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What is the evidence base for fluid resuscitation in Acute Medicine?

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Abstract

Intravenous fluids are commonly prescribed but uncertainty remains about how to assess when fluids are required and how much to give, particularly in our multi-morbid, poly-medicated and ageing population. Furthermore, studies have noted that fluid resuscitation can be harmful even if clinical evidence of hypervolaemia is not present.

Two recent guidelines have acknowledged a limited evidence base to guide fluid assessment. A recommended means to assess hypovolaemia includes assessment of fluid responsiveness. Fluid responsiveness is a rise in stroke volume following an increase in preload, achieved using a fluid challenge or a passive leg raise. However, the means of defining fluid responsiveness and its ability to identify patients who would benefit from fluid resuscitation is currently unclear.

This review discusses the current guidelines about, and the evidence base for the provision of, intravenous fluids in the acutely unwell medical patient. It highlights how little evidence is available to guide medical practice.

Keywords

Fluid resuscitation; fluid assessment; fluid responsiveness; passive leg raise; water-electrolyte balance; fluid therapy.

Introduction

"Medicine is a science of uncertainty and an art of probability." Sir William Osler (1849-1919)

Intravenous (IV) fluid is one of the most commonly prescribed hospital treatments. Despite its low cost[1] the annual NHS spend on IV fluid is in excess of £156 million.[2] IV fluid use in some resuscitation scenarios, such as traumatic blood loss,[3] is well evidenced. In acute medical scenarios such as shock, the benefits are less well documented, although fluid therapy is highly recommended in many guidelines and reviews, for example in a recent review which stated that "fluid therapy…is an essential part of the treatment of any form of shock".[4] Acute kidney injury guidelines advise that we should identify and correct hypovolaemia through "adequate" fluid replacement;[5] and international sepsis guidelines state that the use of IV fluid "is a cornerstone of modern therapy".[6] Despite this, evidence to describe the indications, dose and rate of administration of IV fluid is lacking, as is the use of IV fluid over the course of a patient's illness. Medical practitioners currently rely on their clinical acumen alone to guide prescribing practices, akin to the "science of uncertainty and art of probability" described by Sir William Osler in the last century.

Common practice is to use the clinical features of hypovolaemia and hypervolaemia to signal when treatment should be started and stopped. Such features are well described,[7] however, none are specific to volume status[8] and many are not easy to assess.[9] A recent systematic review of 30 studies found that clinical features (including hypotension and tachycardia) were not reliable predictors of hypovolaemia.[10] The same is true of features of hypervolaemia, which are present in many conditions.[8] Even if it could be diagnosed accurately, hypervolaemia due to excess fluid is an iatrogenic overdose and should not be used as a marker to stop fluid administration. In support of this, a recent trial in Zambia randomised hypotensive, septic adults to a usual care group (IV fluid determined by the treating clinician), or a sepsis protocol (aggressive IV fluid limited only by clinical signs of hypervolaemia, alongside vasopressors and blood transfusion when indicated).[11] Use of the sepsis protocol led to a significant increase in in-hospital mortality (48.1%) compared to usual care (33.0%). However, a high proportion of participants had human immunodeficiency virus (89.5%) making it unclear whether these results can be extrapolated to a general medical population.

Of concern, harm from fluids has been demonstrated even in the absence of hypervolaemia. The FEAST (Fluid Expansion As Supportive Therapy) trial, a randomised controlled trial involving East African children with a severe febrile illness, noted that fluid boluses (using either 0.9% saline or albumin) were associated with an excess three deaths in every hundred patients, compared to conservative maintenance fluids alone.[12] A re-analysis of this study suggested that cardiovascular collapse was linked to the increased mortality rather than respiratory failure due to pulmonary oedema.[13] Despite the lack of high-quality IV fluid trials in developed world populations, there is a signal of harm including complications noted in one in five patients in the NHS.[14] Consistent with this, observational studies performed in an intensive care setting have found associations between a positive fluid balance and increased mortality in inflammatory conditions and AKI.[15-18]

Patient variability and fluid assessment

Variations in patient physiology and pathology impact upon the clinical assessment of fluid status, as summarised in Figure 1.

Physiological ageing impacts organ systems and the 2015 Cochrane review noted there was "limited evidence of the diagnostic utility of *any* individual clinical symptom, sign or test, or combination of tests, to indicate water-loss dehydration in older people."[19] For example. maximal cardiac output declines with age, even in the absence of hypertension or cardiovascular disease.[20] A decrease in heart rate response is seen to stressors, which correlates with a reduced responsiveness of β-adrenoceptors to adrenergic stimuli, blunting the tachycardia that can identify hypovolaemia. This decline is partially compensated by an increase in the venous return, as the α-adrenoceptor-mediated venoconstriction is less affected by ageing.[21]

This physiological variability is further accentuated by comorbidities. Chronic organ dysfunction alters fluid homeostasis. For example, a reduced cardiac output in heart failure causes inappropriate activation of the renin-angiotensin system and a consequent expansion of the extracellular fluid compartment.[22]

Medications used to manage chronic disease can also alter fluid balance, by direct action, e.g. side effects such as diarrhoea and vomiting, or through indirect means. Anticholinergic medications block parasympathetic signals to the salivary glands, causing xerostomia. If mild, this can lead to an increased fluid intake to moisten the mouth. Conversely, if severe, xerostomia can interfere with a patient's ability to swallow and prevent adequate hydration.[23]

Fluid assessment is made yet more complex in the presence of acute illness and injury.[6] For example, sepsis affects the cardiovascular system in multiple ways. Hypovolaemia occurs due to direct fluid loss, including insensible losses due to fever. Sepsis has a direct inhibitory impact on cardiac function, reducing contractility and limiting cardiac output.[24] Vasodilatation causes a reduction in the systemic vascular resistance and, if severe, a fall in blood pressure. Sepsis has also been shown to damage the endothelial glycocalyx, a network of proteoglycans and glycoproteins covering the luminal vascular endothelium allowing fluid leak into the extracellular compartment.[25]

All too commonly, patients attending hospital for unplanned, acute medical care have a combination of these factors. They are old, multi-morbid, poly-medicated and have an acute deterioration in status, making the assessment of fluid status exceptionally challenging.

Recommendations from Guidelines

In the last decade, two major guidelines have attempted to address the uncertainty regarding fluid assessment.

The Surviving Sepsis Campaign (SSC) took a prescriptive approach to fluid use in sepsis, advising a fixed dose once septic shock is identified.[6] It "strongly" recommends 30 ml/kg of IV fluid within three hours in patients who meet the criteria for septic shock (hypotension or lactate ≥4 mmol/L). Despite this advice, the guideline acknowledges the evidence for their recommendation is weak, noting "…there is little available evidence from RCTs to support its [IV fluid] practice".

The recommendation is based on the results of a single-centre, unblinded trial involving 263 septic patients.[26] It found a 16% mortality reduction when an 'early goal-directed therapy' (EGDT) protocol was used in place of usual care. However, three subsequent trials, involving

a combined total of 4,175 patients, found no benefit of EGDT compared to usual care.[27-29] Furthermore, a retrospective cohort study found that 67% of patients had evidence of fluid overload at 24 hours when EGDT recommendations were followed, with a corresponding 92% increased risk of mortality.[30]

If initial fluid resuscitation is followed by ongoing hypotension or hyperlactataemia, the SSC guideline[6] recommends the use of physiological variables to determine the need for additional IV fluid. Recommended variables include central venous pressure (CVP), central venous oxygen saturation ($S_{cv}O_2$), bedside echocardiography and a dynamic assessment of fluid responsiveness. However, these variables measure different physiological processes. A rise in CVP can be a marker of fluid excess in the venous compartment. $S_{cv}O_2$ is a surrogate for the balance between oxygen delivery and consumption. Echocardiography allows the measurement of cardiac contractility and can estimate venous pressures. Fluid responsiveness, discussed in more detail below, describes an increase in cardiac performance following a fluid bolus. There is no recommendation on which assessment tool to use or whether combining these variables may help determine fluid status. Furthermore, many of these variables would be challenging to measure in an Acute Medical setting.

The latest NICE (National Institute for Health and Clinical Excellence) guideline for the recognition, assessment and early management of sepsis adopted a more conservative use of IV fluid in sepsis.[31] It advocated up to 1000mL of IV fluid, if indicated, before senior involvement. To determine whether IV fluid was indicated, it recommended the use of the 2013 NICE guideline for IV fluid use in adults,[14] which included guidance to identify hypovolaemia defined simply as a reduced circulating volume. The diagnostic ability of the parameters within this guidance (as described in Table 1) is questionable. The National Early Warning Score (NEWS) is the recommended early warning score in the UK to identify acutely unwell patients. It, along with tachypnoea, is a marker of acuity, not hypovolaemia. There is little data to support the use of capillary refill time (CRT) in adults and the normal value of fewer than two seconds is an arbitrary figure.[32] One study described the 95% confidence limit for a normal CRT in adults aged over 62 years extends up to 4.5 seconds, raising questions about the recommended cut-off.[33]

The guideline subsequently described a different set of parameters to identify shock, defined as a "life-threatening condition with generalized maldistribution of blood flow causing failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia".[14] If present, the guideline suggests urgent fluid resuscitation to restore vascular volume. While shock can be secondary to hypovolaemia, it can also be caused by conditions where fluid may be harmful, e.g. cardiac failure.

Fluid Responsiveness

A test for hypovolaemia that is mentioned in both the SSC and NICE guidelines is fluid responsiveness. If a physiological variable (e.g. stroke volume) increases following an increase in preload, then the patient is defined as fluid responsive. The concept is based on the Frank-Starling curve (*Figure 2*),[34] which documents the relationship between stroke volume and left ventricular end-diastolic volume (LVEDV) – a measure of preload. Multiple, circulating volume-independent factors can alter the LVEDV including age, multi-morbidity, medications and acute illness.[35] Furthermore, fluid responsiveness is seen in healthy volunteers.[36,37] When three litres of IV fluid were administered to healthy adults over three hours, the cardiac index increased by as much as 30% suggesting it is a normal physiological condition to be a fluid responder.[37] No studies have differentiated fluid responsiveness due to normal physiology from that seen in hypovolaemia.

Evidence to support the use of fluid responsiveness in the acutely unwell patient is mixed. A review suggested that 50% of patients who are given fluid resuscitation in an intensive care setting are not fluid responsive.[38] The use of fluid responsiveness to guide IV fluid administration was linked to reduced mortality in a systematic review of 13 trials in a post-surgical, intensive care population.[39] However, a different systematic review of 23 trials using fluid responsiveness to guide perioperative IV fluid use found no difference in mortality with usual care, although it noted a reduction in post-operative complications .[40] A smaller systematic review based in the emergency department included two randomised-controlled trials which noted no difference in surrogate outcomes (lactate clearance and SOFA score) between a fluid responsiveness protocol and usual care.[41] Furthermore, studies have noted the response to a fluid bolus is transient. One study noted the cardiac output

returned to baseline values after 90 minutes in fluid responsive patients, the majority of whom had septic shock.[42]

A fluid challenge is the most cited approach to increase preload when assessing for fluid responsiveness. No consensus exists regarding the type, rate and amount of fluid that should be used. A recent systematic review of 71 studies explored how a fluid challenge has been defined with 75% of studies using 500mL of fluid and 62% using colloids.[43] More recently, 'mini-fluid challenges' of 100mL have been shown to predict the effects of larger fluid challenges.[44] The rate of fluid also varied widely between 5 and 90 minutes per bolus, with 45% of studies giving fluid over 30 minutes. This wide heterogeneity is a barrier to meaningful comparisons between studies.

Apart from a fluid challenge, two techniques to increase preload and identify the presence or absence of fluid responsiveness have been studied: pulse pressure variation (PPV) and the passive leg raise (PLR). The size of variations in pulse pressure with respiration can be an accurate marker of response to a fluid challenge in stable, perioperative patients.[45] However, these measurements are poor predictors of fluid responsiveness in less controlled scenarios, such as intensive care.[46] PPV is therefore unlikely to be of use in acute medicine.

A PLR describes any manoeuvre in which the legs are elevated. This can be achieved by tilting the bed from a semi-recumbent position (*Figure 3a)* or elevating the legs from a supine position (*Figure 3b*). These manoeuvres lead to a transfer of blood from the legs and abdomen into the thorax and a resultant increase in preload. Radionuclide imaging estimates that the volume of blood in the calves of healthy volunteers, before and after the legs were raised to 20° was reduced by 150mL.[47] This volume will be increased once the movement of blood from the thigh and abdomen is taken into account. The increase in preload from a PLR is completely reversed once the legs are lowered making this a safe manoeuvre for patients at risk of fluid overload.[48]

Systematic reviews have looked at the ability of a PLR to mimic the effects of a fluid bolus.[49] Despite studies using different volumes and forms of fluid challenge and different methods to assess cardiac output, there was a mean PLR-associated change in cardiac output in those subjects who also increased their cardiac output following a fluid challenge, with no difference between patients who were spontaneously breathing and those on a ventilator.[49]

These results suggest that PLR could be used in Acute Medical patients as an assessment of fluid responsiveness but it remains unclear what action this test should prompt. It is unknown what proportion of acutely unwell adults will have evidence of fluid responsiveness as measured by PLR, whether giving fluids to those with a positive PLR will improve outcomes, whether PLR can be used to determine when to stop fluid resuscitation or indeed if PLR is the best (and most pragmatic) means to assess fluid status.

As with a fluid challenge, there are a wide variety of studied methods for measuring fluid responsiveness. This heterogeneity has been recognised with one review suggesting the following definition:

> "An increase in a physiologic parameter, preferably cardiac output, within 15 minutes superseding twice the error of the measuring technique after a 15-minute administration of 6 mL/kg of crystalloids,"[50]

reflecting the uncertainty regarding how fluid responsiveness should be assessed.

Avenues for Future Research

The evidence base for most medical conditions is expanding, including powerful insights into the potentially negative consequences of medical practices which were advocated in the past. Intravenous fluids are commonly given to acutely unwell adults based on the probability of benefit despite evidence of harm in some studies. We still do not know when to give fluids (or when to withhold them), how much to give or how to accurately assess the response, especially in our ageing, multi-morbid and poly-medicated patients. Building an evidence base to help clinicians use IV fluid appropriately is essential.

While there is awareness of the complications of IV fluid therapy, there is a limited understanding of the incidence of these complications and their impact on outcomes. The need to improve our understanding of the harms related to IV fluid has been acknowledged by the NICE guideline and forms a key research recommendation.[14]

How the medical profession currently performs a fluid assessment is ill-defined. Our inability to describe current practice prevents trials from differentiating between effective and

ineffective assessment techniques when usual care is a treatment option. Qualitative analysis to explore the reasons that clinicians give fluid resuscitation would clarify practice and may improve protocol breaches that are common when fluid resuscitation protocols are studied.[51]

Studies have not compared patient outcomes when fluid responsiveness is compared to other means to assess fluid status, such as CVP. Current evidence has shown that assessment tools such as CVP are poor predictors of fluid responsiveness, but not that they are less effective than fluid responsiveness at predicting whether IV fluid is beneficial. The evidence base supporting fluid responsiveness is limited by heterogeneity in definition and practice. It will remain challenging to study hypovolaemia if potential assessment tools have no agreed definition.

Summary

The provision of IV fluid is one of the most common therapeutic interventions, but there is the potential for harm as well as benefit and the ongoing expansion of our ageing, multi-morbid and poly-medicated population will only make fluid assessment more challenging. The evidence to support when and how to prescribe fluids is limited. Because of this, robust, evidence-based recommendations for the use of fluid resuscitation by the acute physician are not currently possible. Instead, there are a high number of review articles and educational pieces which rely upon expert opinion and usual practice. Such as paucity of data is hard to justify in our era of evidence-based practice and there is a clear need for more research to guide how fluid resuscitation should be used in the acutely unwell patient.

Returning to the quote by Osler, given the heterogeneity of medical patients, we may not be able to turn uncertainty into certainty, but the probability of benefit from IV fluids should be based more on science and less on art.

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Figure Legends

Figure 1: Factors that can affect a fluid assessment

Legend: Four groups of factors are depicted that affect a patient's fluid balance and therefore a fluid assessment. These factors are further broken down into subgroups, which illustrate the potential complexities involved.

Figure 2: The Frank-Starling Curve

Legend: This schematic of the Frank-Starling curve describes the effects of an increasing preload on the stroke volume and the factors that can alter this relationship. Some of these factors change a person's position on the curve by altering the preload (diagonal arrows),

and others change the shape of the curve by altering the cardiac function directly (vertical arrows).

Figure 3: Two methods of a passive leg raise

Legend: There are two techniques described for a passive leg raise (PLR) in the literature: (a) a semi-recumbent PLR starts at 45° and the patient is tilted backwards until the torso is horizontal leaving the legs are at 45°; (b) a supine PLR starts with the patient in a supine position and the legs are elevated to 45°.