Clinical Nutrition 42 (2023) 2270–2281

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Narrative Review

The 2023 Sir David Cuthbertson Lecture. A fluid journey: Experiments that influenced clinical practice

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ARTICLE INFO

Article history:
Received 29 September 2023
Accepted 29 September 2023

Keywords:
0.9% saline
Balanced crystalloids
Fluid balance
Hyperchloraemic acidosis
Intravenous fluids
Outcomes
Perioperative fluids

SUMMARY

This review summarises some of my work on fluid and electrolyte balance over the past 25 years and shows how the studies have influenced clinical practice. Missing pieces in the jigsaw are filled in by summarising the work of others. The main theme is the biochemical, physiological and clinical problems caused by inappropriate use of saline solutions including the hyperchloraemic acidosis caused by 0.9% saline. The importance of accurate and near-zero fluid balance in clinical practice is also emphasised. Perioperative fluid and electrolyte therapy has important effects on clinical outcome in a U-shaped dose response fashion, in which excess or deficit progressively increases complications and worsens outcome. Salt and water overload, with weight gain in excess of 2.5 kg worsens surgical outcome, impairs gastrointestinal function and increases the risk of anastomotic dehiscence. Hyperchloraemic acidosis caused by overenthusiastic infusion of 0.9% saline leads to adverse outcomes and dysfunction of many organ systems, especially the kidney. Salt and water deficit causes similar adverse effects as fluid overload at the cellular level and also leads to worse outcomes. Serum albumin is shown to be affected mainly by dilution and inflammation and is not a good nutritional marker. These findings have been incorporated in the British consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) and National Institute for Health and Care Excellence (NICE) guidelines on intravenous fluid therapy in adults in hospital and are helping change clinical practice and improve outcomes.

1. Introduction

Teleologically, the mammalian response to starvation, stress and trauma is designed to preserve vital functions, mainly by attempting to maintain intravascular volume and tissue perfusion, and providing substrate for energy metabolism. Sir David Cuthbertson, in his studies on tibial fractures, recognised two phases in the response to injury [1,2]. The ebb phase, usually associated with prolonged and untreated shock, is characterised by a reduction in metabolic rate, hyperglycaemia, hypotension and a retardation of all metabolic processes. This either leads to death or is succeeded by the flow phase when the metabolic rate and protein catabolism increase. This phase is accompanied by salt and water retention and increased potassium excretion [3,4]. Moore added a third phase – the anabolic or convalescent phase, during which anabolism occurs, healing is accelerated and appetite returns to normal [5]. At the same time cellular potassium uptake increases and the capacity to excrete a salt and water load returns – which Moore called 'the sodium diuresis phase' [5]. Knowledge of these changes and the relationship between the external balance of fluid and electrolytes, between the body and its environment, and internal balance between the body fluid compartments is vital for the rationalisation of perioperative fluid and electrolyte therapy [6,7].

The aim of this review is to summarise some of my work on fluid and electrolyte balance over the past 25 years and show how the studies have influenced clinical practice. Missing pieces in the jigsaw will be filled in by summarising the work of others. The main theme is the biochemical, physiological and clinical problems caused by inappropriate use of saline solutions including

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https://doi.org/10.1016/j.clnu.2023.09.029

Abbreviations

aOR	adjusted odds ratio
aRR	adjusted relative risk
CI	confidence intervals
ERAS	enhanced recovery after surgery
GDFT	goal-directed fluid therapy
GIFTASUP	British consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients
MRI	magnetic resonance imaging
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NICE	National Institute for Health and Care Excellence
OR	odds ratio
RCT	randomised clinical trial
RR	relative risk

hyperchloraemic acidosis caused by 0.9% saline. The importance of accurate and near-zero fluid balance in clinical practice is also emphasised.

2. Historical aspects of intravenous fluids and perioperative fluid therapy

Some important landmarks in the development of intravenous infusions are summarised in Table 1 [8–20] and the reader is also referred to a comprehensive review on the subject [21].

The composition of some commonly used crystalloids is shown in Table 2. 0.9% (w/v) saline [sodium chloride (NaCl)] is constituted by dissolving 9 g NaCl in 1 l water and is often incorrectly referred to as "normal" or "physiological" saline [22]. Chemically normal (molar) saline should contain 1 mol (i.e., 58.5 g NaCl) per litre of water. So, "normal" saline is, in fact, 1/6.5 normal saline. Although the solution is described as isotonic, its osmolarity, at 308 mOsm/l, is slightly higher than that of plasma. Moreover, each litre of the solution contains 154 mmol of sodium and chloride, which exceeds both the sodium (135–145 mmol/l) and chloride (94–105 mmol/l) concentration in plasma. Besides, it does not contain the other mineral and organic constituents of plasma and cannot, therefore, be considered a physiological solution. The 1:1 [Na^+] [Cl^-] ratio is much lower than the 1.28–1.45:1 ratio in plasma and poses a problem by causing hyperchloraemic acidosis [23] which will be described in detail later on. Balanced crystalloids such as Ringer's lactate, Hartmann's solution and Plasma-Lyte 148, are relatively more physiological and may be less likely to cause adverse events than 0.9% saline.

3. Testing the knowledge base

Fluid and electrolytes are the most often prescribed medications in hospital practice and 0.9% saline has been, until recently, the mainstay of intravenous fluid therapy, with patients often receiving a median of 3 l water and 242 mmol sodium (and chloride) per day in the postoperative period [24]. In 1999 the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reported that many patients, especially those at the extremes of age, were dying as a result of the infusion of too much or too little fluid by junior doctors who had little or no knowledge and training in the field [25]. The report also estimated that 20% of the patients studied had either poor documentation of fluid balance or unrecognised or untreated fluid imbalance [25].

Based on this information, we surveyed 200 junior doctors in the UK on knowledge and practice of perioperative fluid therapy and found that there was a wide variability in prescribing practice with the junior most member of the surgical team being responsible for fluid prescribing in 89% of instances [26]. The perception of the

Table 1
Some significant historical events in the development and use of intravenous fluids.

Author, year	Event/development
Reinhard Hermann, 1832 [8,9]	First to analyse blood of patients with cholera. Found that the blood had *"lost 28% of its fluidity"*.
Jächnichen 1832 [8–10]	Hermann's colleague, Jächnichen injected 6 oz of water intravenously into a patient with cholera. Although his pulse returned for a quarter of an hour, he died 2 h later.
William Brooke O'Shaughnessy, 1831 [10]	O'Shaughnessy proposed a new method of treating cholera *"by the injection of highly-oxygenised salts into the venous system"*. Although his paper was published before that of Hermann and Jächnichen, he was aware of their work.
Thomas Latta, 1832 [11–13]	Latta attempted to *"restore the blood to its natural state"* by administration of oral saline solutions only to find that this aggravated the symptoms of vomiting and purging. He, therefore, *"proceeded to throw the fluid immediately into the circulation"* and, with *"no precedent to direct"* him, used *"two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water"*. He followed this with a description of the initial four cases treated: an aged female who had *"reached the last moments of her earthly existence"*, a female of 50 and *"very destitute"* and a *"delicate young female, of strumous habit"*. Three of the four patients died and Latta attributed the deaths to *"deficiency in quantity"* of saline injected, the presence of organic disease and the *"late application of the remedy"*.
Hartog Jacob Hamburger, 1896 (cited by Lazarus Barlow [14]) [15]	The first reference to a solution similar to 0.9% saline appeared in 1896. In his article Lazarus-Barlow cites Hamburger as the main authority for suggesting that a concentration of 0.92% saline was 'normal' for mammalian blood. Hamburger, after comparing the *"freezing-points"* of serum obtained from animals and human subjects, concluded that *"the blood of the majority of warm-blooded animals, including man, was isotonic with a NaCl solution of 0.9* per *cent., and not of 0.6* per *cent., as was generally thought … and which had always been called the physiological NaCl solution"*.
Sidney Ringer, 1882, 1883 [16,17]	Ringer set out to *"ascertain the influence each constituent of the blood exercises on the contraction of the ventricle"* and, having bathed frog heart muscle preparations in solutions of different constituents, found that a 0.75% saline solution *"makes an excellent circulating fluid in experiments with the detached* heart". He later discovered that the saline solution previously used was made using pipe water supplied by the New River Water Company and not distilled water as intended. On repeating the experiments, he found that bathing the heart muscle in saline solution made with distilled water made the ventricle grow *"weaker and weaker"* leading to cessation of contractility in about 20 min. He concluded that the effects he had previously obtained were *"due to some of the inorganic constituents of the pipe water"* and developed Ringer's solution.
Alexis Hartmann and Milton Senn, 1932 [18–20]	Hartmann and Senn modified Ringer's solution by adding sodium lactate to it with the aim of reducing the acidosis seen in infants suffering from diarrhoea, dehydration and oliguria.

Table 2
Properties of some commonly used crystalloids.

	Plasma[a]	0.9% saline†	Ringer's lactate	Hartmann's solution	Plasma-Lyte 148
Na^+ (mmol/l)	135–145	154	130	131	140
Cl^- (mmol/l)	95–105	154	109	111	98
K^+ (mmol/l)	3.5–5.3	–	4	5	5
Ca^{2+} (mmol/l)	2.2–2.6	–	2.7	2	–
Mg^{2+} (mmol/l)	0.8–1.2	–	–	–	1.5
HCO_3^-/Bicarbonate precursor (mmol/l)	24–32	–	Lactate 28	Lactate 29	Acetate 27 Gluconate 23
Na^+:Cl^- ratio	1.28–1.45:1	1:1	1.19:1	1.18:1	1.43:1
Osmolarity (mOsm/l)	275–295	308	274	278	295

[a] Normal laboratory ranges from Nottingham University Hospitals NHS Trust.

quality of teaching on fluid and electrolyte balance in medical schools was very variable, with 33% of respondents rating it as either unsatisfactory or poor. Most respondents had not been given any formal or informal guidelines on fluid and electrolyte prescribing and were not aware of the sodium and potassium content of commonly used intravenous fluids. Postoperative weighing as a measure of fluid balance was not practised on surgical wards in any of the hospitals surveyed and less than 10% of respondents knew that regular weighing was the best serial measure of fluid balance. Only 56% of respondents stated that fluid balance charts were checked on morning ward rounds and less than half were aware of the sodium content of 0.9% saline or the daily sodium requirement. Although potassium supplements were usually correct, 25% of respondents prescribed ≥2 l of 0.9% saline per day, which is three to four times the normal maintenance requirement [26], echoing the observations of Rhoads [27] who in 1957 wrote, "The subject of water and electrolyte balance has been obscured by a long series of efforts to establish short cuts. It is not a simple subject but rather one that requires careful study and thought.", and those of Veech [23] who in 1986 stated, "The use of fluid and electrolyte therapy has become such a familiar part of medicine that it is rarely scrutinised."

We then performed a postal survey of 710 Consultant Surgeons in the UK [28], most of whom felt that present practice in perioperative fluid management was unsatisfactory. Junior staff were given written guidelines in only 22% of instances. Only 16% felt that junior doctors were adequately trained in the subject and 35% felt that fluid balance charts were not accurately maintained, nursing shortages being the commonest perceived reason for inaccuracies. Only 30% felt that postoperative patients were receiving appropriate amounts of water, sodium and potassium [28].

Better training and education of doctors and nurses is the key to improvement in the management of fluid and electrolyte balance and we showed that a dedicated interactive workshop on fluid and electrolyte therapy for postgraduate trainees was a successful way of tackling current inadequacies in knowledge and training [29].

4. An experimental model to study the effects of fluid infusions in healthy subjects

Before examining the response of patients to intravenous fluids, we felt it important to define the response to intravenous infusions of various crystalloids in normal human subjects unaffected by the response to injury or inflammation. We, therefore, developed an experimental model [30] with a cross-over design that has proved fruitful and reproducible [31–37]. We infused 2 l of fluid over 1 h into healthy subjects who were then followed over 6 h with hourly measurements of weight, blood chemistry, and urine volume and chemistry. In the first study we infused 2 l of either 0.9% saline or 5% dextrose (effectively free water), over 1 h on separate occasions [30]. The dextrose infusion was excreted rapidly and the subjects got back to baseline weight fairly quickly whereas approximately 2/3rds of the saline infused remained in the body even 6 h after commencement of the infusion. This was associated with an approximately 8% fall in haematocrit and haemoglobin and a 19% fall in serum albumin concentration on completion of the infusions. The greater fall in serum albumin concentration is because as albumin is distributed mainly in the plasma while the haematocrit is in whole blood, the dilution of albumin is much greater than that of the haematocrit. However, the observed fall in albumin concentration (~19%) was greater than the calculated fall (~14%) [30] and this suggests that there is a redistribution element in addition to dilution, perhaps due to damage to the endothelial glycolcalyx and an increase in capillary permeability caused by rapid volume expansion [38,39]. This reinforces the conclusion that the serum albumin concentration is mainly a marker of dilution, as well as inflammation, and is a poor marker of nutritional status. As might be expected, there was a transient hyperglycaemia and hyponatraemia after the dextrose infusion. All subjects developed a sustained hyperchloraemia after the saline infusions, but at that time we did not heed the importance of this finding.

We also performed dual frequency bioelectrical impedance analysis in these subjects and were surprised to note that after dextrose the impedance increased, resulting in a net fall in calculated total body water and extracellular fluid volume. Impedance decreased after saline, resulting in an increase in calculated total body water and extracellular fluid volume [30]. We hypothesised that the reason for this was that, as there are there are no electrolytes in dextrose, and free water is not a good conductor of electricity, the dextrose solution acts as a resistor and increases impedance, whereas the electrolytes in saline cause it to act as a conductor, resulting in a decrease in measured impedance [30].

Subsequently we further developed Nadler's formula to calculate blood volume from body weight, height and haematocrit [40] to calculate changes in blood volume and interstitial fluid volume based on change in weight and haematocrit over time [34].

5. 0.9% saline and hyperchloraemic acidosis

The problems with 0.9% saline were realised as early as 1911 when Evans [41] commented on the recklessness with which it was administered, particularly in the postoperative period. He wrote, *"It must certainly be admitted, remembering that the normal amount of salt excreted by the human body daily is about* 12 gm., *that the accumulation of this amount of salt in the blood would probably produce a decided irritation to the kidney epithelium, for with the 3 L of solution,* 27 gm. *of salt were introduced. Such overloading of the blood with salt will be more pronounced if, while the tubular epithelium of the kidney is much impaired, the water expelling function of the glomeruli is only slightly so. The water of the subcutaneously infused solution will then be expelled, but not the sodium chlorid."* Even in recent times, deaths have been reported as the result of patients being given excessive amounts of 0.9% saline [42,43].

We use the experimental model that we developed previously [30] to compare the effects of 0.9% saline with those of Hartmann's solution and found that, after infusing 2 l 0.9% saline over 1 h, all the subjects developed hyperchloraemia sustained for over 6 h [31]. The serum chloride concentration rose to as high as 108 mmol/l (the upper limit of normal in our laboratory is 105 mmol/l), whereas with Hartmann's solution the serum chloride concentration remained in the normal physiological range. There was a significantly greater fall in the strong ion difference after saline then after the balance crystalloid which, according to the Stewart hypothesis (Strong ion difference (mmol/l) = $[Na^+]+[K^+]-[Cl^-]$) explains the acidosis that develops after saline [44]. Therefore, an excess of 0.9% saline even in healthy subjects, produces a hyperchloraemic metabolic acidosis that lasts for more than 6 h. Changes in body weight showed that weight increased by approximately 2 kg at the end of both infusions, but decreased more rapidly after Hartmann's solution than saline, indicating that the former was excreted more rapidly than the latter. This was mirrored by the urinary changes seen. Subjects passed urine earlier (70 *vs*. 180 min after commencement of the infusion) and more frequently after Hartmann's solution than after saline. Urinary volume and sodium excretion were also significantly greater after Hartmann's solution, indicating a greater amount of salt and water retention after saline. This retention occurs in the interstitial space rather than the intravascular compartment and leads to the development of oedema. Evolution is a slow process and has occurred in an environment in which salt is scarce, so that, while our kidneys retain salt effectively, they are much less efficient at excreting the excesses to which we have only been exposed in recent times. The metabolic response to injury has also evolved to try and retain salt and water in order to maintain intravascular volume. Measurement of hormonal responses to fluid infusions in the experimental model described above showed that natriuretic peptide levels responded only transiently to volume expansion and were not responsive to sodium overload *per se* [33]. Excretion of a sodium overload was entirely dependent on the slow and passive suppression of the renin-angiotensin-aldosterone system [33].

Hyperchloraemia is a critical determinant of changes in renal blood flow and has been shown to have adverse effects on the kidneys in animal studies [45–49]. Intrarenal infusion of chloride-containing solutions, such as 0.9% saline or ammonium chloride, led to a decrease in renal blood flow and glomerular filtration rate in dogs [46]. Other animal experiments have shown that potassium-induced renal vasoconstriction was both dependent on and responsive to increasing concentrations of extracellular chloride [48,49]. Moreover, chloride concentrations in the pathological range led to severe renal vasoconstriction *in vitro* [49]. On the basis of these studies, we used the previously developed experimental model [30,31] to study the effects of 2 l infusions over 1 h of 0.9% saline and a balanced crystalloid (Plasma-Lyte 148, Baxter Healthcare, Thethford, UK) on renal haemodynamics using magnetic resonance imaging (MRI) [35]. Changes in blood volume calculated using equations we had developed previously [34], were almost identical after the two infusions. However, after saline the expansion of the interstitial fluid volume was much greater than after Plasma-Lyte. As in our previous experiment [31], a sustained hyperchloraemic acidosis was seen after saline and urinary changes were similar [35]. Using MRI, mean renal blood flow velocity was significantly decreased after the saline infusions and remained around baseline after Plasma-Lyte. In addition, renal cortical tissue perfusion fell significantly after saline but remained around baseline after Plasma-Lyte [35]. Renal volume increased after saline to a greater extent than after Plasma-Lyte but this was not statistically significant. However, as the kidney is a relatively small organ enclosed within a tight capsule, even small changes in volumes can increase the intraorgan tissue pressure and disturb haemodynamics.

We repeated the experiment using 1 l infusions over 1 h of 6% hydroxyethyl starch suspended in 0.9% saline or a balanced crystalloid [36]. Although the blood volume expanding capacity of both infusions was almost identical, it was interesting to observe that after the colloid in the balanced crystalloid, renal cortical tissue perfusion increased significantly while it remained around baseline after the colloid in saline. This suggests that colloids in balanced crystalloids could increase renal cortical tissue perfusion and this effect is negated by the presence of saline and the associated hyperchloraemic acidosis [36].

So, what does a hyperchloraemic acidosis do to the kidneys? Collating the information we gathered from our own experiments and those of others, we see that when hyperchloraemia is present in the afferent renal arteriole, chloride is filtered through the glomerulus and is not reabsorbed in the proximal tubule. A high chloride concentration is presented to the distal tubule and the chloride enters the macula densa causing depolarisation of the basement membrane and release of adenosine. In the kidney, unlike the heart, adenosine acts on the A_1 receptor and produces a vasoconstriction rather than a vasodilatation and this leads to increased arterial resistance and a decrease in renal blood flow and perfusion [50]. The net result is that both urinary volume and sodium excretion decrease, leading to salt and water retention [50]. In addition to the effects on the kidney, saline excess and the resultant hyperchloraemic acidosis have adverse effects on various metabolic processes and organ functions [23,50] (Fig. 1).

The next question is do these pathophysiological changes make a difference to postoperative outcomes? The first randomised clinical trial (RCT) comparing 0.9% saline with Ringer's lactate in patients undergoing abdominal aortic aneurysm repair showed that those receiving saline needed significantly greater volumes of packed red blood cells (780 *vs*. 560 ml), platelets (392 *vs*. 223 ml), and bicarbonate therapy (30 *vs*. 4 ml) than those receiving Ringer's [51]. Although median blood loss was 600 ml greater in the saline group, this difference was not statistically significant. Hyperchloraemic acidosis was demonstrable in the saline group, but this did not result in an apparent difference in outcome other than the need for larger amounts of bicarbonate to correct base deficit and the use of greater volumes of blood products [51]. Another RCT comparing 0.9% saline with Ringer's lactate in patients undergoing renal transplantation had to be stopped prematurely because 19% of the patients in one group were shown to develop hyperkalaemia. It was thought that this was in the Ringer's group because of the potassium content of the solution. However, when the randomisation code was broken, this turned out to be in the saline group [52]. In addition, 31% of the patients in the saline group *versus* zero in the Ringer's group were treated for metabolic acidosis. Although there was no statistically significant difference in postoperative renal function when the two groups were compared, patients who received saline tended to have a lower 4 h postoperative urine output (1.6 *vs*. 2.1 l) and 24 h creatinine clearance (84 *vs*. 94 ml/min) than those receiving Ringer's [52]. A third RCT randomised adult patients sustaining trauma to receive either 0.9% saline or Plasma-Lyte A for resuscitation during the first 24 h after injury [53]. Of the 46 patients who were evaluable the improvement in base excess was significantly greater with Plasma-Lyte A than with 0.9% saline. At 24 h, arterial pH was greater and serum chloride concentration was lower with Plasma-Lyte A than with 0.9% saline. However, there was no significant difference between groups when volumes of fluid administered, 24 h urine output, resource utilisation, and clinical outcomes were compared [53]. These RCTs [51–53] were performed on relatively small numbers of patients and it is,

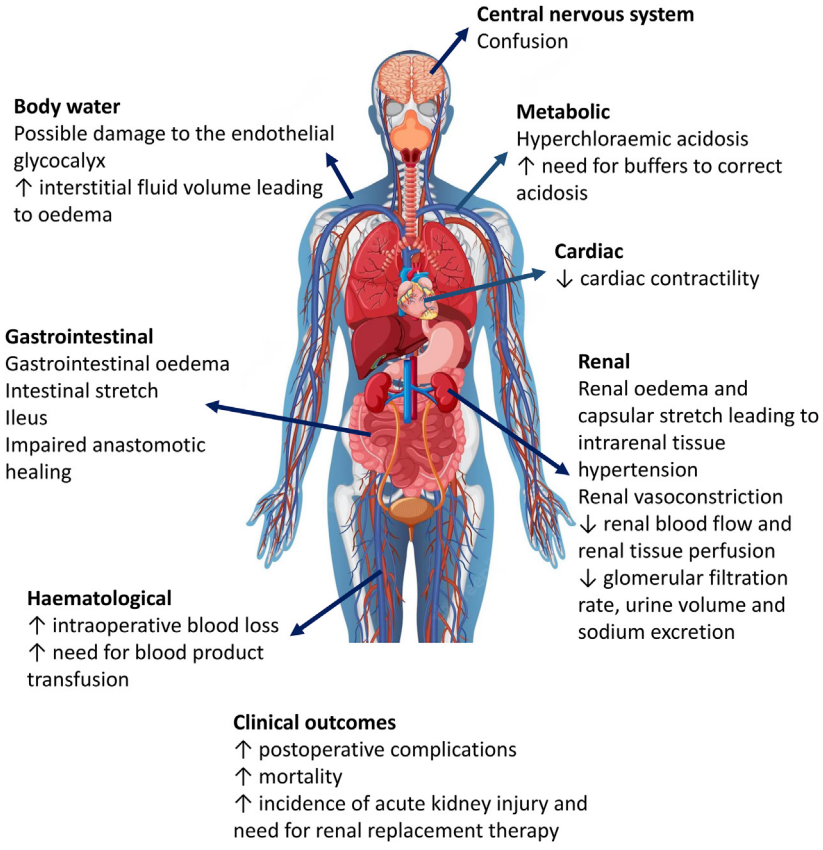

Fig. 1. The adverse effects of excess 0.9% saline (Image: Freepik.com).

therefore, possible that the absence of difference in clinically relevant outcome measures between the two groups may represent a type II error.

Large observational studies have suggested that 0.9% saline may cause adverse events, especially when renal outcomes are studied [54–57]. A propensity-matched study of 2788 adults undergoing major open abdominal surgery who received only 0.9% saline and 926 who received only a balanced crystalloid on the day of surgery, showed that unadjusted in-hospital mortality (5.6 *vs.* 2.9%) and the percentage of patients developing complications (33.7 *vs.* 23%) were significantly greater ($P < 0.01$) in those receiving 0.9% saline [54]. Mortality in the saline group remained higher after correction for confounding variables, but the difference was no longer statistically significant. Patients in the saline group had a significantly greater need for blood transfusion, had more infectious complications, and were 4.8 times more likely to require dialysis (all $P < 0.001$) than those in the balanced crystalloid group. The odds of developing complications were 21% less in the balanced crystalloid group [54]. An open-label prospective sequential study, in which consecutive patients admitted to intensive care (30% after elective surgery) received either chloride-rich ($n = 760$) or chloride-restricted regimens ($n = 773$) found that after adjusting for confounding variables, patients in the chloride-restricted group had a lower risk of developing acute kidney injury [odds ratio (OR) (95% CI): 0.52 (0.37–0.75), $P < 0.001$] and had a decreased requirement for renal replacement therapy [OR (95% CI) 0.52 (0.33–0.81), $P = 0.004$] [55]. However, there were no significant differences in in-hospital mortality, or in the lengths of hospital or intensive care unit stays.

A study on 22,851 surgical patients with normal preoperative renal function and serum chloride concentration demonstrated a 22% incidence of acute postoperative hyperchloraemia (>110 mmol/l) [56]. After propensity matching with patients who had normochloraemia, those with hyperchloraemia were at a greater risk of 30-day postoperative mortality [3.0 *vs.* 1.9%; OR (95% CI): 1.58 (1.25–1.98)] and had a 0.7 day longer median hospital stay than those with normal postoperative serum chloride concentrations [56]. Patients with postoperative hyperchloraemia were also significantly more likely to have postoperative renal dysfunction.

Another propensity-matched study in 3116 patients with the systemic inflammatory response syndrome showed that in-hospital mortality (3.27% *vs.* 1.03%, $P < 0.001$) and length of stay (4.87 *vs.* 4.38 days, $P = 0.016$) were greater in the saline than in the balanced crystalloid group. Readmission rates and cardiac, infectious and coagulopathic complications were also significantly greater in the saline group, but there was no difference in the development of acute renal failure [57].

An RCT randomised 2278 patients admitted to intensive care units to receive either balanced crystalloid or 0.9% saline to determine the effects on renal complications [58]. The proportion of patients requiring renal replacement therapy as well as the survival probability were identical after both solutions. However, the mean total amount of fluid that patients received during their entire stay in the intensive care unit (not just in a day) was 2 l. In addition, the authors did not report serum chloride concentrations. With the relatively low volumes of fluid administered, patients were unlikely to develop fluid overload nor were they likely to have developed a hyperchloraemic acidosis after saline and this may explain the lack of difference between the groups. Our own work has suggested that for adverse events to occur, the serum chloride concentration should be ≥107 mmol/l [35–37].

Two other RCTs performed in the United States looked at balanced crystalloids *versus* 0.9% saline in non-critically ill (SALT-ED study, n = 13,347) [59] and critically ill patients (SMART study, n = 15,802) [60]. In the SALT-ED study there was a significant decrease in the occurrence of major adverse kidney events within 30 days in the patients who received a balanced crystalloid compared with those who received saline [adjusted odds ratio (aOR) 0.82 (95% CI 0.70 to 0.95), P = 0.01] [59]. Similar results were seen in the SMART study where major adverse kidney events were fewer [aOR 0.90 (95% CI 0.82 to 0.99), P = 0.04] and renal replacement therapy-free days were greater [aOR 1.11 (95% CI 1.02 to 1.20), P = 0.01] in the balanced crystalloid group [60].

In a recent *in vitro* experiment published in abstract form we sought to ask the question if there was a vascular component to acute kidney injury caused by hyperchloraemic acidosis [61]. We first used isolated porcine renal arteries and showed that if we placed them in a bath containing increasing concentrations of KCl there was an almost linear relationship between concentration and contraction. We then used increasing concentrations of NaCl and found a similar, albeit smaller degree of contraction, even at clinically relevant concentrations of chloride [61]. The concentration-dependent contractions were greater in the renal than in the mesenteric arteries. The next aim was to determine if these contractions were sodium-dependent or chloride-dependent. We used similar concentrations of sodium gluconate, but this did not produce a concentration-dependent increase in contractility, confirming that the high chloride concentration was responsible for this [61].

A very recent pragmatic, double-blind RCT on deceased donor kidney transplantation in 808 participants showed that intravenous fluid therapy with balanced crystalloids reduced the incidence of delayed graft function compared with 0.9% saline [aRR 0.74 (95% CI 0.66 to 0.84); p < 0.0001], further confirming the deleterious effects of 0.9% saline on the kidney [62].

6. The concept of near-zero fluid balance

Wilkinson and co-workers found that the excretion of both sodium and chloride was reduced for the first six days after surgery [3] and initially thought that this may have been a result of lack of salt intake during the usual period of postoperative starvation. However, these findings persisted even when the salt intake was maintained intravenously or orally, making them conclude that the decrease in sodium and chloride excretion was *"an expression not merely of a failure of intake but also of some active process leading to a retention of sodium and chloride"*. This is akin to the sodium retention that occurs in the catabolic phase of the response of injury described by Moore and leads to sodium and water retention manifesting as oedema [5,63].

Although daily maintenance requirements for water are in the range of 25–30 ml/kg and those for sodium are 1–1.2 mmol/kg and potassium 1 mmol/kg, postoperative patients can receive large amounts of salt and water for maintenance despite the fact that the early postoperative period is associated with a state of salt and water retention. In 1938 Mecray and co-workers [64] rendered a group of ten dogs hypoproteinaemic by a combination of a low protein diet, repeated plasmapheresis and replacement of the blood withdrawn on each occasion by an equal volume of 0.9% saline. They showed that mean gastric emptying time, as measured by fluoroscopic observation of the transit of a barium meal, was inversely proportional to the serum protein concentration [64]. We felt that this may have been due to salt and water overload rather than hypoalbuminaemia *per se*, especially as they were able to demonstrate gross oedema of the stomach in the hypoproteinaemic dogs at surgery and also histologically at autopsy.

We, therefore, designed a physiological experiment to study the clinical consequences of modest fluid gains by randomising patients undergoing uncomplicated colonic surgery to receive postoperative intravenous fluids according to hospital practice at the time [≥3 l water and 154 mmol sodium/day (standard group)] or ≤2 l water and 77 mmol sodium/day (restricted group) [65]. The primary end point was solid and liquid phase gastric emptying time, measured by dual isotope radionuclide scintigraphy [66] on the 4th postoperative day. There was 3 kg weight gain in the standard group, reflecting positive salt and water balance, compared with zero balance in the restricted group. There were no significant differences between the groups when urine output, urinary sodium excretion and blood urea concentration were compared. In the standard group solid and liquid phase gastric emptying times (T_{50}) were significantly longer (median: 175 *vs.* 72.5 min, P = 0.028 and 110 *vs.* 73.5 min, P = 0.017 respectively) and passage of stool 2.5 days later (median: 6.5 *vs.* 4 days, P = 0.001). Although the study was not designed to look for a difference in complication rate, patients in the restricted group had fewer side effects and complications and were able to be discharged 3 days earlier. These results showed that salt and water retention is not a harmless and inevitable epiphenomenon, and should be avoided where possible, by restricting maintenance fluids to the amount necessary to achieve zero balance.

Brandstrup and co-workers performed a similar but larger study where they compared a restricted group who received fluids to maintain them in a state of near-zero fluid balance with those in a standard group who received fluids sufficient to increase their body weight by 3–7 kg [67]. They showed that complications were almost twice as high in the standard group than in the restricted group and, when they broke these down according to the amount of fluid patients received, they found that, if patients received less than 3.5 l on the day of the operation the complication rate was much less than if they received more than 5.5 l. Similarly, if the weight gain was <0.5 kg complications were fewer than if weight gain was >2.5 kg.

Another RCT was unable to show a difference in outcome between patients receiving restricted and standard fluids after colorectal surgery [68]. However, as the patients in the standard group gained about 1 kg in weight and those in the restricted group lost about 1 kg, the lack of difference in clinical outcomes between the two groups could have been because patients in the standard group did not receive an excess of salt and water. By contrast, scrutiny of the fluid regimens shows that the "standard" group in our study [65] and that of Brandstrup and co-workers [67] actually received an excess of salt and water, while the "restricted" group received the right amount of fluid to maintain a state of zero fluid balance.

Another study [69], in which the "standard" group received the right amount of fluid to maintain balance and the "restricted" group may have received too little fluid, showed that the standard group fared better than the restricted group.

Fluids are similar to drugs in having a dose dependent response. As the dose in increased, positive effects are seen until an optimal plateau is reached. As the dose is increased further, the adverse effects of excess become apparent. We performed a meta-analysis of RCTs that randomised patients to receive either standard/liberal fluid regimens or restricted regimens using firstly the authors' definitions then re-examining what the patients actually received and comparing the outcome between those who achieved a state of fluid balance and those who received too little fluid or a significant excess [70]. Using the authors' definitions, there was no difference in complication rates or length of hospital stay between groups. However, when we reanalysed the data according to what patients actually received, we found that patients managed in a state of fluid balance had a 41% reduction in the risk of developing complications

and a 3.4 day shorter length of stay compared with those with a deficit or excess [70]. This has been confirmed in two large US cohort studies on >90,000 patients each [71,72] in which the authors showed that patients given the right amount of fluid fared better than those given too much or too little when length of stay, costs and complications were considered.

Salt and water overload also impairs the healing of gastrointestinal anastomoses. An experimental study on rats showed that animals overloaded with crystalloid developed submucosal intestinal oedema and that anastomotic breaking strength was markedly reduced compared with animals that were not fluid overloaded [73]. A retrospective cohort study in patients undergoing colonic resection and anastomoses after sustaining trauma found that patients who developed anastomotic dehiscence had received more fluids on the each of the first three days than those without dehiscence [74]. After multivariable analysis, the authors determined that there was a 5-fold greater risk of developing anastomotic dehiscence if the cumulative crystalloid load over the first 72 h was >10.5 l [74].

From our own work and that of others, we have shown the ill-effects of excessive salt and water administration and the importance of accurate prescription to achieve as near zero balance as possible. We have also shown the adverse effects of excess saline and its consequent hyperchloraemic acidosis on postoperative outcome, anastomotic healing and gastrointestinal function (Fig. 2) [75]. The evidence shows that a small amount of fluid overload causing weight gain of around 1–2 kg does not have adverse effects, but when the body weight increases by at least 2.5–3 kg due to fluid excess, adverse effects are caused and complications increase [76].

Recently, in a multicentre, multinational RCT, 3000 patients who had a predicted increased risk of complications while undergoing major abdominal surgery were randomly assigned to receive a restrictive or liberal intravenous fluid regimen during and up to 24 h after surgery. The primary outcome, disability-free survival at 1 year was identical in both groups. However, the number of patients who developed surgical site infections and acute kidney injury and needing renal replacement therapy was significantly higher in the restrictive than in the liberal group [77]. However, the fluid used was a balanced crystalloid and not 0.9% saline and it has been shown that balanced crystalloids are less likely to be retained in the body and cause less fluid overload than saline. Fluid balance was not recorded after the first 24 h and the liberal group gained only 1.6 kg in body weight, which is below the threshold of 2.5–3 kg needed to produce adverse effects [76]. Hence, this study shows that a modestly liberal fluid regimen may be safer than a truly restrictive regimen when balanced crystalloids are used.

More recently, a multicentre RCT on goal-directed aggressive or moderate resuscitation using Ringer's lactate in patients with acute pancreatitis had to be stopped prematurely after interim analysis (after recruiting 249 of a planned sample size of 744) because early aggressive fluid resuscitation resulted in a higher incidence of fluid overload [20.5% *vs*. 6.3% (adjusted relative risk (aRR), 2.85; 95% CI, 1.36 to 5.94, P = 0.004)] without improvement in clinical outcomes compared with those who received a more moderate amount of resuscitation fluid [78].

A recent meta-analysis of three RCTs and four non-randomised studies that included a total of 883 patients showed that although the quality of evidence was moderate to low, avoidance of post-operative fluid overload in patients on surgical wards was associated with a reduction in overall complication rate in the RCTs (RR 0.46, 95% CI 0.23 to 0.95; P < 0.03), but not in the non-randomised studies (RR 0.74, 95% CI 0.53 to 1.03; P = 0.07) [79]. In addition, avoidance of fluid overload was associated with a significant reduction in length of stay in the non-randomized studies (mean difference −1.81 days, 95% CI -3.27 to −0.35; P = 0.01) but not in the RCTs (mean difference 0.60 days, 95% CI -0.75 to 1.95; P = 0.38) [79].

7. Dehydration and outcome

While fluid overload is not uncommon, neither is dehydration. Overnight fasting and fluid deprivation been shown to increase urinary osmolality to >800 mOsm/kg [33] indicating dehydration. On the other hand, if current preoperative fasting guidelines are adhered to and patients are allowed to drink clear fluids up to 2 h

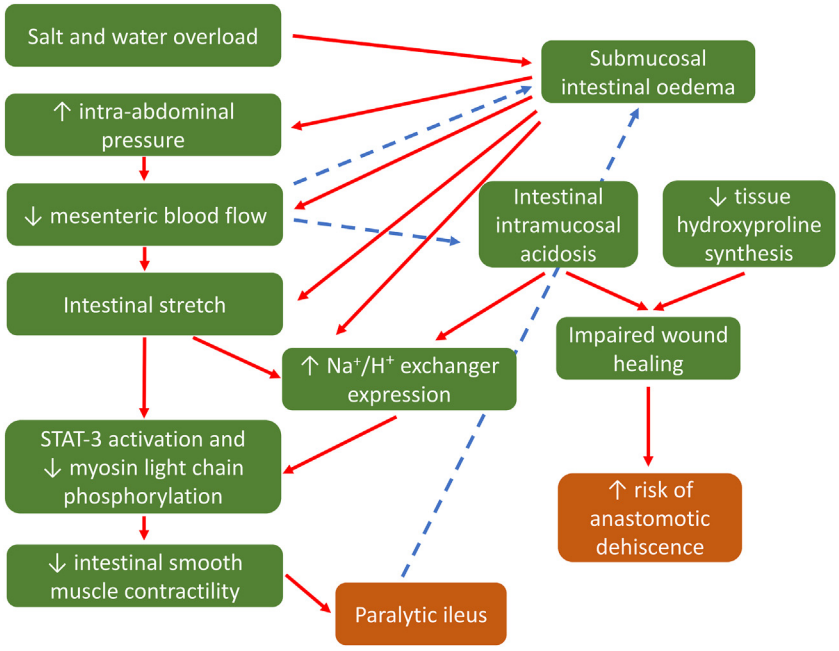

Fig. 2. The effects of salt and water overload on the gastrointestinal tract. STAT-3 = signal transducer and activation of transcription-3 (Modified and redrawn from Chowdhury AH and Lobo DN [75]).

before the induction of anaesthesia, they come to theatre with in a state of normal hydration and with a normal urinary osmolality [34]. Mechanical bowel preparation without adequate rehydration results in a mean loss of about 1.6 kg body weight indicative of a loss of 1.6 l of total body water [80]. A study in patients undergoing paediatric surgery showed that a longer duration of preoperative fluid deprivation was associated with increased risk of hypotension after induction of anaesthesia [81]. Nevertheless, even in this decade, patients are still fasted and fluid deprived for unnecessary lengths of time, with those admitted for emergency surgery likely to fast for even longer than those having elective surgery [82].

In a prospective study in 200 older adult patients who were admitted to medical wards as an emergency we found that 37% were dehydrated and that those who are dehydrated at admission were six times more likely to die in hospital than those who were normally hydrated at admission [83].

In a retrospective cohort study of 32,980 older adults admitted to medical specialties, dehydration was present in 2932 (8.9%) and was the primary reason for admission in 190 (0.6%) [84]. Acute kidney injury was seen in 47.7% of patients with dehydration, compared with 15.9% of patients without dehydration ($P < 0.001$). Patients admitted with a primary diagnosis of dehydration had a 17% 30-day mortality and 44% one-year mortality compared with 7% and 25% respectively in patients without dehydration ($P < 0.001$). Moreover, patients diagnosed with dehydration during hospitalisation were twice as likely to die in hospital than those without dehydration.

In a further retrospective database study, we found that of a total of 6632 older adults admitted to emergency medical wards, 27% had hyperosmolar dehydration and 39% of these had acute kidney injury [85]. Patients with hyperosmolar dehydration were four-times more likely to develop acute kidney injury and had 60% greater 30-day mortality compared with those who were normally hydrated [85].

These studies emphasise yet again the U-shaped relationship between fluid status and complications. Some of the cellular and metabolic effects of fluid overload are similar to those of fluid and electrolyte deficit and deviating in either direction from a state of normal fluid balance can increase complications [7,23,86] (Fig. 3).

8. Goal-directed fluid therapy

Intraoperative goal-directed fluid therapy (GDFT) using measurements of stroke volume and cardiac output to inform administration of a small volume of fluid (usually 200–250 ml of a colloid, sometimes a crystalloid) to optimise stroke volume has been used for over two decades. The aim is to optimise the patient's stroke volume on their individual Frank-Starling curve. An improvement in stroke volume exceeding 10% indicates the requirement for an additional fluid bolus, whereas responsiveness less than 10% suggests adequate cardiac contractility, and that maintenance of the current background fluid infusion is sufficient [87]. Haemodynamic monitoring can be performed using a number of devices such as trans-oesophageal Doppler, lithium dilution techniques, corrected flow time, and stroke volume variation monitoring. Although initial studies indicated that GDFT resulted in fewer complications and shorter length of stay, two meta-analyses, one in patients undergoing major abdominal surgery [88] and the other in those undergoing colorectal surgery [89], have shown that although GDFT is of benefit in patients managed with traditional perioperative regimens, it was of no statistically significant benefit in patients who were managed with enhanced recovery after surgery (ERAS) protocols [90]. This may be because patients managed with ERAS protocols are less likely to be fluid overloaded that those having traditional care.

However, evidence suggests that GDFT may be more beneficial in high-risk patient populations [91]. This is yet to be firmly established, as a large, multicentre, RCT [92] on 734 high-risk patients undergoing major gastrointestinal surgery that compared cardiac output-guided haemodynamic therapy with usual care demonstrated no significant difference in the incidence of a composite outcome of 30-day moderate or major complications and mortality. When these data were included within a meta-analysis within the same paper, the intervention was associated with a significant reduction in the incidence of complications (RR 0.77, 95% CI 0.71 to 0.83) but no significant reduction in hospital or 30-day mortality [92]. Hence, it is recommended that within ERAS programmes GDFT should be used for high-risk patients undergoing high-risk surgery [93]. However, stroke volume variation may be monitored in low-risk patients undergoing high-risk surgery or high-risk patients undergoing low-risk surgery [93].

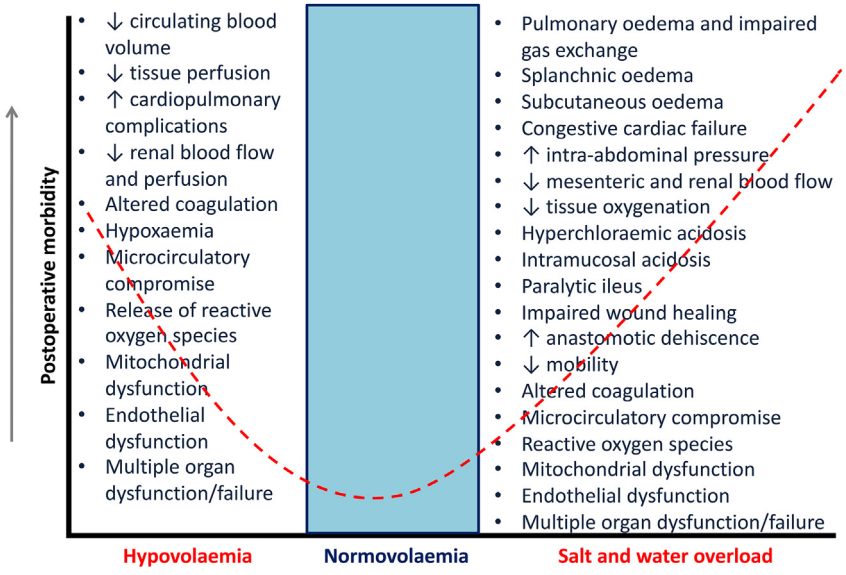

Fig. 3. The U-shaped dose-response curve for fluid therapy showing the adverse effects of too much or too little fluid (Modified and redrawn from Lobo DN et al. [7]).

9. De-escalation

Sometimes, especially in the intensive care unit, salt and water overload is an inevitable consequence of the resuscitation process during the salvage and optimisation phases of resuscitation when the aims are to save life and optimise cardiac output and oxygen delivery [94,95]. It has been shown that in the first 48 h of resuscitation of patients with sepsis, they can gain 12.5 l in total body water, manifest by 12.5 kg increase in body weight [96]. It takes up to three weeks for this retained fluid to be excreted [96]. Therefore, once patients have been stabilised, it is important to de-escalate fluid therapy in order to avoid further unnecessary fluid overload and prevent further organ damage. This can be achieved by weaning patients from vasopressors and aiming for a negative fluid balance [94,95]. We showed that if fluid overloaded patients discharged from the intensive care unit were managed with low sodium, low volume feeds, sometimes combined with a low dose diuretic or occasionally salt-poor 20% albumin infusion, the

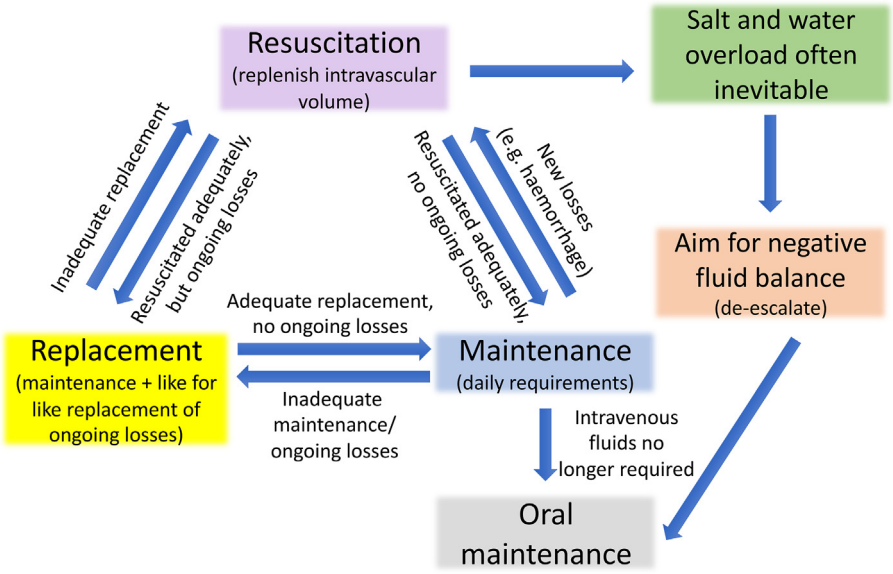

Fig. 4. Indications for intravenous fluid therapy (Modified and redrawn from Lobo DN et al. [7]).

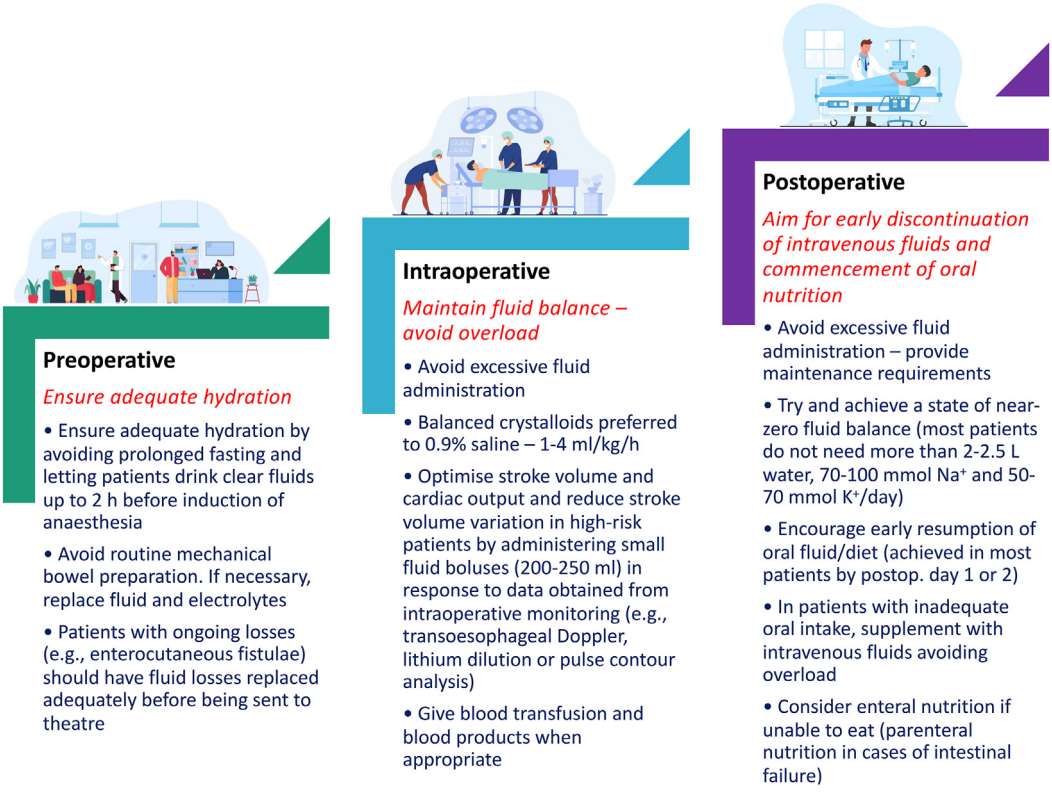

Fig. 5. A suggested practical algorithm for perioperative fluid therapy (Images: Freepik.com).

oedema resolved over 7–14 days with a loss of about 10 kg in body weight, while the serum albumin concentration increased by 10 g/l, mainly as a result of getting rid of the fluid accumulation, and reversing the of dilution and redistribution of albumin rather than being due to increased albumin synthesis [97].

10. A practical guide to perioperative fluid and electrolyte therapy

Before prescribing intravenous fluids, we need to question their necessity. If fluids are necessary, there are three possible reasons for this: resuscitation, maintenance or replacement (Fig. 4). Patients move from one phase to the other fairly rapidly. This should be recognised and appropriate fluid and electrolytes should be prescribed according to the patient's needs. The ultimate goal of fluid therapy is to support the patient until gastrointestinal function is restored and the patient is able to eat and drink. The gut, along with the kidney, is the best regulator of fluid balance.

A practical algorithm for fluid management in the pre-, intra- and postoperative periods of the surgical pathway is suggested in Fig. 5.

11. Conclusions

The provision of fluid and electrolytes is inseparable from that of food and nutrients [6]. The work presented in this review has shown that perioperative fluid and electrolyte therapy has important effects on clinical outcome in a U-shaped dose response fashion, in which excess or deficit progressively increases complications and worsens outcome. Salt and water overload, with weight gain in excess of 2.5kg worsens surgical outcome, impairs gastrointestinal function and increases the risk of anastomotic dehiscence. Hyperchloraemic acidosis caused by overenthusiastic infusion of 0.9% saline leads to adverse outcomes and dysfunction of many organ systems, especially the kidney. Salt and water deficit causes similar adverse effects as fluid overload at the cellular level and also leads to worse outcomes. The importance of accurate and appropriate prescribing of fluid and electrolytes and the value of monitoring (e.g., by weight) has been emphasised. Serum albumin is shown to be affected mainly by dilution and inflammation and is not a good nutritional marker. These findings have been incorporated in the British consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) [98] and National Institute for Health and Care Excellence (NICE) guidelines on intravenous fluid therapy in adults in hospital [99,100] and are helping change clinical practice and improve outcomes.

Funding

This work was supported by the Medical Research Council [grant number MR/K00414X/1], Arthritis Research UK [grant number 19891] and the National Institute for Health Research Nottingham Biomedical Research Centre [grant number NIHR203310]. The funders had no involvement in the development of the protocol, conduct or writing up of this study, or the decision to submit for publication. This work does not represent the views of the funders.

Data sharing

No original data to share.

Ethical statement

As this was a review article, ethical approval was not necessary.

Conference presentation

This paper is based on the 2023 Sir David Cuthbertson Lecture delivered by DNL to the Annual Congress of the European Society for Clinical Nutrition and Metabolism, Lyon, France, 12 September 2023.

Conflict of interest

DNL has received an unrestricted educational grant from B. Braun for unrelated work. He has also received speaker's honoraria for unrelated work from Abbott, Nestlé and Corza.

Author contributions

DNL was the sole contributor contributed to all aspects of this paper.

Acknowledgements

The author wishes to thank the European Society for Clinical Nutrition and Metabolism for the award of the Sir David Cuthbertson Lecture. The original studies referred to in this manuscript were supported by Nottingham University Hospitals Charities, the European Society for Clinical Nutrition and Metabolism, the National Institute for Health and Care Research, the Medical Research Council, the Royal College of Surgeons of England, the ERAS Society, the European Hydration Institute, Baxter Healthcare, B Braun and Nutricia Clinical Care. The author would like to thank the following for their mentorship and advice: Professors Simon Allison, Brian Rowlands, Ian Macdonald, Olle Ljungqvist, Keith Neal, Alan Perkins and Fiona Broughton-Pipkin. The author would also like to thank the following for their contributions to the original studies: Mark Aloysius, John Anderson, Sherif Awad, Kristine Bjarnason, Kate Bostock, Damian Bragg, Sandy Brown, Debbie Bush, Abeed Chowdhury, Eleanor Cox, Mukul Dube, Ahmed El-Sharkawy, Joy Field, Susan Francis, Philip Herrod, Faidah Hj-Ibrahim, Andrew Lewington, David Macafee, Andy Mackenzie, Ron Maughan, Sarah Nduwayo, Quentin Nunes, Ben Prestwich, Fiona Reid, Katie Rollins, Opinder Sahota, Carol Schermer, Andrew Shaw, Kate Shepherd, Alastair Simpson, John Simpson, Pavel Skorepa, Zeno Stanga, Krishna Varadhan, Phillip Watson, Robert Williams, Vincent Wilson and Jeff Wright.

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