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Fluid Management

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Contents

1. Why a Booklet?

Normal saline (0.9 % NaCl) solution is the most frequently used intravenous fluid [169], especially in the perioperative setting [146]. In a clinical trial published in 2003 under the title of "(Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study" [146], however, the authors warn that "clinicians should be aware of the shortcomings of both 0.9 % saline and Hartmann's solution." Embarrassingly, less than 50 % of surgeons in 25 UK hospitals knew the sodium concentration of normal saline after their first year of training [101], and as few as 1 % of anesthesiologists in their sixth year knew the correct composition of 0.9 % saline and Hartmann's solution (Ringer's lactate) [186].

This minor interest and knowledge of the composition of intravenous fluids among the medical profession has for decades been causing substantial problems in fluid therapy resulting from inadequate differentiation between the concepts of volume replacement and fluid replacement: "Fluid is poured into the interstitial space on clinical information gained from changes in the intravascular space, such as blood pressures, pulse rate, peripheral temperature, urine output, etc. The end point … peripheral or pulmonary edema [175]."

2. Volume Replacement Vs. Fluid Replacement: The Two Aspects of Fluid Therapy

Differential intravenous fluid therapy is targeted at EITHER

- the intravascular fluid volume (IVFV, BV) OR
- the extracellular fluid volume (ECFV, extracellular space, ECS) OR
- both the extracellular and intracellular fluid volumes.

The composition and use of intravenous fluids should only be dictated by the targeted fluid space, while there appears to be no merit in differentiating between intraoperative, perioperative, postoperative, and ICU settings.

Volume replacement aims to replace IVFV loss and to correct hypovolemia in order to maintain hemodynamics and vital signs. This is achieved with an essentially physiological solution that contains both colloid osmotic and osmotic components, i.e., a fluid that is both isooncotic and isotonic [192].

Fluid replacement, on the other hand, aims to offset or compensate for an impending or existing ECFV deficit as a result of cutaneous, enteral, or renal fluid loss. This is achieved with an essentially physiological solution that contains all osmotically active components, i.e., an isotonic fluid.

Electrolyte replacement or osmotherapy aims to restore a normal total body fluid volume (intracellular fluid volume plus extracellular fluid volume) when cutaneous, enteral, or renal fluid losses have altered the composition and/or volume of either or both fluid spaces (ICFV and/or ECFV).

The principles of parenteral (intravenous) fluid therapy are summarized in Table 1. The intravenous fluids cited as examples are characterized as follows:

A colloid solution with a physiological colloid osmotic pressure (COP) is essentially retained within the intravascular compartment (intravascular fluid volume), while an isotonic electrolyte solution is distributed in the entire extracellular space (plasma plus interstitial space), and a glucose (dextrose) solution distributes in total body water (total body fluid volume, TBFV).

The qualifier "isotonic in vitro" means that 5 % dextrose solution in water (D5W) has physiological osmolality in vitro, but in vivo it behaves like pure water because dextrose (glucose) rapidly enters the intracellular compartment to be metabolized there.

Table 1:

Target compartments of intravenous fluid therapy and typical intravenous fluids

Use	Compartment	Composition	Typical IV Fluid
Volume Replacement	IVFV	Isooncotic Isotonic Isoionic	6 % HES 130 in balanced solution
Fluid Replacement	ECFV	Isotonic Isoionic	Balanced solution (obsolete: normal saline, Ringer's lactate)
E-Lyte or Osmotherapy	TBFV	H_2O Isotonic in vitro	D5W

3. Why Balanced Solutions?

A balanced electrolyte solution has the physiological electrolyte pattern of plasma in terms of sodium, potassium, calcium, magnesium, chloride and their relative contributions toward osmolality, and achieves a physiological acid-base balance with bicarbonate or metabolizable anions. Infusion of such a balanced solution is devoid of the risk of iatrogenic disruptions except for potential volume overload.

Back in 1970, a Letter to the Editor of *JAMA*, titled "Normal" 0.9 % saline is neither 'normal' nor physiological" [181], gives the following definition of physiological solution: "A balanced multiple electrolyte solution isotonic with plasma and containing sodium, potassium, calcium, magnesium, chloride, and dextrose in concentrations physiologically proportionate to the corresponding plasma constituents would be far superior as a routine replacement and maintenance therapeutic solution." This definition was expanded in 2000 in "Call for a new crystalloid fluid" [36], reiterating the old demand for "a solution containing sodium bicarbonate" [49] because it was clear that "the predominate physiologic deficit is metabolic acidosis" [115]. Appeals have since been published [47, 113, 116] along the lines of "We encourage anaesthesiologists to consider the role of fluids in acid-base change," or "acid base disorders may be avoided."

The development of a balanced solution was summarized in 2003 [146] in these words: "The attempt to find a truly physiological crystalloid preparation for both scientific and clinical work has been going on for over three-quarters of a century, and the results have inevitably been a compromise."

However, there has also been opposition to this concept of physiological, balanced solutions for volume and/or fluid replacement – fluid therapy using different solutions in an effort to restore or maintain physiological conditions [39].

4. What Should Go Into a Balanced Solution?

The electrolyte pattern of plasma should be mimicked as closely as possible. A balanced solution should reflect the physiological roles of the sodium, potassium, calcium, and magnesium cations, and also contain chloride and phosphate anions, and, above all, bicarbonate (or suitable metabolizable anions in lieu of bicarbonate).

Table 2:

Composition of plasma and often used infusion solutions

	Plasma	6 % HES in 0.9 % saline	Ringer's Lactate
Na^+ (mmol/L)	142	154	130
K^+ (mmol/L)	4.5		5
Ca^{2+} (mmol/L)	2.5		1
Mg^{2+} (mmol/L)	1.25		1
Cl^- (mmol/L)	103	154	112
HCO_3^- (mmol/L)	24		
$Lactate^-$ (mmol/L)	1.5		27
$Acetate^-$ (mmol/L)			
$Malate^{2-}$ (mmol/L)			
Colloid (g/L)	albumin: 30–52 g/L	starch: 60 g/L	
$Proteinate^-$ (mmol/L)	20		

Such a balanced solution automatically corrects any electrolyte imbalances in the entire extracellular compartment. A major benefit for the physician is that there is no risk of overdosage with this type of intravenous fluid – apart from the avoidable risk of volume overload.

4.1. Cations

Sodium has a crucial impact on the extracellular fluid volume (ECFV) and thus automatically also on the circulating blood volume (BV), or intravascular fluid volume (IVFV). If the sodium concentration of a balanced intravenous solution ranges from 138 to 146 mmol/L, the normal plasma sodium concentration of 142 mmol/L can be adequately maintained.

Potassium is the predominant cation in the intracellular compartment and has a central electrophysiological role, especially in cardiac arrhythmias, and is crucial to renal function. The normal plasma potassium concentration is 4.5 mmol/L; the potassium concentration of a balanced solution should therefore range from 4 to 5 mmol/L.

Calcium is crucial to neuronal excitability and electromechanical coupling of muscle cells, and it is involved in blood clotting. Magnesium is needed for neuromuscular stimulation. Normal plasma concentrations of 2.5 mmol/L (5.0 meq/L) and 1.25 mmol/L (2.5 meq/L) should therefore be maintained for calcium and magnesium, respectively.

4.2. Chloride

Similarly to the sodium cation, chloride is the most important anion in the extracellular space (ECS).

Chloride accounts for one-third of all extracellular osmotically active particles and, after sodium, is the second most important determinant of the ECFV. It is also responsible for setting the membrane potential. The normal chloride concentration in plasma is 103 mmol/L. Ideally, a balanced solution should therefore have a chloride concentration ranging from 100 to 106 mmol/L, but this is difficult to achieve in practice.

Compare this to the sodium and chloride concentrations of "normal" ("physiological") saline (0.9 g/dL): 154 mmol/L Na^+ and 154 mmol/L Cl^-.

These concentrations are much too high. Ringer's lactate solution contains too little sodium (130 mmol/L) and too much chloride (112 mmol/L).

Are there arguments against infusing a too-high chloride concentration?

Indeed there are, as emerges from various animal studies [86, 141, 187, 188]:

An increase in the ECS chloride concentration, but not in the ECS sodium concentration, causes specifically renal vasoconstriction and a decrease in the glomerular filtration rate (GFR), or diuresis. An increase in the plasma chloride concentration by 12 mmol/L above normal (to 115 mmol/L) leads to an increase in renal vascular resistance by as much as 35 %, a decrease in GFR by 20 %, and a drop in blood pressure as a result of an acute and chronic decrease in plasma renin activity. The induction of hyperchloremia apparently depends on the infusion of substantial volumes of a hyperchloremic infusion fluid.

Example: When a 75-kg individual (ECFV, 15 L) is infused with 5 L of normal saline (154 mmol/L Cl^-), the plasma chloride concentration will increase from 103 mmol/L to 116 mmol/L, assuming that none of the infused volume is excreted during the infusion.

4.3. Bicarbonat and Dilutional Acidosis

Infusion fluids that do not contain the physiological buffer base bicarbonate – i.e., all of the infusion fluids that are currently available worldwide – produce dilutional acidosis because infusion of such a solution dilutes (reduces) the HCO_3^- concentration (buffer base) of the entire extracellular compartment, while the partial pressure of CO_2 (buffer acid) remains constant. Dilution may be isovolemic (normovolemic), i.e., HCO_3^- is lost along with the blood and the blood or extracellular fluid volume is restored to normal with a solution that is free of HCO_3^-, or the ECFV is expanded with a bicarbonate-free solution to produce hypervolemia.

Dilutional acidosis was first described in qualitative terms in vivo in 1948 [160]: A decrease in arterial pH to 7.20 was observed in a dog model after infusion of

1,500 mL of 0.9 % NaCl solution in 5 minutes, while no such effect was observed in dogs infused with the same volume of a solution containing 30 mmol/L of $NaHCO_3$. In 1966, Asano et al. [10], in another dog study, infused 3.5 mL/kg/min of 0.9 % NaCl, 5 % dextrose, or 5 % mannitol solution for 25 minutes and produced similar dilutional acidosis which, therefore, was solely due to HCO_3^- dilution, rather than to chloride delivery. In a clinical setting, dilutional acidosis only occurs at large dilution volumes: Normovolemic hemodilution with gelatin solution reduces the Hb concentration from 11 to 6 g/dL and base excess (BE) by 6 mmol/L with no lactate increase as a result of tissue hypoxia [162].

In summary, dilutional acidosis is predictable and defined as an iatrogenic disruption brought on by bicarbonate dilution in the entire extracellular space which may be associated with hyperchloremia or hypochloremia depending on whether dilution was produced by infusion of a hyperchloremic or hypochloremic solution [95]. It still needs to be seen whether hyperchloremic iatrogenic acidosis is indeed associated with lower mortality than lactic acidosis, as recently claimed [19].
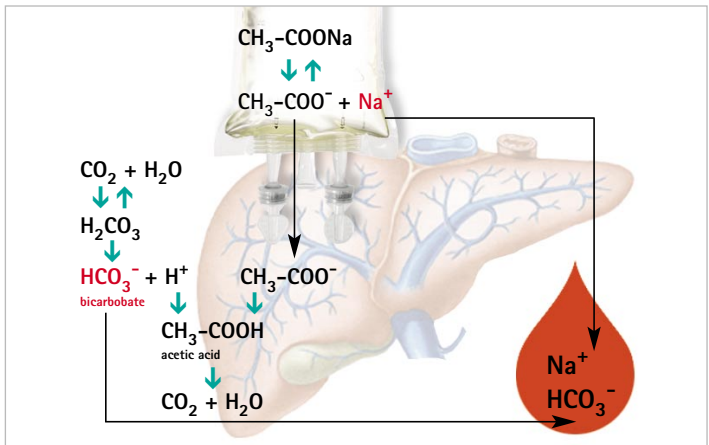

Figure 1: Synthesis of bicarbonate from metabolizable anions e.g. acetate

4.4. Metabolizable Anions

Dilutional acidosis can be prevented by the use of adequate concentrations of metabolizable anions to replace HCO_3^-.

The following anions of organic acids may be used as metabolizable bases: acetate (acetic acid), lactate (lactic acid), gluconate (gluconic acid), malate or hydrogen malate (malic acid), and citrate (citric acid). Consuming H^+ ions and oxygen in the process, these anions are metabolized in the intact liver (mainly lactate) or in muscle (mainly acetate and malate) to produce HCO_3^-. At pH 7.40, carbonic acid (H_2CO_3) is the only H^+ ion source of the body (while supplied at a low concentration of 1.2 mmol/L, H_2CO_3 can be synthesized freely from $CO_2 + H_2O$). HCO_3^- is therefore released in equimolar amounts. For every mole of acetate, gluconate, or lactate oxidized, one mole of bicarbonate is produced, while for every mole of malate or citrate oxidized, 2 or 3 moles of bicarbonate are produced, respectively (Fig. 1).

Example: If an infusion fluid contained 24 mmol/L of one of these anion species for replacement of bicarbonate, infusion of 1 L of that solution would result in the production of 24 mmol/L of bicarbonate (physiological concentration) from acetate, gluconate, or lactate; 48 mmol/L from malate; or 72 mmol/L from citrate. The two latter metabolizable anions would thus produce excessively high, unphysiological bicarbonate concentrations.

If an infusion fluid contains metabolizable anions in concentrations exceeding the lack of bicarbonate, infusion-induced alkalosis is a likely consequence, called rebound alkalosis. Metabolic alkalosis is always iatrogenic.

In surgery, posttraumatic alkalosis is considered iatrogenic [109]: Of 1,414 critically ill patients, 12.5 % had an arterial pH greater than 7.55. Alkalosis is the most frequent disruption of the acid-base balance: As many as 66 % of all disturbances of the acid-base balance are meta-

bolic or combined metabolic and respiratory iatrogenic alkaloses. At pH 7.58 or higher, mortality among these patients is approximately 50 % [191].

4.4.1. Acetate

Normal Plasma Acetate Concentration
The normal plasma acetate concentration is very low and has been reported to range from 0.06 to 0.2 mmol/L [12, 35, 45, 92, 107, 147]. Patients undergoing acetate hemodialysis have had plasma acetate levels as high as 6.5 mmol/L [93]. As acetate is also an ethanol metabolite, the plasma acetate concentration may increase to 0.8 mmol/L during administration of ethanol [12, 45, 78, 88, 106].

Acetate Metabolism
Any metabolic pathway must be electroneutral on balance. Acetate (the base the patient is infused with) is therefore oxidized in the form of acetic acid (after taking up H^+). Two moles of O_2 are required per mole of acetic acid. The chemical equation for the reaction of sodium acetate with oxygen is:

$$CH_3\text{-}COONa + 2\,O_2 \rightleftharpoons CO_2 + H_2O + NaHCO_3$$
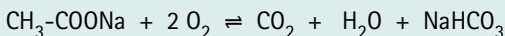
Two important conclusions can be drawn from this equation:

1. For every mole of acetate oxidized, one mole of bicarbonate is produced; this is the expected effect of acetate for HCO_3^- replacement or alkalization.

2. For every two moles of O_2 consumed, only one mole of CO_2 is produced. This is a surprising "side" effect in that the respiratory quotient (RQ) for acetate is only 0.5 [132]. Compared with glucose (dextrose), which has a RQ of 1.0, this means that the metabolism of acetate causes only half the inhaled O_2 to be exhaled as CO_2.

Acetate to Replace HCO_3^-

The alkalizing effect of acetate was first described in 1910 in the treatment of cholera [23, 40] and first used in hemodialysis in 1964 [117]. Compared with HCO_3^-, acetate has practically the same effect [23, 84, 99, 126, 147].

Other uses of acetate for alkalization include correction of acidosis in preterm infants [41], treatment of diabetic lactic acidosis [62], urinary alkalization, reduction of calcium excretion [14], and, unlike lactate, clinical situations in which hepatic metabolism is more or less impaired, such as in hemorrhagic shock [92], dialysis patients with severe hepatic impairment [42], or during hepatectomy [128].

In-depth studies of acetate metabolism, frequently using C^{14} acetate, have produced a number of important findings:

1. Acetate has a pivotal role in carbohydrate and lipid metabolism. Its effect(s) can therefore be summarized as follows: "Acetate replaces fat as an oxidative fuel, without effecting glucose oxidation" [4]; all tissues have the enzymes required for acetate metabolism, especially the liver, muscle, myocardium, and renal cortex [85, 91]; acetate rarely produces a slight increase in glucose concentrations [82].
   Myocardial metabolism shows significant changes in response to acetate from ethanol administered to volunteers: Oxidation of free fatty acids (FFA) decreased from approximately 50 % to 25 %, and lactate and acetate turnover increased from approximately 5 % to 20 % [98]. Following direct administration of acetate, myocardial glucose oxidation decreased from 75 % to practically 0 %, as did FFA oxidation, with 80 % of metabolic activity occurring via acetate oxidation [144]. The heart (300 g) as a whole oxidizes approximately 2 mmol/min [12].

2. The alkalizing effect of acetate is very rapid (healthy volunteer study): The HCO_3^- concentration increased as early as 15 minutes after the start of an acetate infusion [126]; 90 % of the infused amount of acetate was oxidized in a matter of minutes [4, 5, 32]; and 60 % to 80 % of the administered acetate was eliminated as CO_2 via the lungs within 1 to 12 hours [32, 91, 123].

3. Acetate is metabolized significantly faster compared with lactate [9, 59, 84].

4. Acetate metabolism is unchanged in patients with diabetes: There was no change in glucose or insulin concentrations [4, 5, 60].

5. Although the renal threshold has been reported to be practically 0 mmol/L, less than 10 % of an acetate dose is eliminated via the kidneys [67, 147]. However, rapid acetate administration to healthy volunteers (300 mmol within 1 hour in a 75-kg individual) may, as a result of alkalization, lead to substantial HCO_3^- elimination via the kidneys, similar to that observed for a control HCO_3^- infusion administered to a similar subject at the same rate [147].

6. Acetate turnover has shown no age-related differences [165].

7. Acetate is a fuel delivering 209 kcal/mol [166].

Acetate thus has a number of significant advantages over other metabolizable anions.

Clinically Relevant Observations During Acetate Use

Maximum turnover of acetate, used mainly in hemodialysis, has been reported to be approximately 350 mmol/hour in a 75-kg patient [93], and this quantity is substantially greater than the amount of acetate delivered when infusing a patient with 1 liter of a solution containing 24 mmol/L. The RQ theoretically predicted for acetate (0.5) has been documented experimentally: the lowest measured RQ was 0.62 [135]. Hypoventilation accompanied by arterial hypoxia as a result of the decrease in RQ during acetate hemodialysis became only relevant at very high acetate concentrations (3 to 6 mmol/L) and did not necessitate any therapeutic intervention.

There is conflicting evidence in the literature regarding the question of whether or not acetate increases total oxygen consumption. However, any increase in O_2 consumption in response to acetate administration would be expected to be moderate because acetate oxidation is not additive to total substrate turnover but rather competitively displaces other substrates.

Does Acetate Have Side Effects?

Used in hemodialysis, acetate has also been associated with vasodilator effects: "Acetate exerts a depressant action on the cardiovascular system [3]."

There have been reports of transient blood pressure drop [68, 74, 83, 110], constant blood pressure readings [83, 93, 97, 137], or blood pressure increase [130, 153] after the administration of acetate.

It is generally recognized that local, highly concentrated administration of acetate, citrate, malate, fumarate, or succinate, but not lactate or HCO_3^-, produces vasodilation [46, 134] presumably mediated by the release of adenosine from tissues [168].

Practically all studies have described decreases in systemic vascular resistance, ranging from 10 % to 65 % as a function of dose [31, 74, 83, 97, 130, 153], offset in many instances by a commensurate increase in cardiac output though.

The observation that the coronary vessels also benefit from vasodilation [97, 120] suggests that acetate may also have a "possible inotropic action" [153]. A review of the conflicting evidence available on the potential positive inotropic activity of acetate in humans (4 studies supporting such an activity, 2 studies suggesting otherwise) cannot resolve this issue either [130].

What is clear though is that these effects are only observed when high acetate doses are administered at high rates. In healthy volunteers, 85 mmol of acetate administered within 20 minutes [130] or 150 mmol administered within 60 minutes [4], up to a plasma acetate concentration of 6 mmol/L [93], produced no blood pressure drop; nor did similar doses in dogs [83, 153].

Rapid infusion of pooled protein fraction (PPF), with a high acetate concentration, also produced a transient drop in blood pressure [133].

In summary, this cardiocirculatory side effect is likely only with rapid administration of high doses (in the range of 50 to 100 mmol of acetate within one hour), if at all, and this would hardly appear possible with an infusion fluid that contains 24 mmol/L of acetate.

4.4.2. Lactate

Lactate has, for decades, been the most popular metabolizable anion in a wide variety of infusion fluids, in particular Ringer's lactate (Hartmann's solution).

A number of considerations argue against the use of lactate, especially in patients with pre-existing elevated plasma lactate concentrations (lactic acidosis):

Lactic acidosis is a manifestation of disproportionate tissue lactate formation in relation to potentially impaired hepatic lactate metabolism. It makes no sense to further increase oxygen consumption in a patient with pre-existing tissue hypoxia. In a patient with lactic acidosis, Ringer's lactate will invariably exacerbate pre-existing acidosis by producing dilutional acidosis; unnecessarily increase the risk of rebound alkalosis; and preclude the diagnostic use of lactate as an important marker of hypoxia.

These considerations will be discussed in more detail below, making comparisons with acetate where appropriate.

Lactate Metabolism
At the basal metabolic rate (BMR), the myocardium, muscle, brain, intestinal mucosa, and red blood cells produce approximately 1 mmol of lactate/kg/h, and more than half of it is eliminated by the liver [20, 32, 89].

$$CH_3\text{-}CHOH\text{-}COONa + 3\ O_2 \rightleftharpoons 2\ CO_2 + 2\ H_2O + NaHCO_3$$
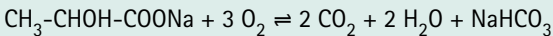
At the BMR, gluconeogenesis accounts for approximately 20 % and oxidation for approximately 80 % of lactate metabolism [20]. When lactate is supplied exogenously, up to 70 % of lactate can be used as a substrate for gluconeogenesis [139].

Intrahepatic gluconeogenesis ceases once pH falls below 7.1, or a BE of −15 mmol/L [15, 64]. Incipient hepatic dysfunction (increases in bilirubin and SGOT) quickly results in lactate concentrations as high as 8 mmol/L, which are associated with very high mortality [34]. Compared with acetate, lactate infusion is characterized by a relatively slow onset of alkalization and, therefore, has been called "delayed HCO_3^- infusion" [28]. Peak lactate turnover has been reported to be approximately 450 mmol/h [30]. As glucose levels may increase quite significantly after lactate administration [2, 8, 171], it comes as no surprise that intraoperatively administered Ringer's lactate may cause glucose concentrations to double in diabetics [171].

The D-lactic acidosis issue is not covered here because in Europe only physiological L-lactate is used, whereas racemic lactate (D and L) is traditionally used in the United States [176].

Does Lactate Increase Oxygen Consumption?
Oxygen consumption in laboratory animals increased very rapidly after the administration of lactate [6, 16]. Similarly, healthy volunteers given a bolus of 330 mmol of lactate showed an increase in O_2 consumption by almost 30 %, and this was mainly due to an increase in hepatic (almost 30 %) and muscle oxygen consumption (over 40 %) [2].

Lactate Clearance
The rate of lactate metabolism – above all in the liver – has become a major criterion for evaluating the therapeutic management of critically ill patients [1, 44, 52, 77, 121, 177]: "Changes in lactate concentration can provide an early and objective evaluation of the patient's response to therapy" [177].

Lactate and Mortality

Plasma lactate has similarly high predictive power to base excess for mortality in patients with various forms of shock including cardiac, hemorrhagic, and septic shock: Subsequent mortality is approximately 50 % when plasma lactate (not blood lactate) exceeds 4 to 7 mmol/L in the first 24 to 48 hours of shock [10a, 21, 22, 65, 76, 80, 137, 138, 148a, 179, 183, 184].

Corresponding data of 6 different studies with a total of 839 patients are summarized in figure 2: An initial value of only 3 mmol/L plasma lactate concentration predicts a 25 % mortality of cardiac, hemorrhagic, and septic shock patients.
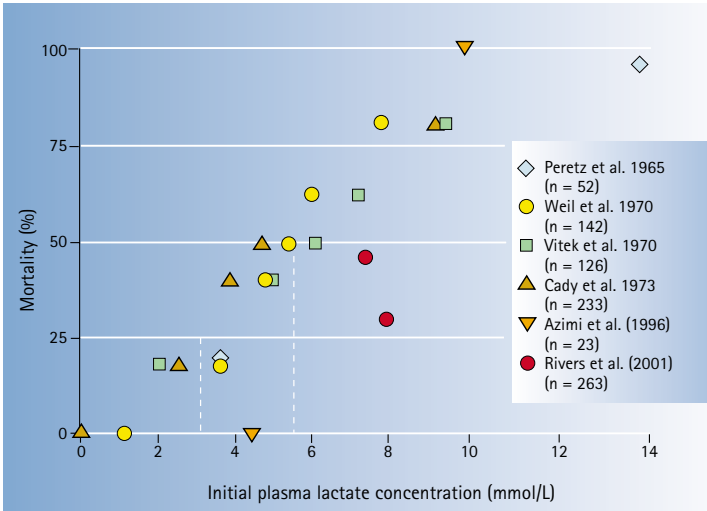
Figure 2: Mortality vs. plasma lactate concentration in shock patients

Ringer's Lactate and Lactate Assay

Many physicians apparently are not aware that the use of lactate-containing infusion fluids (such as Ringer's lactate) or blood products (such as packed red cells) and the diagnostic use of lactate as a marker of hypoxia are mutually exclusive [34]. Unfortunately, this error tends to be re-published time and time again [1, 22, 29, 70]. It is medical nonsense to infuse up to 50 L of Ringer's lactate within 24 hours [69] and at the same time attempt to establish a correlation between lactate concentration and oxygen deficiency: "Lactate levels seem to correlate with oxygen failure and death [70]."

Specific Problems With Lactate

The potential correlation between plasma lactate and panic attacks and the increase in lactate concentrations after hyperventilation and epileptic seizures are beyond the scope of this booklet.

4.4.3. Malate

The effects of malate are less well documented than those of acetate. At a patient pH of 7.40, all of malate is present as a divalent anion (malate^{2-}) so that for every mole of malate oxidized, two moles of bicarbonate (HCO_3^-) are produced [193]. The resultant alkalizing effect is significantly slower than that of acetate – which may be quite desirable when using malate in combination with acetate.

4.4.4. Gluconate

Compared with HCO_3^-, lactate, or acetate, the alkalizing effect of gluconate is almost zero [84, 129]. Therefore, there is no clinical merit in using gluconate.

4.4.5. Citrate

Citrate is another potential metabolizable anion because it has a substantial alkalizing effect (3 moles of H^+ are consumed for every mole of citrate) and is metabolized in practically all organs [72], especially in the liver [87].

In hemofiltration, citrate is used for anticoagulation and replacement of HCO_3^- [7, 43, 81]; undesirable alkalosis may occur with PPF administration [143], during plasmapheresis [111, 136], or following massive transfusions [100]. The maximum dose of citrate is very limited because of its potential to bind calcium; its LD_{50} (50 % mortality in a group of laboratory animals) is as low as 1.75 mmol/kg [53].

5. Isotonicity

A physiological, i.e., balanced, infusion fluid is isotonic if it has the same actual osmolality as plasma (288 mosmol/kg H_2O) or the same theoretical osmolarity of a physiological (isotonic) NaCl solution of 308 mosmol/L. What counts is the osmolality that is effective in vivo rather than that measured in vitro. This should be kept in mind because additives to infusion fluids are metabolized and have their osmotic effect altered in the process. Dextrose 5 % in water (D5W), for instance, is clearly isotonic in vitro, but its in vivo effect is that of pure water because glucose rapidly enters the intracellular compartment to be metabolized there. If, however, a solution contains metabolizable anions, these osmotically active species must be taken into account:

While 24 mmol of acetate is metabolized to 24 mmol of bicarbonate in equimolar fashion (these two species are osmotically equivalent), 5 mmol of malate is metabolized to 10 mmol of bicarbonate (which means that the osmotic activity of malate is doubled).

6. The Osmolarity (mosmol/L) and Osmolality (mosmol/kg H₂O) of an Infusion Fluid

The osmotic activity of an infusion fluid is described in terms of its osmolarity or osmolality. Unfortunately, usage of these two terms in the literature is often confusing or incorrect.

The theoretical osmolarity of a solution is obtained by the addition of all osmotically active species as per analytical composition of the infusion fluid relative to 1 L of solution. These data can be used to calculate the actual (real) osmolality of the solution based on the osmotic coefficients and the water content (if different from 100 %), but now relative to 1 kg of the solvent water. Actual osmolality can also be determined from freezing-point depression.

The physiological, actual osmolality of all human body fluids including plasma is 288 ± 5 mosmol/kg H_2O. By pure chance, the actual, physiologically active osmolality of plasma is practically identical to the theoretical osmolarity (291 mosmol/L) that can be calculated from its analytical composition.

Normal saline (0.9 % NaCl solution) has a theoretical osmolarity of 308 mosmol/L (154 mosmol/L Na^+ and 154 mosmol/L Cl^-) and an osmotic coefficient of 0.926 (only 93 % of NaCl is osmotically active); its osmolality is therefore 286 mosmol/kg H_2O.

Table 3:

Osmolarity versus osmolality

	Plasma Electrolytes (mmol/L)	Plasma active osmotic particles (mosmol/L)	Ringer's Acetate (mmol/L)	NaCl (mmol/L)
Na^+	142	142	130	154
K^+	4.5	4.5	5	
Ca^{2+}	2.5	1.3*	1	
Mg^{2+}	1.25	0.7*	1	
CL^-	103	103	112	154
HCO_3^-	24	24		
Phosphate^{2-}	1	1		
Sulfate^{2-}	0.5	0.5		
Organic acids	1.5	1.5	27	
Proteinate$^-$	20	1		
Glucose		5		
Urea		5		
Σ	$\Sigma = 291$		$\Sigma = 276$	$\Sigma = 308$
Theor. osmolarity (mmol/L)	291		276	308
Water content (%)	94		99.7	99.7
Theor. osmolality (mosmol/kg H_2O)	310		276	308
Osmotic coefficient	0.926		0.926	0.926
Actual osmolality (mosmol/kg H_2O)	287		256	286
Measured osmolality** (mosmol/kg H_2O)	288		256	286

* due to linkage to proteins
** freezing point depression

7. Hypotonic Infusion Fluids and Intracranial Pressure (ICP)

All body fluids have the same osmotic pressure as plasma, characterized by osmolarity or osmolality. As a result, infusion of a hypertonic solution may cause water to move from the intracellular to the extracellular fluid compartment. Conversely, infusion of a hypotonic solution may move water to the intracellular space. The latter situation is increasingly being viewed with a critical eye because many infusion fluids used in clinical practice are hypotonic. Typical examples include Ringer's lactate or Ringer's acetate (276 instead of 308 mosmol/L or 256 instead of 288 mosmol/kg H_2O), possibly leading to water uptake by organs with no particular consequences.

The brain (CNS), however, is a critical exception.

The rigidly shaped skull contains three incompressible fluid compartments, two of which – blood and cerebro-spinal fluid (CSF) – can be partially shifted outside the skull: brain, 1350 mL (g); blood, 125 mL; CSF, 145 mL.

Any volume change in any of these three compartments invariably results in an identical volume change in another compartment (cerebral edema, intracerebral hemorrhage, subdural hematoma, tumor, etc).

The compliance of the CNS describes the change in blood or CSF volume in response to a change in ICP, expressed in mL/mmHg. This means that any, even a minute, increase in CNS volume invariably produces an increase in ICP and thus a shift of CSF or blood from the skull and hence a decrease in cerebral blood flow. Compliance decreases substantially with increasing ICP because the blood or CSF volume shifts are limited.

The normal compliance of the CNS is approximately 0.5 mL/mmHg [154]. This means that there must be a 2-mmHg ICP increase in response to any 1-mL increase in CNS volume. This rise in ICP increases

disproportionately as the volume increases further because the compliance of the CNS decreases. A patient experiencing an increase in ICP to 30 mmHg for longer than a day can hardly survive without permanent damage [154].

This issue can be illustrated on the example of Ringer's lactate (RL).

Larger volumes of RL have long been known to produce a transient rise in ICP [172], but this increase is less pronounced than that observed after infusion of larger volumes of D5W [11]. Another fact is that the osmolality of plasma may be reduced by infusing RL [146, 158]; this has also been demonstrated in healthy volunteers infused with 3.75 L of RL within 1 hour [190].

The magnitude of the rise in ICP can be predicted from the reduction of plasma osmolality.

A decrease in osmolality from 288 to 287 mosmol/kg H_2O (-0.35 %) would be expected to produce an osmotic increase in CNS volume from 1,350 to 1,355 mL (+ 0.35 % from the influx of water), or an increase by 5 mL, which would be expected to produce an increase in ICP by 10 mmHg. This value is significantly smaller than the estimated 19 mmHg increase for every mosmol/L reported in the literature [155].

This rough estimate still appears to be realistic, as demonstrated by the data in Figure 3: The mean (large scatter) ICP increase (mmHg) measured after reduction of plasma osmolality in animal model(s) [73, 79, 158, 182, 195, 196] is 1.5 mmHg for every mosmol/kg H_2O reduction in plasma osmolality.

Measurement of the change in brain water content after reduction of osmolality by 13 mosmol/L and a 8.1 mmHg increase in ICP [196] produced a similar result: A 0.5 % change in (brain) water content (6.75 mL) would be equivalent to a 13.5 mmHg rise in ICP for a brain compliance of 0.5 mL/mmHg, and this value is quite comparable to 8.1 mmHg.

Conclusion: Infusion of larger volumes of hypotonic solutions should be avoided especially in the presence of space-occupying intracranial lesions or processes (cerebral edema, intracerebral hemorrhage, subdural hematoma, tumor, etc). Isotonic solutions are preferable at all events.
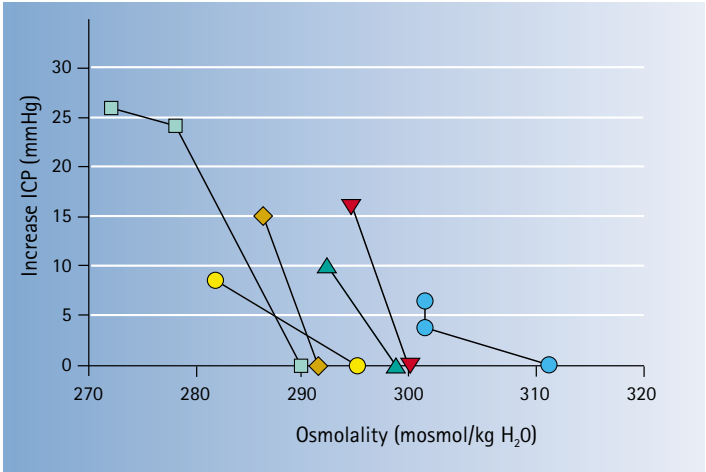

Figure 3: ICP increase in response to a change in plasma osmolality

Increase in intracranial pressure (ICP, mmHg) measured in laboratory animals in response to reduction of plasma osmolality (mosmol/kg H_2O) induced by infusion of Ringer's lactate, as reported by various authors [73, 79*, 158, 182, 195, 196].

* This author most likely meant osmolarity rather than osmolality (●).

8. Effects of Infusion Fluids on a Patient's Acid–Base Balance

8.1. Base Excess and Mortality in Multiple Trauma Patients

The base deficit (negative base excess, BE) of arterial blood has been shown to be the best quantitative indicator of acute blood loss in animal models, outperforming 27 other hemodynamic parameters and laboratory chemistries [180].

Early observations from 1979 in 50 patients had suggested that BE might also be a good prognostic indicator for multiple trauma patients [131]. Since 1990, four clinical trials [33,149, 151, 161] enrolling about 8,000 patients with multiple injuries have demonstrated that base excess on admission, compared with a large number of other parameters, is indeed the best prognostic indicator for mortality, complication rate, transfusions needs, etc. It has also been shown that a potential increase in base deficit (negative base excess) from hospital to ICU admission is a valid estimate of later risk [150, 167]. These results are illustrated in Figure 4.

Of course, these data cannot establish that base excess is indeed the cause of the observed mortality. One might come away with this idea when one considers the magnitude of the replacement fluid volume administered during this time:

The same studies found that a combined volume of 5 to 14 L of crystalloids and colloids was administered in the first 24 hours or until ICU admission. This suggests the following conclusion:

"Common sense suggests that in critically traumatized patients with multiple organic causes of acidosis any iatrogenic acidosis should best be avoided, especially when the advantages of using normal saline in most cases are not compelling [66]."
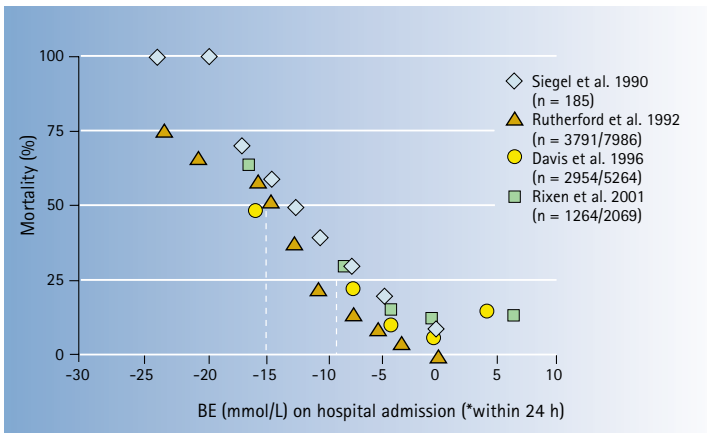
Figure 4: Mortality vs. BE in multiple trauma patients

Correlation between mortality (%) among multiple trauma patients and base excess (BE, mmol/L) on or within 24 hours of hospital admission in a population of approximately 8,200 patients statistically selected from about 15,300 patients [33, 149, 151, 161]: BE on or within 24 hours of hospital admission is a remarkably strong predictor of later mortality.

8.2. Labeling

The product label (composition) must alert the treating physician to potential effects of an infusion fluid on a patient's acid–base balance. The following parameters are available:

While mandatory for inclusion in the product label, titration acidity (TA, mmol/L) is practically useless in this regard.

The base excess (BE, mmol/L) of an infusion fluid, defined in analogy to blood [193], indicates the amount of HCO_3^- (mmol/L) needed to bring the pH of the solution to the patient's pH (7.40).

The potential base excess (BEpot, mmol/L) of an infusion fluid indicates the amount of HCO_3^- that can potentially be consumed or released in the body after infusion and metabolism of metabolizable anions. This value is obtained by adding BE (with a negative sign) in mmol/L to the sum of metabolizable anions, taking account of their valence.

Described as "infusion of actual or potential hydrogen ions" back in 1972 on the example of acid and alkaline amino acid infusions [63], BEpot was defined in 1993 [193] and, in 2002, applied to a large number of infusion fluids [194].

8.3. What Does a BEpot of 0 mmol/L Mean to the Patient?

Any infusion fluid that does not contain the physiological buffer base HCO_3^- will invariably produce dilutional acidosis when administered to a patient; the extent of dilutional acidosis obviously depends on the volume administered and the infusion rate.

Example: A solution contains 24 mmol/L of acetate and 5 mmol/L of malate, which between them release 34 mmol/L of bicarbonate. The BE of this solution is thus 34 mmol/L, but this value reflects the theoretical effect of the solution, in the absence of anion metabolism. However, as both acetate and malate are rapidly metabolized in the muscle

and liver, the potential base excess of the solution is 0 mmol/L. This means that, after infusion plus metabolism of acetate and malate, this solution has no effect on the patient's acid–base balance and, therefore, can cause neither acidosis nor alkalosis.

9. Differentiation Between Volume Replacement and Fluid Replacement

Successful differential intravenous fluid therapy crucially depends on clinicians to make a clear distinction between these two disparate therapeutic goals / indications (see above):

■ intravascular volume replacement with colloidal isotonic, isooncotic solutions VERSUS

■ extracellular fluid replacement with crystalloid isotonic solutions.

As either indication involves treatment of the extracellular fluid volume – either all (fluid replacement) or part of it (volume replacement) – there is a clear need for physiological, i.e., balanced, infusion fluids.

9.1 The Clinical Physiology of Major Fluid Compartments

Typical volumes of the major fluid compartments in a 75-kg individual: intracellular fluid volume (ICFV), 30 L (40 % of body weight); extracellular fluid volume (ECFV), 15 L (20 % of body weight); intravascular blood (fluid) volume (BV), 5 L (plasma volume, PV 3 L); the latter is part of the ECFV. The ratio of PV (3 L) to ECFV (15 L) is thus 1:5, and the ratio of PV to the extravascular fluid volume (EVFV, interstitial volume, 12 L) is 1:4. These ratios are essential to the infusion of an isotonic electrolyte solution, which distributes throughout the ECFV: Given a PV/EVFV (12 L) ratio of 1:4, infusion of 5 L of such a solution produces a blood volume increase by only 1 L (20 %), while the EVFV increases by as much as 4 L (80 %).

These figures (blood volume increases) have been confirmed many times over by measurements performed in healthy volunteers or patients following the infusion of normal saline, for example: 180 mL after an infused volume of 1 L [94], 375 mL after 2 L [102], 483 mL after 2 L [146], 768 mL after 3.2 L [50], and 1,085 mL after 3.5 L [51]. All of these BV increases are equivalent to 18 % to 31 % of the infused volume. The respective figures obtained with Ringer's lactate are 194 mL after infusion of 1 L [61] and 369 mL after 2 L [146], and approximately 225 mL of Ringer's acetate solution remained within the intravascular space after infusion of 1.5 L [56], confirming the normal saline data.

Conversely, if the objective is to increase the blood volume by increasing the plasma volume with a colloid (i.e., isooncotic) solution, a blood loss/volume replacement ratio of 1:1 can be safely assumed [192].

On principle, different possibilities for an increase of blood volume (IVFV) by 1 L as a result of different infused fluids are demonstrated in figure 5: 9.4 L of D5W (pure water) vs. 5 L of 0.9 % NaCl (isotonic cristalloid) vs. only 1 L of 6 % HES (isooncotic colloid) are necessary.
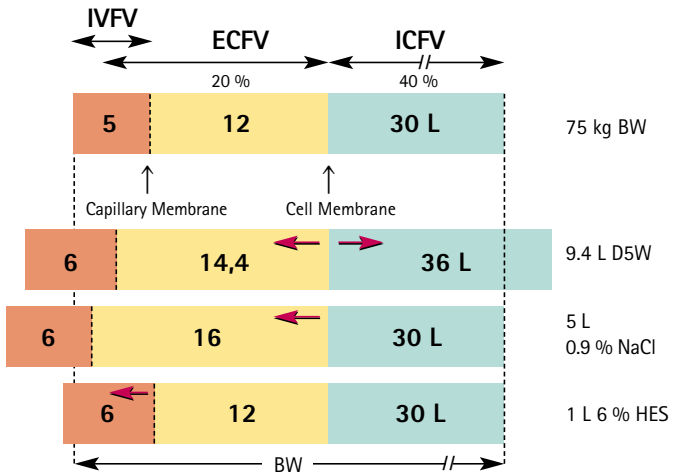
Figure 5: Possibilities for an increase of blood volume (IVFV) by 1 L

9.2. Would-Be Volume Replacement Through Fluid Replacement

Over the past few decades, clinicians have almost routinely – though with little success – been trying to achieve intravascular volume replacement through extracellular fluid replacement: "The most obvious clinical problems of inappropriate fluid resuscitation are shock from insufficient volume replacement and overhydration with subsequent pulmonary edema [145]."

Numerous animal studies of isovolemic hemodilution have demonstrated that animals do survive substantial blood volume loss when they are infused with crystalloids such as Ringer's lactate alone.

Following the removal of massive blood volumes and replacement of the removed blood with a crystalloid solution, 20 % to 100 % of animals survived down to a hematocrit of 20 % to 25 % when the blood volume loss was replaced with 2.5 to 3 times the removed blood volume [13, 170]. At a hematocrit of 10 % (two-thirds of blood volume removed), 50 % of the animals survived when three times the removed volume was replaced [173, 174]. Animals even survived a hematocrit of 5.8 % in one study replacing three times the removed blood volume [114].

However, it is inappropriate to consider these findings as evidence in support of a rational approach to hypovolemia because too many arguments suggest otherwise:

■ Any crystalloid volume replacement therapy increases the EVFV, causing an increase in body weight, which may be quite substantial. Overhydration (hyperhydration, intra-venous fluid overload) has been defined as >10 % weight gain [103] after a prospective study in 48 ICU patients had shown that mortality was 10 % in those with 5 % weight gain, 20 % in patients gaining 15 %, and 100 % in those with 32 % weight gain. A >10 % increase in body weight means that a 75-kg patient gains 7.5 kg (= L), which entails a 30 % increase in blood volume (from 5 to 6.5 L) and a 50 % increase in ECFV (from 15

to 22.5 L). As the compliance of the EVFV increases further above the 5 L/mmHg baseline value (in a 75-kg individual) with increasing expansion [55], weight gain is not limited by a pressure increase in the EVFV until extreme levels are reached.

■ Volume replacement therapy without the use of colloids reduces the albumin concentration and hence colloid osmotic pressure (COP, mmHg), invariably causing more water to move from the intravascular to the extravascular compartment. Unlike fluid accumulating in skin and muscle, pulmonary edema may lead to very serious problems. An impressive correlation between mortality among 99 critically ill cardiopulmonary patients and COP [124] is depicted in Figure 6: Reduction of COP to approximately 14 mmHg was associated with about 50 % mortality.

■ Crystalloid volumes must be increased overlinearly to replace increasing blood losses: An estimate shows that 5 L of crystalloid must be infused to replace the first liter of blood loss, while 6.7 L are needed to replace the second liter:

After replacing the first liter of blood loss with 5 L of a crystalloid solution, plasma volume has returned to normal, but the EVFV has increased from 12 to 16 L. The physiological PV/ECFV ratio of 1:5 (3 L/15 L) has therefore increased to 1:6.7 (3 L/20 L). To replace the next liter of blood loss, as much as 6.7 L of crystalloid must be infused to retain 1 L within the plasma compartment.

This phenomenon has been demonstrated in animal studies where the ratio of blood loss to crystalloid replacement volume increases from 1:3 to as much as 1:12 [24, 25, 26].
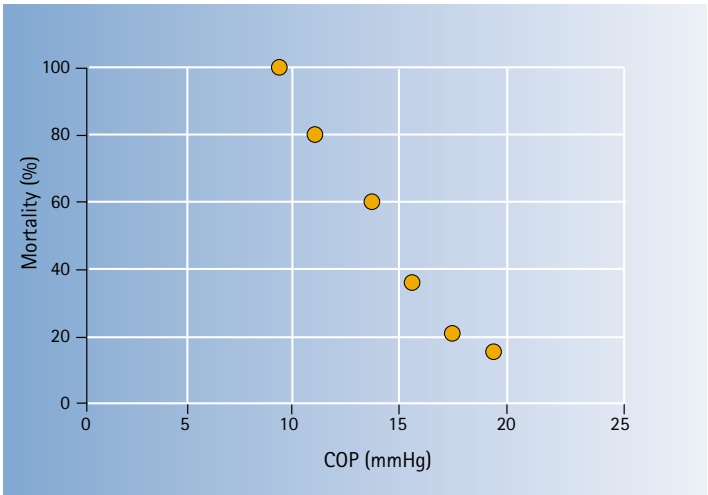
Figure 6: Mortality vs. COP in ICU patients

Correlation between mortality (%) and colloid osmotic pressure (COP, mmHg) in 99 critically ill cardiopulmonary patients [124]. Mortality increased substantially with decreasing COP: A decrease in COP to approximately 14 mmHg was associated with about 50 % mortality.

Approximately the same ratios apply to humans: When using crystalloids, minor blood loss should be replaced in a ratio of 1:3, moderate blood loss in a ratio of 1:5, and major blood loss (>1.5 L) in a ratio of 1:10 [125].

■ Crystalloid volume replacement therapy requires the use of increasing volumes that are the larger, the slower the infusion rate: To increase the PV in healthy volunteers by 250 mL, 750 mL of crystalloid must be infused over 15 minutes (the ratio is 1:3), but 1,125 mL is needed if this volume is administered over 45 minutes (the ratio is now 1:4.5) [58]. The most likely explanation for this observation is that the increasing expansion of the EVFV expands the distribution space for albumin ("albumin hemodilution") [163], leading to extravasation of albumin [24, 125].

■ The plasma albumin concentration is the major determinant of crystalloid volume replacement: The lower the albumin concentration, the greater the fluid shift from the intravascular to the extravascular space, i.e., there is an increase in EVFV [163].

■ How best to monitor and control crystalloid-based volume replacement therapy is apparently still a matter of much debate: "It does not make sense to titrate a fluid, most of which enters the interstitial space, against measurements taken of the intravascular space [175]."

Three of these six arguments outlined above will now be analyzed in more detail.

9.3. Fluid Overload – Pulmonary Edema

As early as 1973 [17], investigators urgently warned clinicians against overhydrating their patients: "currently overhydration is a far more frequent and serious problem in surgical patients than is dehydration."

The development of pulmonary edema was elucidated by Guyton's classical animal experiments in 1959 [54]: Once the artificially altered pulmonary capillary pressure (PCP) (even minimally) exceeded 25 mmHg, a laboratory animal would develop pulmonary edema within 30 to 180 minutes. When the plasma protein concentration was halved, pulmonary edema developed immediately after PCP (even minimally) exceeded 12 mmHg. Clinicians should therefore always maintain a clearly positive COP – PC(W)P difference to prevent any fluid shift to the extravascular space [142, 178].

The need for this precaution is particularly evident in patients with septic or hypovolemic shock [142]: After infusion of a mean volume of 8.6 L of 0.9 % NaCl solution, 88 % of those patients developed pulmonary edema once the COP–PCWP difference had decreased to 2 mmHg (COP, 14.7 mmHg; PCWP, 12.7 mmHg). Following the infusion of 5.2 L of a 6 % HES solution, as few as 22 % of the patients developed pulmonary edema (COP 23.5 mmHg minus PCWP 16.8 mmHg = 6.7 mmHg). Patients undergoing aortic surgery who were intraoperatively infused with 8.4 L of Ringer's lactate did not develop pulmonary edema despite a COP drop to 12 mmHg if PCWP was maintained at 6 mmHg [159]. The teaching points of these studies are clear enough: Avoid a significant drop in COP and avoid overhydrating your patients.

9.4. Fluid Overload – Weight Gain

Weight gain from overhydration should not be taken lightly: "Weight gain and systemic edema are not benign problems [145]."

Here are a few extreme values to illustrate the issue: A patient with a right heart infarction within 24 hours received 14 L of normal saline and D5W, had a urinary output of 2.7 L and 17 % weight gain [75]. An animal model simulating septic shock involved the infusion of 8.3 L of Ringer's lactate within 6 hours, resulting in a measured 37 % weight gain [112]. Burn patients with a mean burned body surface area of 46 % received up to 50 L of Ringer's lactate within 24 hours [69]; their estimated weight gain was 40 kg, or 60 % of their baseline body weight.

A closer look at the elimination kinetics of crystalloid fluids helps explain this phenomenon:

Normovolemic subjects intravenously infused with 1 to 3 L of normal saline, Ringer's lactate/Ringer's acetate, or D5W within 1 hour, excreted only 25 % to 40 % of NS within 4 to 6 hours, 45 % to 60 % of RL/RA within 2 to 24 hours, or 100 % of D5W within as little as 2 hours [37, 38, 71, 102, 146, 164]. If hypovolemia or hypervolemia was induced (by removal of up to 900 mL of blood or overinfusion, respectively), the elimination kinetics of the infused 2 L of Ringer's acetate were essentially unchanged [38]. The elimination kinetics are thus determined by the sodium/chloride content: Of 1 L of D5W with or without 70 mmol/L of sodium, as much as 85 % to 100 % was excreted within 2 hours, while only 50 % was eliminated of the same volume of Ringer's acetate with 130 mmol/L of sodium (chloride) [164].

Rapid osmoregulation – the elimination of free water (D5W) – apparently takes precedence over slow volume regulation – via essentially isotonic solutions (NS, RL/RA), distributed throughout the ECFV. In other words, free water is excreted rapidly, while sodium and chloride are eliminated significantly more slowly [57].

Applied to patients in the intra- and postoperative setting, these findings have the following consequences [9, 156, 157]: Intraoperative infusion of 9.5 L of Ringer's lactate (130 mmol/L of sodium) produces an 11 % to 14 % postoperative weight gain until the intraoperative

sodium load of 1,235 mmol has been excreted in a maximum daily urine output of approximately 3.5 L. The increase in body weight, or ECFV overhydration, is still 8 % on postoperative day 3 and 5 % on postoperative day 4.

9.5. Parameters Used for Control of Volume Replacement Therapy

Central venous pressure (CVP, mmHg), a classical parameter for evaluating a patient's volume status, can be used to demonstrate how differently such variables are used in clinical practice.

Compared with the very low normal CVP reading of 4 to 6 mmHg, which remains essentially unchanged even during acute hypovolemia or isovolemic hemodilution, the target values [see Table 4] are obviously subject to exceedingly high variability, and this would appear to carry a high risk of failure to control much-dreaded hypovolemia.

Table 4:

Random selection of typical CVP targets for various indications

Ref.	Indication	CVP Target (mmHg)
Mittelstaedt et al. [118]	Intraop. liver resection	0 – 3.7
Modig [119]	Traumatic shock	> 4.4
Lowery et al. [104]	Hemorrhagic shock	2 - 7
Sander et al. [152]	Intraop. GYN surgery	> 4.4
Mythen et al. [127]	Intraop. cardiac surgery[1]	5.5
Lucas et al. [105]	Intraop. casualties[2]	6.2 / 11.3
Kumle et al. [90]	Intraop. abdominal surgery	10 - 14
Boldt et al. [18]	Intraop. abdominal surgery	10 - 14
Gan et al. [48]	Intraop. blood loss > 0.5 L	$\geq$ 15
Riddez et al. [148]	Acute hypovolemia[3]	5.7 $\pm$ 3.2
Weiskopf et al. [185]	Acute isovolemic anemia[4]	5.5 $\pm$ 4.5

[1] 200 mL boluses of 6 % HES were injected until CVP responded with a >3 mmHg increase.

[2] A CVP of 11.3 mmHg was considered an "adverse effect" of albumin therapy because patients receiving crystalloid volume replacement therapy only showed a CVP of 6.2 mmHg.

[3] Volunteers (77 kg) before and after removal of 900 mL of blood.

[4] Acute isovolemic hemodilution in volunteers down to a cHb of 5 g/dL.

9.6. Is There a Particular Level of Volume Loss That Should Trigger a Switch From Fluid to Volume Replacement?

The typically smooth transition from fluid to volume replacement should be based on a patient's pathophysiological responses to blood loss.

> Healthy volunteers subjected to experimental hypovolemia experienced a shift of 500 to 700 mL of fluid from the extravascular to the intravascular compartment within 5 to 10 minutes; this process has been called "autotransfusion" [96, 108]. After removal of 645 mL of blood (12 % of BV), 250 mL, or approximately 40 % of the blood loss, was replaced with volume moved from the EVFV [122]. Removal of 900 to 1,000 mL of blood (18 % to 20 % of BV) can, of course, be isovolemically compensated by replacement with 5 % human albumin in a ratio of 1:1, but this can also be achieved with Ringer's lactate or Ringer's acetate in a ratio of 1:2 or 1:2.5, respectively, because the intravascular albumin concentration returns to normal within the subsequent 24 hours (both via synthesis and a shift from the extravascular compartment) [140, 148].

The level of blood loss that should trigger the switch from **crystalloid extracellular fluid replacement** to **colloid intravascular volume replacement** would thus appear to be approximately 15 % of total blood volume, or approximately 750 mL: Blood loss up to 15 % of BV (approximately 750 mL) can be replaced with crystalloid balanced solutions, while blood loss in excess of 15 % of BV should be replaced with colloid balanced solutions. Major blood loss should always be replaced with balanced colloids.

If true volume replacement is indicated, crystalloids should always be used with caution: "Crystalloids should be kept to a minimum, especially as the complications are now well recognized [175]."

The currently most popular colloid volume replacement fluids are 4 % modified fluid gelatin solution (MW 30 kD) with a maximum (initial) volume effect of 100 % and a volume effect half-life of 5 hours, and a

6 % hydroxyethyl starch solution (HES, MW 130 kD, molar of substitution 0.42) with a maximum (initial) volume effect of 120 % and a volume effect half-life of 7 hours [192]. The therapeutic effect of these products is significantly improved by formulating these colloids in a balanced solution rather than in normal saline.

To illustrate this point, comments on selected studies conducted in 2001 [189] are given: Surgical patients were assigned to two groups: One group received HES in normal saline and the other group was infused with HES in a balanced solution. The difference in chloride concentrations between the two solutions – 154 mmol/L (NS) versus 124 mmol/L (balanced solution) – increased the ECFV chloride concentration from 104.2 to 114.0 mmol/L in the NS group and from 104.9 to 108.2 mmol/L in the balanced solution group. Calculation of the chloride concentration from the ECFV plus administered volume (13.6 L + 4.1 L vs. 14.6 L + 3.7 L) yields a chloride concentration of 114.8 vs. 107.2 mmol/L. This good agreement between figures clearly demonstrates that the chloride administered is intraoperatively distributed in the entire ECFV, expanding this space accordingly (urinary outputs were as low as 200 to 350 mL). The same level of agreement is obtained for base excess: The decrease in BE was -6.9 mmol/L in the NS group (dilutional acidosis) versus -0.8 mmol/L in the balanced solution group. This 6.1 mmol/L difference compares optimally with the 5.7 mmol/L difference obtained when the amount of lactate administered (105 mmol/L) is divided by the ECFV at the end of surgery (18.3 L).

In conclusion, a balanced intravenous fluid completely prevents dilutional acidosis and very substantially reduces hyperchloremia, thus conferring two major benefits. There are currently no arguments in support of the use of human albumin [192].

10. Summary & Conclusion

A balanced intravenous fluid with the attributes described in this booklet for use as either a **colloid isotonic, isooncotic solution for intravascular volume replacement** or a **crystalloid isotonic solution for extracellular fluid replacement** might render the following rather pessimistic opinion from 1999 [27] no longer justified: "Despite >20 years of animal and human studies, the optimal fluid for resuscitation in a clinical situation remains unclear."

A balanced solution has the physiological electrolyte pattern of plasma in terms of sodium, potassium, calcium, magnesium and chloride and their relative contributions toward osmolality, and a physiological acid-base balance achieved with metabolizable anions to replace bicarbonate. Such a balanced intravenous fluid confers the following benefits:

- The same balanced solution could be used as a crystalloid or a colloid solution for fluid replacement or volume replacement, respectively.

- Other than volume overload, infusion of such a balanced solution would be devoid of the potential to produce any iatrogenic electrolyte imbalances. In particular, there would be no risk of hyperchloremia of the extracellular space and the attendant risk of renal vasoconstriction and reduced diuresis, possibly leading to significant, prolonged overhydration and weight gain persisting for several days.

- After infusion and anion metabolism, a solution with a BE_{pot} of 0 mmol/L has no effect on the patient's acid–base balance and, therefore, can cause neither acidosis nor alkalosis nor dilutional acidosis, an iatrogenic disorder caused by bicarbonate dilution in the entire extracellular space.

- Compared with other metabolizable anions, acetate has a number of advantages, especially over lactate, which should no longer be used as a metabolizable anion.

- A strictly isotonic solution rules out the risk of development of cerebral edema.

- Blood loss up to 15 % of BV (approximately 750 mL) can be replaced with crystalloid balanced solutions, while blood loss in excess of 15 % of BV should be replaced with colloid balanced solutions.

- Colloids can maintain a physiological COP to prevent any edema, especially pulmonary edema. Synthetic colloids such as MFG and HES are preferable to human albumin.

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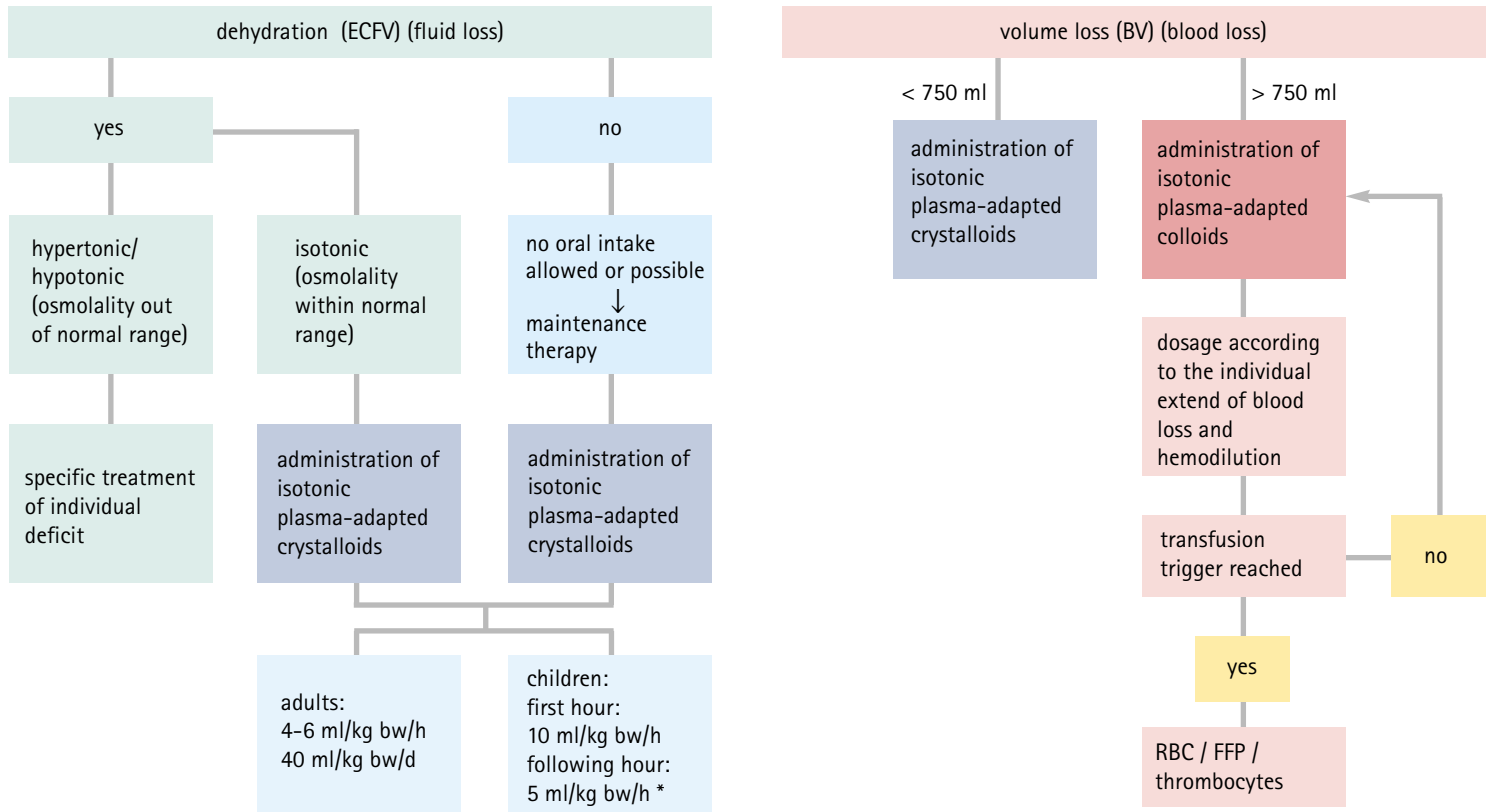   Anesthesiology 1987; 67: 936–941

List of abbreviations

BE	base excess
BEpot	potential base excess
BMR	basal metabolic rate
BV	blood volume
CNS	central nervous system
COP	colloid osmotic pressure
CSF	cerebrospinal fluid
CVP	central venous pressure
D5W	5 % dextrose solution in water
ECFV	extracellular fluid volume
ECS	extracellular space
EFVF	extra vascular fluid volume
FFA	free fatty acid
GFR	glomerular filtration rate
HES	hydroxyethyl starch
ICFV	intracellular fluid volume
ICP	intracranial pressure
IV	intravenous
IVFV	intravascular fluid volume (blood volume)
LD_{50}	lethal dose in 50 % of animals
MFG	modified fluid gelatin
NaCl	sodium chloride
NS	normal saline (0.9 % NaCl)
PCP	pulmonary capillary pressure
PCWP	pulmonary capillary wedge pressure
PPF	pooled protein fraction
PV	plasma volume
RL	Ringer's lactate
RA	Ringer's acetate
RQ	respiratory quotient
SGOT	serum-glutamat-oxalacetat-transaminase
TA	titration acidity
TBFV	total body fluid volume

Fluid therapy
= administration of crystalloids and colloids

infusion solutions substitute fluid loss
kind and composition of solution is dictated by the targeted fluid space only

dehydration (ECFV) (fluid loss)	volume loss (BV) (blood loss)

dehydration (ECFV) (fluid loss)

yes

no

hypertonic/ hypotonic (osmolality out of normal range)

isotonic (osmolality within normal range)

no oral intake allowed or possible
↓
maintenance therapy

specific treatment of individual deficit

administration of isotonic plasma-adapted crystalloids

administration of isotonic plasma-adapted crystalloids

adults:
4-6 ml/kg bw/h
40 ml/kg bw/d

children:
first hour:
10 ml/kg bw/h
following hour:
5 ml/kg bw/h *

volume loss (BV) (blood loss)

< 750 ml

> 750 ml

administration of isotonic plasma-adapted crystalloids

administration of isotonic plasma-adapted colloids

dosage according to the individual extend of blood loss and hemodilution

transfusion trigger reached

no

yes

RBC / FFP / thrombocytes

* fever increases the fluid requirements by 10 % per 1° above 37.5°C

R. Zander:

Fluid Management