Are we close to the ideal intravenous fluid?

N. MacDonald¹ and R. M. Pearse²,*

¹Department of Perioperative and Pain Medicine, Barts Health NHS Trust, London E1 1BB, UK and ²Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK

*Corresponding author. E-mail: r.pearse@qmul.ac.uk

Abstract

The approach to i.v. fluid therapy for hypovolaemia may significantly influence outcomes for patients who experience a systemic inflammatory response after sepsis, trauma, or major surgery. Currently, there is no single i.v. fluid agent that meets all the criteria for the ideal treatment for hypovolaemia. The physician must choose the best available agent(s) for each patient, and then decide when and how much to administer. Findings from large randomized trials suggest that some colloid-based fluids, particularly starch-based colloids, may be harmful in some situations, but it is unclear whether they should be withdrawn from use completely. Meanwhile, crystalloid fluids, such as saline 0.9% and Ringer’s lactate, are more frequently used, but debate continues over which preparation is preferable. Perhaps most importantly, it remains unclear how to select the optimal dose of fluid in different patients and different clinical scenarios. There is good reason to believe that both inadequate and excessive i.v. fluid administration may lead to poor outcomes, including increased risk of infection and organ dysfunction, for hypovolaemic patients. In this review, we summarize the current knowledge on this topic and identify some key pitfalls and some areas of agreed best practice.

Key words: colloids; Crystalloid solutions; fluid therapy

During the past 100 yr, i.v. fluid therapy has become an integral part of perioperative care, and yet the question of the ‘ideal’ fluid remains elusive. For both the intensive care physician and the anaesthetist, i.v. fluid resuscitation is considered a core skill, which we expect to deliver safely and effectively. Despite this, the evidence base for fluid therapy remains a hotly debated topic. In this review, we explore the reasons behind these debates and provide an objective summary of the current knowledge on this topic. The scope of this review includes manufactured i.v. fluid solutions used for fluid resuscitation. With the exception of albumin solution, we do not cover the use of blood products or the use of i.v. fluids for specialized indications, such as traumatic brain injury.

Historical context

In 1831, William O’Shaughnessy wrote to The Lancet to report some fascinating and remarkably detailed observations on the blood drawn from cholera sufferers.¹ His account included a detailed description of reduction in water content, low bicarbonate concentrations, and uraemia ‘... where suppression of urine has been a marked symptom’. A few months later, Thomas Latta achieved some success with the i.v. administration of a solution of saline and sodium bicarbonate to moribund cholera victims in Sunderland. In another detailed letter to The Lancet, he provided a fascinating account of the clinical response to fluid therapy.² We can trace the history of fluid therapy as modern medicine itself has evolved. Hartmann used a modified Ringer’s solution to rehydrate children suffering from gastroenteritis in the 1930s, and by World War II the benefits of i.v. fluid in the treatment of haemorrhagic shock were widely acknowledged.³ Four million bottles of i.v. fluid solutions were purchased by the US Army during this period.⁴ The improvement in outcome associated with the use of fluid therapy during surgery for combat casualties was subsequently reported during the Korean War.⁵ Improvement in patient outcomes remains the
driving factor in fluid therapy research, which continues to highlight the importance of choosing the optimal type and dose of fluid for each individual patient.

**Relevant physiology**

It is important to separate fluid therapy into fluid maintenance and fluid resuscitation (or volume replacement). This is helpful because there is comparatively little debate about maintenance fluid therapy. The daily requirements for water and electrolytes are well described and easily delivered either enterally or intravenously. It is usually best to view replacement of fluid deficits after prolonged preoperative fasting as part of the maintenance fluid strategy, by calculating water and electrolyte needs based on body mass and the time since last intake. Most controversies around fluid therapy centre on the replacement of hypovolaemia or significant fluid losses (i.e. fluid resuscitation). Each doctor’s approach to fluid resuscitation is heavily influenced by their beliefs about the pathophysiology of the acute disease states characterized by significant fluid loss and the pharmacokinetics and pharmacodynamics of the fluid agents used to replace this loss. The major causes of hypovolaemia are dehydration, haemorrhage, sepsis, and the systemic inflammatory response to other acute disease, such as trauma or pancreatitis. The pathophysiology of the main categories of hypovolaemia is summarized in Table 1. The immediate purpose of fluid resuscitation is quickly to replace circulating volume to restore organ perfusion. However, the heterogeneity of acute illness results in wide variation in the precise nature and volume of fluid lost, from whole blood in acute haemorrhage to almost pure water in some forms of gastroenteritis. Fluid resuscitation is further complicated by the presence or absence of continued fluid loss and the associated mechanism. In the event of dehydration, this may be simple to treat, whereas continued bleeding and the need for haemorrhage control may greatly complicate resuscitation for victims of trauma.

**Concepts and misconceptions in the pathophysiology of hypovolaemia**

**Fluid compartments and the pharmacokinetics of i.v. fluid**

The intravascular half-life of i.v. fluid is thought to vary depending on the pharmacokinetic and pharmacodynamic properties of the fluid. All fluids will redistribute throughout the body eventually, but longer intravascular half-lives may make effective fluid resuscitation easier. Dextrose solutions are thought to remain in the circulation for only a very short period because the small amount of sugar is rapidly metabolized, leaving free water to diffuse throughout the fluid compartments. Thus, although dextrose 5% and similar solutions may be suitable as part of a calculated maintenance fluid regimen, they are of limited value in fluid resuscitation, where maintaining the intravascular volume is important. The sodium, chloride, and other electrolyte content in isotonic fluids is believed to help retain water in the circulation, resulting in a volume expansion effect lasting between 20 and 100 min depending on the concentration and quantity of fluid. In the case of colloid solutions, expansion effects of 2–5 h have been quoted. However, it is important to understand that much of this teaching is based on theoretical principles or the effects of fluids on healthy volunteers. The actions of i.v. fluids may differ widely between patients and disease states, or the differential effects of solutions may be much less than previously thought. It is essential to balance theoretical benefits of any given fluid against what we know about potential harm. Important examples include the risk of coagulopathy and nephrotoxicity associated with hydroxyethyl starch solutions, and the endocrine effects of total

<table>
<thead>
<tr>
<th>Table 1 Summary of principal causes of hypovolaemia, current understanding of pathophysiology, and treatment</th>
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<tr>
<td><strong>Cause of hypovolaemia</strong></td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Sepsis</td>
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<tr>
<td>Systemic inflammatory response</td>
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</tbody>
</table>
Body sodium and chloride excess associated with hypertonic crystalloids, such as saline 0.9%.\textsuperscript{15}

**Stress response to injury and surgery**

The stress response to surgery and trauma is an evolutionary response to injury that involves a complex interaction of biochemical and humoral mediators, including vasopressin and the renin-angiotensin system.\textsuperscript{16, 17} In the initial response, these combine to ensure the retention of fluid and electrolytes with reduced urine output. This can be understood by recognizing the need to recover from injury before being able to search for water and food. This response varies between individuals and may be less pronounced with minimally invasive surgical techniques, where the volume of tissue injury is less. Maintenance fluid and electrolyte requirements will be reduced after major surgery, and this is one important reason why patients are vulnerable to fluid and electrolyte overload in the early postoperative period.\textsuperscript{18} Monitoring of urine output is an important tool, but we must recognize that the healthy normal output is reduced during and after surgery. In patients with healthy kidneys, a urine output of 0.5 ml kg\textsuperscript{-1} h\textsuperscript{-1} should not cause concern in the context of carefully monitored fluid and electrolyte balance. Fluid prescriptions thoughtfully tailored to individual patients, and reviewed by experienced doctors on a daily basis, will reduce harm.

**Third space loss and capillary leak**

For many years, anaesthetists were taught that large volumes of fluid leaked into the extracellular space during surgery. This so called ‘third space’ loss was thought to be a widespread cause of hypovolaemia.\textsuperscript{19} However, detailed calculations have shown that these and other insensible fluid losses, such as evaporation from exposed viscera, were significantly overestimated.\textsuperscript{19} The consequent administration of large volumes of i.v. fluid resulted in accumulation of fluid in the interstitial space (tissue oedema), which may have resulted in worse patient outcomes. It now seems likely that the observed fluid losses were attributable to increased capillary permeability caused by the systemic inflammatory response to surgery. Importantly, this inflammatory response, and the associated fluid loss from the circulation, are likely to vary from patient to patient, especially in major body cavity surgery. For many procedures, the inflammatory response will be mild and will not result in a significant fluid deficit. However, these patients will still require replacement of fluid deficits because of preoperative fasting, ongoing fluid maintenance, and replacement of any estimated blood loss. Confusion around the indication for fluid is a common cause of suboptimal fluid therapy, because the clinician is unclear what the successful treatment end point should be.

**Endothelial glycocalyx**

The discovery of the endothelial glycocalyx demonstrated that fluid movement in the human vascular system is much more complex than Starling’s original description of fluid dynamics across blood vessel walls.\textsuperscript{20} The glycocalyx consists of glycoproteins bound to the vascular luminal surface of the endothelium, providing a semi-permeable membrane between circulating blood and the cell surface.\textsuperscript{21} The glycocalyx has several important functions, especially in the initiation of tissue inflammation, but it also plays a key role in the regulation of vascular permeability. In health, the glycocalyx functions as a barrier to large molecules, but in illness the glycocalyx can be severely compromised, particularly by active inflammatory states including sepsis, trauma, and surgery. When damaged, the passage of fluid and larger molecules is not regulated, and fluid is lost from the microcirculation.\textsuperscript{22, 23}

**Theoretical properties of the ideal fluid**

The concept of the ‘ideal’ fluid is a popular topic for anaesthesia teaching and examinations. The acute illness will determine the nature of the fluid lost, from whole blood to almost pure water. Thus, the ideal fluid will also vary from patient to patient, a fact not well understood by doctors who seek a one-size-fits-all formulation for fluid therapy. The ideal resuscitation fluid should remain within the intravascular space for several hours. The chemical composition should be similar to that of extracellular fluid, and any constituents should be readily metabolized and excreted by the body. The fluid must be safe, sterile, and not prone to cause allergic reactions, organ toxicity, or other side effects. From a practical perspective, we may also want the fluid to be easy to transport and store, easy to administer, and modestly priced. The reader will appreciate that no such fluid yet exists.

The fluids that are used in perioperative care are commonly classified into crystalloids and colloids. Crystalloids can further be categorized into hypertonic, hypotonic, and isotonic (or balanced) fluids. Saline 0.9% (also termed normal saline) is the most commonly used hypertonic solution. Hypotonic solutions, such as dextrose 5% and saline 0.45%, are mostly appropriate for maintenance rather than resuscitation. The fluid developed by Hartmann from Ringer’s solution can be termed isotonic or ‘balanced’, and many commercially available fluids are based on this formulation. Although these fluids are closest to the physiological norm, none is identical to plasma. Colloids consist of large molecules dispersed in a crystalloid solvent. The first colloid to be used in perioperative care was albumin solution fractionated from autologous blood. The high oncotic pressure of colloid molecules is thought to ensure that the fluid remains in the intravascular space for longer periods, providing more effective resuscitation with smaller fluid volumes. In blinded studies, clinicians do indeed prescribe smaller volumes of colloid solution when compared with crystalloids.\textsuperscript{21, 22} However, if the endothelial glycocalyx is disrupted by an acute inflammatory response, the intravascular half-life may not be much greater than that of crystalloid solutions. There are many different colloid solutions, but succinylated gelatins, hydroxyethyl starches, and human albumin solution account for the great majority of colloid prescriptions. Table 2 summarizes the more commonly used fluids and their composition.

**Controversies: choosing the correct type of fluid for resuscitation**

**Crystalloid solutions**

Crystalloids have traditionally been categorized as hypertonic, isotonic, and hypotonic solutions to contrast their composition with that of plasma. Most hypertonic solutions in common use have a slightly higher osmotic load than plasma, with the exception of hypertonic saline solutions used in neurocritical care to control elevated intracranial pressure. Hartmann’s and similar balanced solutions are widely used in anaesthesia and critical care, although saline 0.9% is also popular in many countries. The choice of saline 0.9% is debated by many because the high concentrations of sodium and chloride (154 mmol litre\textsuperscript{-1})
### Table 2 Commonly used fluid solutions. Note that use of different solutions varies widely between countries

<table>
<thead>
<tr>
<th>Fluid solution</th>
<th>Category</th>
<th>Chemical constituents</th>
<th>Common uses</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringer’s lactate/</td>
<td>Isotonic crystalloid</td>
<td>Na⁺ 130 mmol litre⁻¹</td>
<td>Used as both resuscitation and maintenance fluid</td>
<td>Composition can vary slightly between different commercial products. Lactate is metabolized to bicarbonate</td>
</tr>
<tr>
<td>Hartmann’s solution</td>
<td></td>
<td>Cl⁻ 109 mmol litre⁻¹</td>
<td></td>
<td>Aims to mimic ‘normal physiology’ as much as possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactate 28 mmol litre⁻¹</td>
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<td></td>
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<td></td>
<td></td>
<td>K⁺ 4 mmol litre⁻¹</td>
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<td></td>
<td></td>
<td>Ca²⁺ 2 mmol litre⁻¹</td>
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<tr>
<td></td>
<td></td>
<td>Na⁺ 140 mmol litre⁻¹</td>
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<td></td>
<td></td>
<td>Cl⁻ 98 mmol litre⁻¹</td>
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<tr>
<td></td>
<td></td>
<td>Acetate 27 mmol litre⁻¹</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Gluconate 23 mmol litre⁻¹</td>
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<tr>
<td></td>
<td></td>
<td>Mg²⁺ 1.5 mmol litre⁻¹</td>
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<td></td>
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<tr>
<td>Plasmalyte</td>
<td>Isotonic crystalloid</td>
<td>Na⁺ 154 mmol litre⁻¹</td>
<td>Used as both resuscitation and maintenance fluid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cl⁻ 154 mmol litre⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal saline</td>
<td>Hypertonic crystalloid</td>
<td>Na⁺ 154 mmol litre⁻¹</td>
<td>Still commonly used as a resuscitation fluid.</td>
<td>Concerns about development of metabolic acidosis with continued use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cl⁻ 154 mmol litre⁻¹</td>
<td>Being superseded in some areas by more ‘physiological’ solutions</td>
<td></td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>Hypotonic crystalloid</td>
<td>Dextrose 50 g litre⁻¹</td>
<td>Part of maintenance regimen. Used to rehydrate whole-body water loss</td>
<td>Overuse can lead to hyponatraemia</td>
</tr>
<tr>
<td>Dextrose 5% in saline 0.45%</td>
<td>Hypertonic crystalloid</td>
<td>Na⁺ 77 mmol litre⁻¹</td>
<td>Part of maintenance regimen. Used to replace carbohydrates and electrolytes</td>
<td>Various strengths of dextrose in various strengths of saline are available</td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>Starch-based colloid</td>
<td>Na⁺ 154 mmol litre⁻¹</td>
<td>Resuscitation fluid</td>
<td>No longer licensed for use in critically ill patients in many countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cl⁻ 154 mmol litre⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatin</td>
<td>Gelatin-based colloid</td>
<td>Na⁺ 151 mmol litre⁻¹</td>
<td>Resuscitation fluid</td>
<td>Composition varies between products. Move towards carrier fluid being more physiological. Anaphylaxis rate appears to be less than thought</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cl⁻ 103 mmol litre⁻¹</td>
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<td>K⁺ 4 mmol litre⁻¹</td>
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<td>Ca²⁺ 1 mmol litre⁻¹</td>
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<td></td>
<td></td>
<td>Mg²⁺ 1 mmol litre⁻¹</td>
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<td></td>
<td></td>
<td>Acetate 24 mmol litre⁻¹</td>
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<tr>
<td></td>
<td></td>
<td>Gelatin 60 g litre⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human albumin 5%</td>
<td>Derived blood product</td>
<td>Albumin 50 g litre⁻¹</td>
<td>Resuscitation fluid in specific circumstances</td>
<td>Varying compositions available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Na⁺ 145 mmol litre⁻¹</td>
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lead to salt overload and hyperchlaemic acidosis. This may also occur less frequently with any solution containing supraphysiological doses of electrolytes, including several popular colloid solutions. However, at present there is only circumstantial evidence that this phenomenon leads to permanent harm.

**Colloids**

Many different i.v. colloid solutions, with a diverse range of properties, have been developed for clinical practice. However, most of these have fallen from use. Human albumin solution, hydroxyethyl starch, and succinylated gelatins are the only types of colloid solutions still in widespread use, and their clinical value is hotly debated. The CHEST and 6S trials have provided very high-quality data on the effects of hydroxyethyl starch in critically ill patients. Both trials included two active treatment arms comparing starch solutions with crystalloids, it being unethical to withhold fluid resuscitation as a ‘control’ therapy. Taken together, the findings of these trials suggest that starch solutions are associated with an excess rate of acute kidney injury requiring renal replacement therapy, which may lead to a higher mortality rate. In the USA, hydroxyethyl starch solutions are no longer licensed for use in critically ill patients and those with renal dysfunction, whereas they have been completely withdrawn in the UK. However, the European Medicines Agency has permitted ongoing use of these agents to treat haemorrhage in surgical patients and victims of major trauma. A systematic review did not identify any excess mortality associated with hydroxyethyl starch solutions in surgical patients, but did not suggest benefit either. Multicentre trials are planned to confirm the safety of these solutions to treat...
haemorrhage in surgical and trauma patients, but many clinicians are sceptical of this strategy. Succinylated gelatins are not available in all countries because of data suggesting a high incidence of anaphylaxis. However, in one recent major trial of goal-directed haemodynamic therapy there were no reported instances of anaphylaxis despite widespread use of these solutions within the trial. We are not aware of any recent major studies specifically evaluating gelatin solutions, but given the general concern about harm from colloid solutions, there may be limited equipoise for the pragmatic trials needed to confirm safety and effectiveness.

**Chronic disease**
As the population ages, the incidence of co-morbidity in the population is increasing. This manifests in a patient population with not only more advanced cardiac and kidney disease but also an increase in baseline cognitive dysfunction and frailty scores. Currently, there is not a clear consensus on the best fluid therapy for the patient with multiple co-morbidities who is at risk of more than one organ dysfunction. For these patients, it is important that a patient-specific fluid strategy is decided, agreed upon, and followed by all members of the team responsible for the patient’s perioperative care.

**Restrictive vs liberal fluid management formulae**
The stress response to surgery, trauma, or critical illness will result in salt and water retention. Such patients should therefore receive lower doses of maintenance fluid during the period of this response. Anecdotal evidence suggests that most patients receive more fluid than they need. A ‘restrictive’ approach to fluid therapy is therefore an attractive concept. There is an extensive literature comparing restrictive and liberal fluid regimens during and after surgery, but with inconsistent findings. Much of this apparent contradiction can be explained by differences in the fluid algorithms used. Regimens described as restrictive in one trial will meet the definition of liberal in another. Most algorithms were developed from expert opinion and not experimental observation, but the opinions of experts may be prejudicial and often vary widely. The major limitation of current restrictive fluid algorithms is that they combine fluid maintenance and resuscitation into a single algorithm based on body mass. The prescription of maintenance fluid is very simple and should indeed be determined by body mass (Table 3). However, the optimal dose of resuscitation fluid will have a weak relationship with body mass and should primarily be determined by physiology. Nonetheless, the concept of a restrictive approach to fluid therapy is valuable, and UK guidelines on postoperative fluid maintenance therapy promote this approach.

**Controversies: choosing the correct dose in fluid resuscitation**

**Routine or usual care**
Although we may debate at length the choice of resuscitation fluid, the differences in outcomes achieved with the commonly used agents are often modest. In large trials, relative risk reductions of between 10 and 20% are considered important, as are absolute risk reductions as small as 1%. Indeed, the purpose of large, simple trials is to detect these small but important differences in outcomes between alternative treatments. At a global level, the cumulative patient benefit of implementing such evidence is reflected in a gradual and sustained decrease in control group mortality in major trials. However, such evidence must be seen in the context of the huge variations in volumes of fluid administered. Clinical trials frequently demonstrate wide variations in the volume of fluid resuscitation between patients, and there is evidence of differences at an institutional level that is hard to explain on the basis of casemix alone. These differences are the likely dominant factor in the profile of side-effects experienced by individual patients. Not all side-effects of resuscitation fluids are dose related, but most are. If the difference in routine practice of two doctors results in one giving 50% more fluid than the other, the patients in their care are likely to experience important differences in harm that outweigh any differences in the types of fluids used. Nonetheless, even differences in outcomes between clinicians will be hard to identify in daily practice because they in turn are much smaller than the variation between patients. The absence of clear guidance on fluid dose in drug formularies is notable. Our community must accept that the variations in the routine practice of fluid therapy cannot all be appropriate, and some will be associated with harm.

**Cardiac output-guided fluid or ‘goal-directed therapy’ algorithms**
One possible solution to the challenge of finding the optimal dose of resuscitation fluid is the use of cardiac output monitoring to guide the administration of i.v. fluid and inotropic drugs as part of a haemodynamic therapy algorithm. Many terms have been used to describe this technique, including goal-directed therapy, fluid optimization, and flow-directed therapy. This therapeutic approach has been shown to modify inflammatory pathways and to improve tissue perfusion and oxygenation. Importantly, modern cardiac output-guided fluid algorithms do not apply an absolute haemodynamic end point that must be attained regardless of the circumstances. Instead, they use haemodynamic monitoring to inform whether a fluid bolus has achieved a physiological response. This information can then be used to predict more accurately whether further fluid resuscitation will be beneficial. The use of algorithms guided by cardiac output monitoring has been recommended in a report commissioned by the Centers for Medicare and Medicaid Services in the USA and by the National Institute for Health and Care Excellence (NICE) in the UK. However, the majority of the evidence base consists of small trials, and this is insufficient to resolve controversies regarding potential harm associated with fluid excess, myocardial injury, and invasive
forms of monitoring. More recently, the findings of the largest trial did not confirm the clinical benefit of this approach, which may have related to a lack of statistical power, but this trial did provide important evidence that this treatment approach is safe. It seems likely that cardiac output-guided fluid therapy will offer most benefit to patients with fluid deficits that are hard to estimate. This might explain the stronger signals of benefit in major gut surgery, whereas the evidence for efficacy in vascular surgery is much weaker.

**Haemodynamic end points**

Several haemodynamic end points have been used in attempts to optimize fluid delivery objectively. Before the pulmonary artery catheter (PAC), end points such as urine output, peripheral perfusion, and capillary refill time had all been suggested. In addition to the variation in clinician interpretation, the varying physiological responses to insults such as surgery, trauma, and sepsis make these variables unreliable to guide fluid therapy, although they can be used as a fall back in the absence of more objective parameters. Central venous pressure (CVP), when available, was commonly used to guide fluid therapy in hospital, but research has demonstrated that neither CVP nor changes in CVP accurately predict fluid responsiveness. Central venous pressure is no longer first line in fluid therapy guidelines, although it can be used in the absence of other parameters. The introduction of the PAC allowed accurate measurement of cardiac output and stroke volume, amongst other indices, and this monitor was initially used to guide fluid therapy in major surgical procedures and intensive care unit patients. The suggestion that the PAC itself was associated with harm lead to a decline in its use, and although two subsequent papers suggested no difference in outcomes associated with use of the PAC, this technology has been largely superseded by less invasive monitoring that derives haemodynamic indices including cardiac output and stroke volume.

Most fluid therapy algorithms now use stroke volume rather than cardiac output as an end point for fluid therapy. More recently, dynamic parameters, such as pulse pressure variation (PPV) and stroke volume variation (SVV), have been used as indicators of the fluid responsiveness of the patient.

**Dynamic predictors of fluid responsiveness**

There has been a great deal of interest in so-called ‘dynamic indices of fluid responsiveness’, such as PPV and SVV. These indices reflect the variation in cardiac output during the respiratory cycle and provide an attractive concept of a simple number that tells us whether the patient is or is not fluid responsive. However, these indices should be interpreted with caution. Spontaneous ventilation, irregular cardiac rhythm or frequent extrasystoles, pneumoperitoneum, and low-tidal-volume ventilation may all affect the predictive accuracy of PPV and SVV. The principal value of these indices may be as a guide for when not to give fluid. A patient is highly unlikely to be hypovolaemic when the value of either parameter is <5%, even in the presence of spontaneous ventilation or irregular rhythm.

**Closed-loop fluid administration**

An interesting emerging technology in this field is the ‘closed-loop’ automated fluid management system, which uses computer software to interpret haemodynamic physiology on a second-by-second basis to determine the optimal rate of fluid administration. Such technologies have passed the proof-of-concept stage and are now being tested in clinical trials. Patients may receive comparable amounts of fluid when driven by a closed-loop system, whilst spending more time in the optimal haemodynamic target zone. This is an exciting development, but we must avoid the errors of previous research on i.v. fluid therapy and ensure that the safety and efficacy of
Has clinical research defined safe and effective fluid therapy?

Challenges of fluid research

Some commentators debate the value of large multicentre trials, which frequently fail to confirm the clinical effectiveness of study treatments. This may be because of the numerous challenges of designing and completing a trial to provide high-quality data. Clinical trials of fluid therapy are very heterogeneous because they are designed to answer different questions in different patient populations. Trials use a variety of clinical outcome measures, from safety end points and explanatory mechanisms through to patient-centred outcomes, such as morbidity and mortality. It is often difficult to identify a simple well-defined population who may benefit from the fluid treatment in an easily measurable way. The indications for fluid, and its dose, are almost always subjective, making the trial intervention hard to standardise and adding further variability. This is a particular problem when so many randomized trials of i.v. fluid therapy have been conducted in only one hospital, where clinical practice may not fully reflect wider international standards. These differences can make comparison of studies difficult. In many instances, however, randomized trials have failed because the researchers failed to pose a relevant question or design a trial appropriately to answer it, or both. Our understanding of the purpose of large trials may also be poor. The purpose of clinical effectiveness (or pragmatic) trials is to balance the benefits of a treatment that has shown promise in smaller efficacy (or explanatory) trials with the practicalities of widespread use in the clinical environment. It is therefore very important that we do not progress to large clinical effectiveness trials until efficacy trials have established a sound biological basis for our treatment strategy in a given patient population. Clinical effectiveness trials must focus on a small number of clinical outcomes that may realistically be modified by the study treatment and are of direct relevance to patients. Clinical effectiveness trials are not designed to extend knowledge into new areas but to enhance the acuity of clinical evidence on an existing question. Well-conceived and well-designed clinical effectiveness trials improve patient care regardless of findings; they prove the value of some treatments, demonstrate the marginal benefit and hence lack of utility of others, and confirm the importance of harms that were previously thought insignificant. The findings of successful multicentre trials may deliver more value than excitement.

Poor interpretation of good research

Clinicians commonly dispute outcome data from studies, not because of limitations in trial design, but because the findings do not fit their own pre-existing understanding and knowledge base. In anaesthesia and intensive care, we are taught about fluid therapy from the very start of our careers. Not unreasonably, we have each come to firmly believe in our own understanding of the topic. However, these physiological teachings can be outdated and incorrect, and frequently, differ widely between doctors. Sometimes, the findings of high-quality research may strongly challenge our beliefs. We place emphasis on certain harms but ignore others. We must learn to accept the unexpected or even unwelcome findings of large trials that have been well designed and conducted. Instead of dismissing results we cannot explain, we must seek to identify and understand the alternative mechanisms by which fluid can benefit or harm patients. We must also be prepared to accept that some benefits or harms are simply not as important as we previously thought.

Making sense of i.v. fluid prescribing

Sadly, there is no single ideal i.v. fluid preparation, either overall or for specific situations. It seems easy to demonstrate the flaws in any given approach to fluid prescribing, but increasingly difficult to define best clinical practice. What hope then, for rational harmonized clinical practice? The key to safe fluid prescribing may have much more to do with general principles than with the finer detail. Despite the uncertainty of many of our conclusions, there remain some simple dos and don’ts that can promote safe and effective patient care. These are summarized in Table 4.

Conclusions

The evidence base for fluid therapy will continue to be debated for some years to come, and the ‘ideal’ fluid remains elusive. We do not appear to be close to the ideal i.v. fluid, and given the

Table 4 Some key principles that can help to ensure safe i.v. fluid prescribing

<table>
<thead>
<tr>
<th>Take-home message</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Question yourself</td>
<td>No-one has all the answers. Safe prescribing involves recognition that our clinical decision could be wrong, so we are better able to change the strategy if required.</td>
</tr>
<tr>
<td>Context</td>
<td>Context is key. Patients generally need additional fluid during and early after major surgery. In the days that follow, they generally need less than the standard maintenance dose. A similar principle applies to critically ill patients.</td>
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<tr>
<td>Do they need it?</td>
<td>Why are you giving the fluid? Consider each indication separately, even if you administer the fluid at the same time. This applies especially to maintenance and resuscitation fluids. Vasodilators may be a better treatment for vasodilation associated with anaesthesia.</td>
</tr>
<tr>
<td>Dose</td>
<td>The dose of fluid you give is likely to be more important than the type of fluid you give. Aim to prescribe the lowest effective dose of fluid. When we give a drug that is not indicated, we can only do harm.</td>
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<tr>
<td>Observation</td>
<td>If a patient genuinely needs fluid, they also need continued observation. Many errors in fluid prescribing relate to a failure to adapt fluid therapies to the needs of the patient.</td>
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complexity and heterogeneous disease states that require fluid therapy, it appears unlikely that the ideal fluid for all situations exists. Nonetheless, we know that our approach to i.v. fluid therapy for hypovolaemia may significantly influence outcomes for our patients. Best practice will involve the use of a variety of different fluids, carefully chosen for each specific indication. We continue to use large, simple trials to explore the relative merits of different fluids, and different methods of choosing the dose of fluids. Meanwhile, we must remember that both inadequate and excessive i.v. fluid administration may lead to poor outcomes for hypovolaemic patients. There are some simple principles for safe prescribing that allow us to be confident we are providing the best possible care for our patients.

Authors’ contributions
Concept of the article: R.M.P.
Design, initial drafting, and final version of the article: N.M., R.M.P.

Declaration of interests
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