Title: Fluid Therapy in the ED – an Expert Practice Review

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Intravenous fluid therapy is one of the most common therapeutic interventions performed in the Emergency Department (ED), and is a long-established treatment. The potential benefits of fluid therapy were initially described by DR W B O'Shaughnessy in 1831 and first administered to an elderly woman with cholera by Dr Thomas Latta in 1832, with a marked initial clinical response. However, it was not until the end of the 19th century that medicine had gained understanding of infection risk that practice became safer and that the practice gained acceptance.

The majority of fluid research has been performed on patients with critical illness, most commonly sepsis as this accounts for around two thirds of shocked patients treated in the ED. However, there are few data to guide clinicians on fluid therapy choices in the non-critically unwell; by far our largest patient group. In this paper, we will discuss the best evidence and controversies for fluid therapy in medically ill patients.

Clinical Setting

Imagine an elderly patient presenting with a pneumonia, who needs admission to hospital but is not critically unwell (normal observations). This simple daily ED scenario raises a number of questions and there is likely to be great variation both within and between Emergency Departments in the treatment that this patient will receive. The deceptively simple questions of what fluid should be prescribed and how much are asked of junior doctors on a daily basis.

Which Fluid should I prescribe?

Normal saline was described around 150 years ago, initially to store red blood cells. It is hyperosmolar to plasma (osmolality 308 as compared to 275-285) with the initial errors in calculating its composition remaining uncorrected since the initial formulation. Solutions balanced both by electrolyte composition and osmolality to approximate to (human) plasma include Hartmann's, Ringers and Plasma-Lyte (table 1). However, the inability to manufacture plastic that can store bicarbonate sees all solutions replace this with an alternative, most commonly lactate, so the term 'balanced' is relative. Colloids were developed post World War II to offer a cheaper alternative to albumin. Manufacturers suggested that these offered a lower volume of fluid be delivered for a given expansion of the intravascular space, thereby reducing tissue oedema and required volumes to be infused. Data from the Saline

versus Albumin Fluids Evaluation (SAFE) trial suggest that this does not translate to clinical practice with a replacement volume ratio of 1:1.4 reported[1].

Data suggest that Emergency Physicians (EPs) most commonly prescribe 0.9% saline while colleagues in critical care favour (so called) balanced solutions, most commonly Hartmann's Solution in the UK.[2, 3] Colloids are also more rarely used in the ED.

Table 1 Composition of common crystalloid solutions compared to plasma

	Plasma	0.9% saline	Hartmann's	Lactated Ringer's	Ringer's Acetate	Plasma-Lyte 148
Osmolality (mOsm/L)	275-295	308	278	273	276	294
pH	7.35-7.45	4.5-7.0	5.0-7.0	6.0-7.5	6.0-8.0	
Sodium (mmol/L)	135-145	154	131	130	130	140
Potassium (mmol/L)	3.5-5.0		5.0	4.0	5.0	5.0
Magnesium (mmol/L)	0.8-1.2				1.0	1.5
Chloride (mmol/L)	96-106	154	111	109	112	98
Calcium (mmol/L)	2.2-2.6		2.0	1.4	1.0	
Acetate (mmol/L)					27	27
Lactate (mmol/L)	1-2		29	28		
Bicarbonate (mmol/L)	22-28					
Gluconate (mmol/L)						23

The last 20 years has seen advances in our understanding of fluid management, but most of this literature relates to critical care patients, and in particular those who have suffered severe injury. In 2004 Alderson published a Cochrane review suggesting an association between the use of colloids (as opposed to crystalloids) and increased mortality. This led to the SAFE trial, which took place in Australia where low cost meant that albumin was regularly used in resuscitation, particularly in the Intensive Care setting.[1] This randomized controlled trial (RCT) provided high quality data to support the safe use of albumin (delivered in 0.9% Saline) as compared to 0.9% saline in all patient groups other than those with traumatic brain injury (Potential harm in brain injury may be related to the hypo-osmolar albumin solution contributing to cerebral oedema). The authors followed this with a similarly large RCT to

compare 6% hydroxyethyl starch (delivered in 0.9% saline) to 0.9% saline[4]. This study showed no mortality advantage for either solution, but did show significant increase in the requirement for renal replacement therapy and higher creatinine levels in the patients randomised to 6% hydroxyethyl starch. Both trials recruited a wide range of patients admitted to intensive care (ICU) requiring fluid resuscitation. The '6 S' RCT, also performed in the ICU setting but focused on sepsis, reported an increase in mortality for patients resuscitated with 6% Hydroxyethyl starch as compared to Ringers acetate solution. These and other trials were included in a 2013 Cochrane review, which concluded that the use of starch based resuscitation fluids was associated with an increased mortality and renal impairment while albumin offered no significant mortality difference to crystalloids[5]. There were insufficient data to offer conclusions on the use of other colloids. It is likely, but not certain, that this ICU derived data can be generalized to the Emergency Department.

The supraphysiological level of chloride in 0.9% Saline (154 mmol/L as compared to around 96 -106 mmol/L in plasma) is associated with a reduced renal blood flow and a higher rate of hyperchloraemic acidosis after large volume infusion[6, 7]. Observational data suggest that the incidence of renal impairment increases with the use of 0.9% Saline as compared to balanced solutions in a wide range of patient groups[8-10]. A before and after Emergency Department (ED) study reported an association between chloride rich (compared to chloride poor) solutions, and acute kidney injury[8]. However, an Intensive care unit (ICU) based RCT showed no advantage of Plasma-Lyte as compared to saline in mortality or renal function[11]. Larger clinical trials are planned in diverse patient groups.

Infusion of 0.9% saline is the most common cause of in-hospital hyperchloraemic acidosis while Plasma-Lyte, Ringer's and Hartmann's solutions are associated with minimal disturbance of blood pH [12] [7, 10, 13, 14]. The crystalloid-induced changes in lactate, electrolyte, clotting profiles and pH levels are well described but there are few data to guide clinicians on the impact of these on final clinical outcomes.

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 174 (Fluid therapy in adults) supports the use of crystalloids with a sodium content of 130-154 mmol/L, which includes all of the Crystalloids described above[15].

There is a paucity of ED-based literature so we can only base our practice by extrapolating from ICU studies, and there are no large RCTs that focus on patients who do not require resuscitation. We can guess that a crystalloid will be a reasonable first-choice intravenous fluid and that the type of fluid should be directed by the electrolytes and clinical presentation. Thus, we may choose 0.9% saline for patients with intracerebral pathology taking advantage of the higher osmolality. However, we may choose a balanced solution for patient with renal impairment and a lower pH fluid (Plasma-Lyte) for patients with acidosis.

How much fluid should we prescribe?

This is a more complex and less well researched question. Fluid therapy is used for resuscitation, to replace losses or prevent dehydration. Fluid research has centred around patients with shock and there is little to guide clinical practice in the other groups. Shock may be defined as life threatening generalised maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue hypoxia. The key intervention in hypovolaemic shock and the early phase of septic shock is fluid therapy. Fluids are also used to optimize cardiac output in obstructive and cardiac shock. In all cases fluids are administered to increase stroke volume and thus cardiac output aiming at correcting tissue hypoperfusion. The underlying physiological principal is that increasing venous return increases stroke volume; the Frank-Starling law of the heart. At rest, the human heart operates below its optimal contraction sarcomere length of 2.2 micrometers, increasing towards this with progressive increases in venous return. Beyond this increasing fluid loading will increase end diastolic pressure but not stroke volume so risking increased extravascular lung water and tissue oedema[16].

As assessing stroke volume has (previously) required complex invasive devices EPs have commonly used surrogate physiological end points to guide fluid resuscitation, such as blood pressure, pulse and urine output. However, as shock may exist with pulse and blood pressure within the normal range resuscitation to normalize these parameters may still be inadequate[17]. Oliguria has been criticized as both a trigger and end point for fluid resuscitation and is no longer a therapeutic goal in recent sepsis guidelines[18, 19].

The inadequacy of conventional physiological parameters and observations that patients with higher levels of oxygen delivery had improved survival saw

the development of goal directed therapy (GDT)[20-22]. GDT bases resuscitation on maximizing a measure of oxygen delivery such as stroke volume, cardiac output or central venous oxygen saturations[20, 21, 23].Early studies suggested improved outcomes in a wide range of patients but three large trials focused on sepsis in the ED setting showed that resuscitation against the goals of central venous pressure (CVP) and central venous oxygen saturations did not result in improved mortality compared to physician directed care based on basic physiological parameters[24-28].

Central venous pressure monitoring has been shown to be unreliable in guiding fluid therapy and is no longer recommended as a resuscitation end point[29-31]. Although it can be a useful diagnostic parameter in extreme values and when its trend is combined with cardiac output measurement[32], it is resource intensive and carries risk of infection and mechanical complications. Therefore, it is likely a poor choice in ED.

As inferior vena cava (IVC) diameter is a surrogate to CVP, it is subject to the same limitations. Respiratory variation in inferior vena cava (IVC) has been suggested as a non-invasive measure for preload. While the IVC collapsibility index (IVCCI) has initially shown promising results in mechanically ventilated patients.[33, 34], studies in spontaneously breathing patients suggest a limited role[35, 36]. There is considerable inter-observer variation[37] and while an IVCCI > 30-50% identifies patients likely to improve stroke volume with additional fluid loading patients with lower levels of collapse < 30-50% may or may not benefit from additional fluid[35].

Lactate is commonly used in the ED as a marker of hypoperfusion. High lactate is an independent predictor of mortality in critically ill patients[38, 39]. Its use has been recommended in NICE sepsis guidelines to risk stratify patients with suspected sepsis by monitoring lactate clearance at 1 hour. While failure to clear lactate is an ominous sign, good lactate clearance may be a misleading resuscitation end point[40]. This is because lactataemia is a product of aerobic mechanisms driven by physiological and pathophysiological increases in sympathetic drive (stress response) and drug effects (e.g. adrenaline, salbutamol)[41]. Lactataemia with accompanying acidosis is associated with a worse prognosis as compared to lactataemia alone.

The majority of GDT trials have aimed at maximizing oxygen delivery as opposed to matching it to the needs of the patient. This risks creating fluid

delivered in excess of cellular requirements, with some studies suggesting this approach worsens organ perfusion and function as a consequence of fluid overload[42]. A recent study randomized 212 adults with sepsis in ED in a resource-limited setting to either an early resuscitation protocol guided by clinical and basic monitoring parameters or usual care. Significantly higher mortality was observed in the protocol group. Patients in the protocol group received an average of 1.2 L more fluids and more vasopressors compared to usual care[43]. Similarly, in a large RCT, significantly higher mortality was observed in sub-Saharan children with severe febrile illness and hypoperfusion randomized to receive a fluid bolus (saline or albumin) vs no bolus[44]. No detectable difference was found between the saline and albumin groups. While both studies were performed in hospitals without intensive care facilities and included respectively a high proportion of HIV positive patients and children with malaria these results question the current practice and guidelines of fluid resuscitation, particularly in sepsis.

The ability to increase stroke volume and cardiac output in response to preload challenge is termed preload responsiveness and is most commonly defined as an increase of > 10-15% following a 500 ml fluid challenge. This figure is based on the estimated precision of the Swann Ganz catheter and there is no universally accepted international definition of the volume or delivery rate Different fluid bolus volumes delivered over different times are associated with different proportions of fluid responders identified[45, 46]. However, this approach is advocated in the NICE Guideline on fluid therapy in adults.
A fluid challenge is different from fluid loading, where fluids are administered without real time monitoring[47]. Fluid challenge, on the other hand, is a test for preload responsiveness and can be used as a controlled method for resuscitation where a repeated fluid challenge is guided by the haemodynamic response. A similar approach has been advocated by the NICE sepsis guidance where a repeated 500ml crystalloid fluid bolus is recommended over less than 15 minutes with repeated assessment.

The main disadvantage of fluid challenge is that a negative test would mean that fluids have been irreversibly administered to patient. This is particularly important in patients at risk of overload (e.g. cardiac failure and renal impairment) and if repeated fluid challenges are to be given in a short time frame. In this context, passive leg raise, a reversible self-fluid challenge, may be a more suitable alternative. PLR predicts fluid responsiveness in both spontaneously breathing and mechanically ventilated patients[48-50]. Stroke volume changes resulting from a PLR may occur from some seconds to minutes

after the manouver and are transitory, so best assessed with continuous cardiac output monitoring or by a skilled echocardiography operator[48, 51].

There is a sound theoretical framework to base fluid resuscitation on identifying fluid responders. Under resuscitation risks inadequate oxygen delivery for optimal tissue perfusion while prescribing fluids to non-responders risks fluid overload[52]. Fluid overload in the ICU population is associated with increased mortality, length of stay, time undergoing mechanical ventilation and renal impairment[53-58]. Current use of physiological markers such as pulse and blood pressure without measurement of cardiac function means that emergency physicians are unaware of the effect of fluid therapy on stroke volume/cardiac output and how this is altered by either unknown existing or acquired cardiac dysfunction, or improved cardiac function resulting from medical therapy. Assessing fluid responsiveness is associated with an altered volume of fluids administered in both the ED and ICU [59-61]. However, a recent systematic review found no mortality benefit for assessing fluids responsiveness in the ED setting [62]. This included only 8 studies and 489 patients highlighting the paucity of research in this field. Trials to date have focused on identifying fluid responders to maximize cardiac output and stroke volume to maximize oxygen delivery with the assumption that shock related organ dysfunction will be rapidly reversed. However, the benefit may be reducing the harm of unnecessary fluid resuscitation and preventing the harm of fluid overload by identifying fluid non-responders for whom an alternative resuscitation strategy is preferred.

Recent studies on the ED population report the proportion of fluid responders in the ED setting as 31-85%, similar to on arrival on ICU at a later stage of resuscitation[61, 62]. A meta-analysis of fluid bolus therapy in the ICU setting identified an increase in cardiac index of 800 ml/min/m^2 immediately following the fluid bolus but this fell to 300 ml/min/m^2 after 60 minutes. The figures for mean arterial pressure and pulse rate were 7 to 3 mmHg and 2 to 1 beats per minute[63]. Observational data on 500 diverse ED patients who received a fluid bolus also suggest that fluid therapy has limited effect on improving blood pressure and pulse in the ED setting[46]. This study reported an increase in blood pressure and decrease in heart rate 10 minutes after administering a fluid bolus but these had returned to base line by one hour, presumably as the fluid delivered had redistributed from the intravascular space. There was a significant increase in respiratory rate and only 26% of patients responded to a fluid bolus by increasing their mean arterial pressure by 5 mmHg or more. Younger patients and those with lower presenting blood pressures were more

likely to be fluid responders. In the subgroup of patients with shock there was a 3 mmHg increase in mean arterial pressure but no significant change in pulse rate at one hour. There was a significant decrease in temperature following fluid therapy.

These data suggest that the Frank Starling law of the heart cannot be applied to all patients. This is not surprising; the response of most humans who offer themselves a fluid load is to increase bladder volume and not stroke volume! It should be noted that cardiac output can increase five-fold in exercise with minimal change to preload but with increases in end diastolic pressure and volume consequent upon increases in sympathetic tone[16]. In illness, excluding evident hypovolaemia, it may be that a second factor other than fluid loading is required to increase stroke volume/cardiac output, such as pressor therapy so seeing the infused fluid increasing end diastolic pressure and obeying the Frank Starling relationship.

Conclusion

Emergency Physicians should be aware that current 'best practice' guidance in fluid therapy in the Emergency Department, based on surrogate physiological measures, is not evidence based and that there is the potential to cause harm as well as benefit. We should be wary of applying evidence derived from ICU patients to the majority of our patients who are not critically ill and should lobby the funders of research to invest in the large clinical trials that are required to better define optimal fluid therapy in Emergency Care.

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