrants further investigation and should be considered experimental at this stage.

Conflict of interest statement

None.

Practice points

- Fluid strategy for intensive care patients should be individualized and based on the clinical scenario.
- The timing, the type and the amount of fluid given to critically ill patients have an impact on relevant patient outcomes.
- Based on best available but not high-quality evidence, early adequate resuscitation followed by a restrictive fluid strategy provides the best outcomes for critically ill patients.
- There is no clear role for the use of albumin as resuscitation fluid in ICU patients. This is based on evidence of lack of benefit (as opposed to lack of evidence of benefit), as well as because of an unfavourable pharmaco-economical balance.
- The use of colloids for resuscitation of patients in shock provides more timely shock reversal and could possibly improve outcomes.
- Modern HES can be safely used during surgery, but should be avoided in intensive care patients who have already been resuscitated, specifically in patients who have a high risk of developing acute kidney injury.

Research agenda

- More work is needed to understand the different effects and side effects (including renal effects) of different modern HES products, specifically between potato-based and maize-based products.
- Future volume therapy studies should take into account well-defined criteria for correct indications for fluid administration, including the use of a consistent algorithm for haemodynamic stabilization and reproducible indicators of hypovolaemia.
- We need to investigate further whether the use of hypertonic fluids improves relevant patient-related outcomes in sepsis and acute lung injury.
- There is an ongoing need for relevant basic research into the physiology of fluid administration (e.g., bolus vs. continuous infusion vs. no fluid resuscitation), as well as into the in vitro and in vivo effects of different compositions of fluids (e.g., chloride level, tonicity and strong ion difference).

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