R. Zander

Fluid Management

Second expanded edition

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1. Why a Booklet?

Against the background that normal saline (0.9% NaCl) solution is the most frequently used intravenous fluid [361], especially in the perioperative setting [315], a 2003 publication titled "(Ab)normal saline" [315] warned 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 [217], 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) [403].

This lack of interest in the composition of intravenous fluids among the medical profession has for decades been causing substantial problems in fluid management resulting from clinicians' failure to differentiate 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 oedema" [377].

1.1. Why a Second Edition?

A number of new facts have been published since the first edition of this booklet, putting a new perspective on fluid management – or fluid and volume replacement therapy to be precise:

- Fluid management in pediatric patients – a particularly vulnerable patient population – is a matter of heated debate worldwide because it has been made responsible for numerous deaths in "media hype" fashion. The one-of-a-kind 2007 appeal to the pharmaceutical industry, "please provide us with this special perioperative infusion fluid as it will definitely have the potential of saving lives!" vividly describes the predicament pediatricians are in [219].

- The "crux of coagulopathy" is frequently deplored in patients with massive injuries requiring massive transfusions [16]. Aggressive management of the "lethal triad" – coagulopathy plus metabolic acidosis plus hypothermia – therefore has the greatest potential of reducing mortality in severely injured patients [181].
- Balanced solutions provide greater safety for patients and physicians alike [416] because they prevent any acidosis and hence any coagulation disorder.
- Blood therapy (hemotherapy), the logical extension of volume replacement therapy, has shortcomings that mandate substantial restrictions on the use of packed red cells (PRCs) because balanced volume replacement therapy is devoid of these deficiencies, as aptly pointed up in the title of an editorial from 2008: "New blood, old blood, or no blood?" [3].

2. Volume Replacement Vs. Fluid Replacement: Two Aspects of Fluid Management

Differential intravenous fluid therapy is targeted at EITHER

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

The composition and discriminate use of intravenous fluids should solely 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 [411].

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 physiological 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 management 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; see below) 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 discriminate intravenous fluid management and typical IV 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% salt saline is neither 'normal' nor physiological" [319], gave the following definition of a balanced 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" [85], reiterating the old demand for "a solution containing sodium bicarbonate" [121] because it was clear that "the predominate physiologic deficit is metabolic acidosis" [253]. Appeals have since been published [117, 245, 254] along the lines of "We encourage anaesthesiologists to consider the role of fluids in acid-base change," or "acid base disorders may be avoided."

This development of a balanced solution was summarized in 2003 [315] 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, *i.e.,* discriminate fluid management using different solutions in an effort to restore or maintain physiological conditions [88].

4. What Should Go Into a Balanced Solution?

The physiological 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.

The physiological composition of plasma is described in Table 2, and compared to two common intravenous (IV) fluids: a colloid (6% HES in 0.9% NaCl) and a crystalloid (Ringer's lactate).

Table 2:

Composition of plasma and common IV fluids

	Plasma	6% HES in 0.9% NaCl	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 of the patient. A major benefit for the physician is that there is no risk of overdosage with this type of IV 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 effective circulating (blood) volume (ECV, BV), or intravascular fluid volume (IVFV). If the sodium concentration of a balanced 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 it is electrophysiologically active, especially in cardiac arrhythmias, and 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.

For special considerations regarding calcium, see "Coagulation and Ionized Calcium."

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 volume of the ECS. 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" (so-called physiological) saline (0.9 g/dL): 154 mmol/L Na^+ and 154 mmol/L Cl^-. These concentrations are much too high. Ringer's lactate (RL) solution contains too little sodium (130 mmol/L) and too much chloride (112 mmol/L).

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

Indeed there are, as emerges from various animal studies [192, 303, 404, 405].

> An increase in the ECS chloride concentration, but not an increase 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 (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. Induction of hyperchloremia requires the infusion of substantial volumes of a hyperchloremic infusion fluid, as demonstrated by the following 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.

This problem has also been demonstrated in humans [89].

Following infusion of 2 L of 0.9% NaCl solution, the hematocrit decreased by 10% (as little as 20% of the infused volume remained in the IVFV), the plasma chloride concentration increased predictably to 108 mmol/L, and the fluid balance of the supine subjects took about 2 days to normalize because the renin-aldosterone system was suppressed to approximately 60% for 2 days.

These findings on hyperchloremia have recently raised concern that the intraoperative use of hyperchloremic solutions (0.9% NaCl solution or normal saline (NS) used as a carrier solution for colloids) may trigger dysfunction of the transplanted kidney in renal transplant recipients [282]. This concern was subsequently dispelled by kidney function tests post-transplantation; Ringer's lactate proved to be better than NS in that the number of cases with acidosis was reduced from 31% to 0% of patients, and hyperchloremia was reduced from 111 to 106 mmol/L [283].

4.3. Bicarbonate and Dilutional Acidosis

Infusion fluids that do not contain the physiological buffer base bicarbonate – *i.e.*, all of the IV fluids that are currently available worldwide – produce dilutional acidosis in the patient 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 [346]: 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. [17], 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 that would lead to tissue hypoxia [349].

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 [206].

The interpretation of dilutional acidosis being simply the result of bicarbonate dilution in the entire ECFV keeps being negated [264]. Therefore a chloride balance and, later on, a bicarbonate balance is presented here to establish that this interpretation is, in fact, correct. Attempts to deduce a BE decrease of 0.4 mmol/L from a chloride supply of 1 mmol/kg of body weight [281] have failed, as have attempts to establish a correlation between an increase in chloride and a decrease in BE, since it was erroneously presupposed that chloride distributes in total body water [353]. When doing a careful balance, however – *i.e.,* chloride intake minus urinary chloride excretion – chloride intake (from various infusion fluids) correlates with the resulting decrease in BE; this applies to both dilutional acidosis and hyperchloremia [396].

Using 4 examples, demonstrated, in quantitative terms, how easy it is to intraoperatively produce iatrogenic hyperchloremia plus dilutional acidosis with IV fluids with different chloride concentrations (0.9% NaCl containing 154 mmol/L of chloride and Ringer's lactate containing 112 mmol/L of chloride).

In the first case [406], the ECFV was diluted by 29% within a good 3 hours (4.1 L of HES in 0.9% NaCl plus 0.9% NaCl, urine output 0.2 L) or by 23% (3.7 L of Ringer's lactate, urine output 0.3 L); in the second case [41], the ECFV was diluted by 35% in a little under 2 hours (5.7 L of 0.9% NaCl, urine output 0.8 L) or by 26% (5.4 L of Ringer's lactate, urine output 1.2 L); in the third case [367], the observed dilution was 37% in 5 hours with 5.1 L of 0.9% NaCl (urine output 0.6 L) or 36% with 5.1 L of Ringer's lactate (urine output 0.5 L); in the fourth case [395], the dilution was 36% within approximately 5 hours with 7.0 L of 0.9% NaCl (urine output 1.2 L) or 36% with 6.9 L of Ringer's lactate (urine output 1.0 L). The concentration changes rather than the absolute values were used in the two latter cases.

The simple balance of the ECFV (20% of body weight) chloride concentration based on a normal reference value of 103 mmol/L shows a good correlation between calculated and author-measured chloride concentrations (Figure 1). The following model calculation (mmol/L) is given as an example: 15 L of ECFV with 103 + 5 L with 154 (0.9% NaCl) yields 20 L with 115.8. This hyperchloremia demonstrates overhydration, which equally manifests as dilutional acidosis via the change in HCO_3^- concentration (see below).

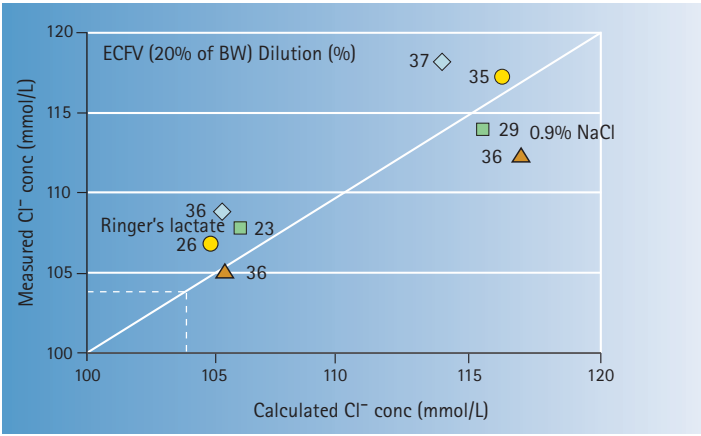


Figure 1: Four typical clinical examples [41, 367, 395, 406] of overhydration as a result of intraoperative dilution of the ECFV with IV fluids of different chloride concentrations (0.9% NaCl and Ringer's lactate).

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 are 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 replace 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. This is illustrated in Figure 2 on the example of acetate.

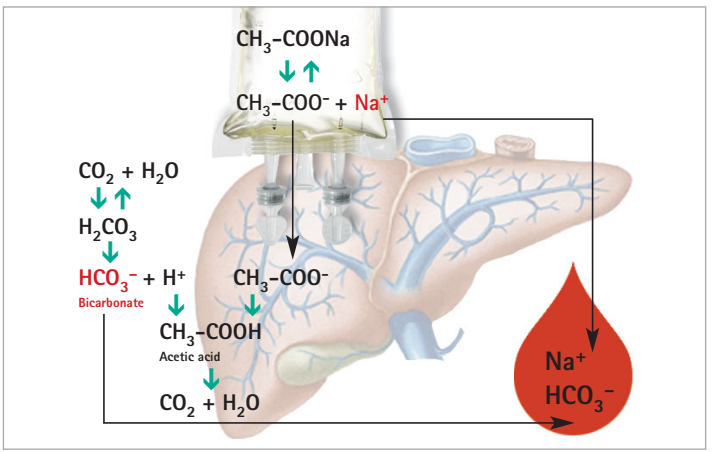


Figure 2: Synthesis of bicarbonate from metabolizable anions illustrated on the example of acetate.

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. Metabolic alkalosis is always iatrogenic.

In surgery, posttraumatic alkalosis is considered iatrogenic [227]: 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 metabolic or combined metabolic and respiratory iatrogenic alkaloses. At pH 7.58 or higher, mortality among these patients is approximately 50% [409].

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 [22, 83, 111, 203, 224, 318]. Patients undergoing acetate hemodialysis have had plasma acetate levels as high as 6.5 mmol/L [204]. As acetate is also an ethanol metabolite, the plasma acetate concentration may increase to 0.8 mmol/L during administration of ethanol [22, 111, 176, 196, 223].

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 [289]. Compared with glucose (dextrose), which has an 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 [50, 93] and first used in hemodialysis in 1964 [257]. Compared to HCO_3^-, acetate has practically the same effect [49, 188, 215, 270, 318].

Other uses of acetate for alkalization include correction of acidosis in preterm infants [97], treatment of diabetic lactic acidosis [145], urinary alkalization, reduction of calcium excretion [29], and, unlike lactate, clinical situations in which hepatic metabolism is more or less impaired, such as in hemorrhagic shock [203], dialysis patients with severe hepatic impairment [98], or during hepatectomy [275].

In-depth studies of acetate metabolism, frequently using C14 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" [6]; all tissues have the enzymes required for acetate metabolism, especially the liver, muscle, myocardium, and renal cortex [189, 202]; acetate rarely produces a slight increase in glucose concentration [184].
   Myocardial metabolism also shows significant changes in response to acetate production 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% [214]. 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 [308]. The heart (300 g) as a whole oxidizes approximately 2 mmol/min [22].
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 [270]; 90% of the infused amount of acetate was oxidized in a matter of minutes [6, 7, 76]; and 60% to 80% of the administered acetate was eliminated as CO_2 via the lungs within 1 to 12 hours [76, 202, 265].
3. Acetate is metabolized significantly faster compared to lactate [15, 139, 188].
4. Acetate metabolism is unchanged in patients with diabetes: There was no change in glucose or insulin concentrations [6, 7, 141].
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 [154, 318]. 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 [318].
6. Acetate turnover has shown no age-related differences [354].
7. Acetate is a fuel delivering 209 kcal/mol [355].

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 [203], 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 [294]. The hypoventilation accompanied by arterial hypoxia observed as a result of the decrease in the RQ during acetate hemodialysis became only relevant at very high acetate concentrations (3–6 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. This question can therefore not be answered. However, an increase in O_2 consumption in response to acetate administration, if any, would be expected to be moderate because acetate oxidation is not additive to total substrate turnover, but acetate metabolism rather competitively displaces other metabolites.

Does Acetate Have Side Effects?

Again when used in hemodialysis, acetate has been associated with vasodilator effects: "Acetate exerts a depressant action on the cardiovascular system" [5].

There have been reports of transient drops in blood pressure [155, 166, 187, 233], constant blood pressure readings [187, 204, 213, 297], or blood pressure increases [280, 333] after the administration of acetate.

It is generally recognized that the local administration of high concentrations of acetate, citrate, malate, fumarate, or succinate, but not of lactate or HCO_3^-, produces vasodilation [116, 293] which is presumably mediated by the release of adenosine from tissues [359].

Practically all studies have described decreases in systemic vascular resistance, ranging from 10% to 65% as a function of acetate dose [74, 166, 196, 213, 280, 333], offset in many instances by a commensurate increase in cardiac output though.

The observation that the coronary arteries also benefit from vasodilation [213, 260] suggests that acetate may also have a "possible inotropic action" [333]. A review of the conflicting evidence available for the potential positive inotropic activity of acetate in humans (4 studies supporting such an activity, 2 studies suggesting otherwise) cannot resolve this issue either [280].

> 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 [280] or 150 mmol administered within 60 minutes [6], up to a plasma acetate concentration of 6 mmol/L [204], produced no blood pressure drop; nor did similar doses in dogs [187, 333]. Too-rapid infusion of [PPL / PPS], also with a high acetate concentration, also produced a transient drop in blood pressure [290].

In summary, this cardiocirculatory side effect is likely to occur only with rapid administration of high acetate doses – in a range of 50 to 100 mmol of acetate within one hour –, if at all, and this would hardly appear possible with an IV 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 (RL, Hartmann's solution). The chemical equation for the oxidative breakdown of lactate to produce bicarbonate is:

$$CH_3\text{-}CHOH\text{-}COONa + 3\ O_2 \rightleftharpoons 2\ CO_2 + 2\ H_2O + NaHCO_3$$

A number of considerations argue against the use of lactate, especially in patients with preexisting 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 preexisting tissue hypoxia. In a patient with lactic acidosis, RL will invariably exacerbate preexisting 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.

4.4.2.1. 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/hr, and more than half of it is eliminated by the liver [43, 76, 197].

At the BMR, gluconeogenesis accounts for approximately 20% and oxidation for approximately 80% of lactate metabolism [43].

Intrahepatic gluconeogenesis ceases once the pH falls below 7.1, or a BE of –15 mmol/L [31, 147]. Incipient hepatic dysfunction (increases in bilirubin and SGOT) quickly results in lactate concentrations of 8 mmol/L, which are associated with very high mortality [82].

Compared to acetate, lactate infusion is characterized by a relatively slow onset of alkalization and, therefore, has been called "delayed HCO_3^- infusion" [62]. Peak lactate turnover has been reported to be approximately 450 mmol/hr [73].

When lactate is supplied exogenously, however, gluconeogenesis is the principal metabolic pathway for lactate [59]: up to 70% of exogenous lactate is utilized for gluconeogenesis [300]. Plasma lactate levels as low as 1–3 mmol/L triple the rate of gluconeogenesis, *i.e.,* glucose synthesis from exogenously supplied lactate [173]. Healthy volunteers experience practically no increase in glucose concentrations following lactate infusion [4, 59, 173], while patients show significant intraoperative increases [10]. And in diabetics, intraoperative glucose levels even double following administration of RL [370].

The situation is a substantially different one in shock patients.

When lactate production and glucose turnover more than double [317], e.g., in sepsis patients with mainly hepatic (gluconeogenesis) disruption of lactate clearance [211, 212], the additional infusion of lactate is, of course, contraindicated, since as little as 15% of exogenous lactate is utilized for gluconeogenesis in these circumstances [317]. The quantitation of this disrupted lactate clearance after lactate infusion in sepsis patients with plasma lactate concentrations of less than 3 mmol/L has high predictive power for subsequent mortality among these patients [212]. The correlation between lactate supply and glucose metabolism is mentioned because tight control of physiological glucose concentrations may have an impact on mortality among ICU patients [411].

Tight control of plasma glucose concentrations within a range of 80–110 mg/dL (4.4–6.1 mmol/L) has recently been shown to be associated with lower mortality in ICU patients, compared to a treatment strategy that permits higher plasma glucose levels (180–200 mg/dL) [381]. Further data analysis revealed that the observed favorable effect on the incidence of organ failure was primarily only due to tight control of plasma glucose rather than to insulin use *per se* [382].

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 [378].

4.4.2.2. Does Lactate Increase Oxygen Consumption?

Oxygen consumption in laboratory animals increases very rapidly after the administration of lactate [8, 32]. 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%) [4].

4.4.2.3. Lactate Clearance

The rate of lactate metabolism – above all hepatic clearance – has become a major criterion for evaluating the therapeutic management of critically ill patients [2, 19, 21, 41, 72, 105, 112, 129, 150, 174, 234, 247, 261, 320, 376, 385]: "Changes in lactate concentration can provide an early and objective evaluation of the patients response to therapy" [385].

In terms of prognosis and response to therapy, this applies especially to septic shock patients [19, 21, 72, 112, 129, 234, 247, 320, 376].

Lactate concentration in this context always refers to the (higher) plasma lactate concentration, which, in a few cases, was calculated from the blood lactate concentration using a conversion factor of 1.38 (blood with normal hematocrit) [413].

Figure 3 presents lactate clearance data for (hemorrhagic, cardiac, septic, traumatic) shock patients from 10 studies (543 patients) [2, 19, 21, 72, 105, 112, 150, 164, 234, 376]. These data demonstrate impressively that survivors, unlike nonsurvivors, can normalize their lactate concentration within 24 hours. Healthy individuals (e.g., athletes) manage to reduce a lactate concentration of, say, 12 mmol/L to a normal level of 1.5 mmol/L within approximately 30 minutes.

Some authors have suggested rather hard-and-fast rules for plasma lactate normalization:

For *myocardial infarction patients* [150], the following observation has been reported: "no patient survived in whom the arterial plasma lactate was greater than 5 mmol/l for more than 12 h."

Trauma, sepsis, and surgical ICU patients have been reported to survive only if their plasma lactate levels normalize to <2 mmol/L within 12–24 hours [2, 112, 164, 185, 247].

For *patients in circulatory shock,* fluid management is only successful if lactate can be lowered within the first two hours [385].

Conversely, the following holds for an increase in plasma lactate concentrations:

During cardiopulmonary bypass, an increase by more than 4 mmol/L predicts subsequent mortality with high sensitivity [271]; during congenital heart defect surgery in children (<1 yr), an increase by 0.75 mmol/L/hr is associated with subsequent death [56]; if a value greater than 9 mmol/L is measured one hour after successful cardiopulmonary resuscitation (CPR), survival is highly unlikely [401].

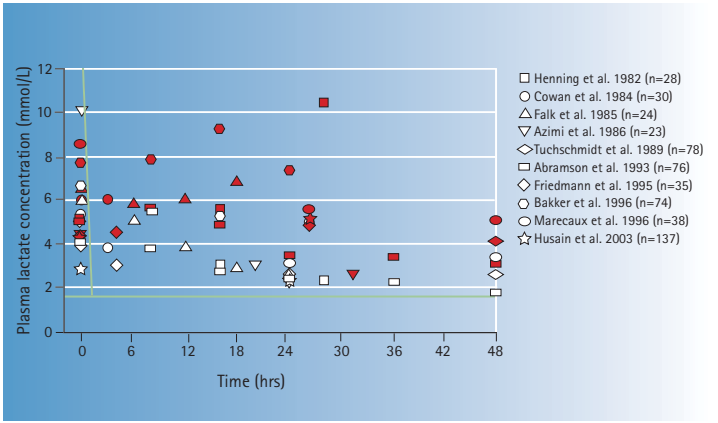


Figure 3: Lactate clearance in shock patients captured in terms of plasma lactate concentration (mmol/L) over time (hrs); survivors (white), nonsurvivors (red), and healthy individuals (green) [2, 19, 21, 72, 105, 112, 150, 164, 234, 376].

4.4.2.4. 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% if plasma lactate exceeds 5 to 8 mmol/L in the first 24 to 48 hours of shock [46, 49, 150, 170, 179, 297, 298, 387, 398, 400].

Data from 11 studies involving a total of 7,326 patients are summarized in Figure 4 [19, 46, 47, 247, 256, 298, 320, 321, 387, 398, 401]: A baseline plasma lactate concentration of approximately 6 mmol/L predicts 50% mortality for patients with cardiac, hemorrhagic or septic shock.

The baseline plasma lactate concentration in a wide variety of patient populations including surgical ICU patients, trauma patients, septic shock patients, and children undergoing cardiac surgery, can be used to very clearly differentiate between survivors and nonsurvivors: a value of 5 (2–8) mmol/L for survivors and of 8 (4–13) mmol/L for nonsurvivors [21, 56, 57, 234, 240, 247, 348].

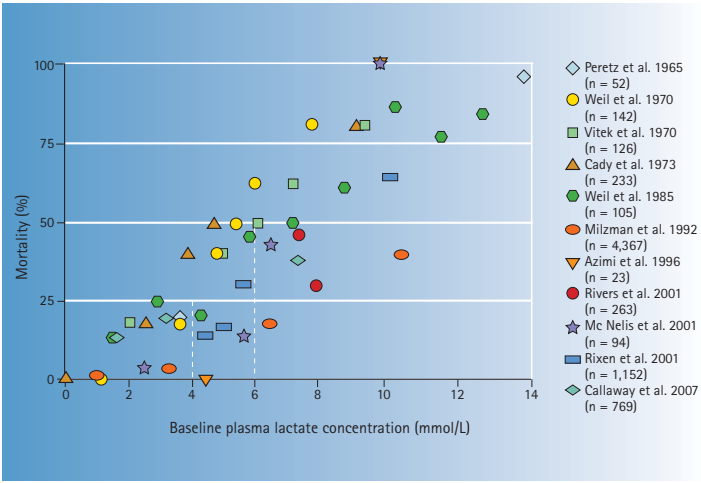


Figure 4: Mortality as a function of baseline plasma lactate concentration in shock patients [19, 46, 47, 247, 256, 298, 320, 321, 387, 398, 401].

4.4.2.5. Ringer's Lactate and Lactate Assay

Many clinicians apparently are not aware that the use of lactate-containing infusion fluids (such as RL) or blood products (such as packed red cells) and the diagnostic use of lactate as a marker of hypoxia are mutually exclusive [82]. Unfortunately, this error tends to be re-published time and time again [2, 49, 66, 158]. It is medical nonsense to

infuse up to 25 L [55] or even 50 L of RL within 24 hours [157] 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." [158].

4.4.2.6. Specific Issues 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.

Calcium binding by lactate will be discussed later.

4.4.3. Advantages of Acetate Over Lactate

Table 3 summarizes obvious advantages of acetate over lactate for use as a metabolizable anion.

Table 3:

Advantages of acetate over lactate

Effect		Acetate	Lactate
Metabolism			
HCO_3^- production		~15 min	Delayed
O_2 consumption		→	↑
Respiratory quotient (RQ)		0.5	0.67
Metabol. organs	Normal	All	Liver
	Shock	All	No
Gluconeogenesis (liver)		→	↑
Hyperglycemia (diabetes)		→	↑
Binding of ionized calcium		No	Yes
Lactate as hypoxia marker		Yes	No

4.4.4. 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 [419]. The resultant alkalizing effect is significantly slower than that of acetate – which may be quite desirable when using malate in combination with acetate.

4.4.5. Gluconate

Compared with HCO_3^-, lactate or acetate, the alkalizing effect of gluconate is almost zero [188, 276]; therefore, it cannot be used as a metabolizable anion.

4.4.6. 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 [162], especially in the liver [195].

In hemofiltration, citrate is used for anticoagulation and replacement of HCO_3^- [9, 104, 182]; undesirable alkalosis may occur with PPF administration [307], during plasmapheresis [237, 295], or following massive transfusions [216]. The maximum dose of citrate is very limited because of its potential to bind calcium; its LD50 is as low as 1.75 mmol/kg of body weight [131].

Conclusion: IV fluids without HCO_3^-, such as NS, produce dilutional acidosis which can be prevented by the use of metabolizable anions in appropriate concentrations. Acetate and malate are clearly superior to lactate, and gluconate has no alkalizing effect. The use of lactate-containing solutions, such as Ringer's lactate, is strongly discouraged.

5. Isotonicity

Any infusion solution used in fluid management should meet this requirement [411]: It should be isotonic to plasma, *i.e.,* its (actual) osmolality determined by cryoscopy (freezing point depression, FPD) should be in a range from 280 to 300 mosmol/kg H_2O; isotonicity should be labeled in terms of its calculated actual osmolality (mosmol/kg H_2O) *in vivo.* This requirement is currently met by no manufacturer; what they usually do is report only the theoretical osmolarity (mosmol/L), as determined by the addition of all osmotically active species contained in a solution.

In theory, consideration might be given to replacing the calculated osmolality values with cryoscopic data, determined by FPD. Two considerations argue against this. First, measured osmolality describes the values obtained *in vitro* (laboratory) rather than those encountered *in vivo* (patient) (see below). Second, preliminary (unpublished) results show that the mean deviation of less than 1% between measured and calculated osmolality observed for the three classical products (plasma, NS, and 5% glucose) is not attained by HES solutions (overestimated by almost 3% on average). Until this issue has been resolved, calculated *in vivo* osmolality should be given preference over measured values.

Reporting the calculated *in vivo* osmolality (mosmol/kg H_2O) on the IV fluid label is therefore the better choice when it comes to providing the best possible information for health care providers; an infusion fluid is "isotonic" if its calculated *in vivo* osmolality ranges between 280 and 300 mosmol/kg H_2O [411].

5.1. Osmolarity (mosmol/L) and Osmolality (mosmol/kg H_2O)

Different body compartments are in osmotic equilibrium if the number of osmotically active particles (osmoles) within the available water space is balanced. For example, freely permeable glucose is in equilibrium between erythrocytes (water content, 71%) and plasma (water content, 94%) if the concentrations in the available water space are equal. Making reference to one kilogram of water, *i.e.,* osmolality

(mosmol/kg H_2O), is therefore required for physiological considerations, since reference to one liter of erythrocytes or one liter of plasma would result in very different concentrations despite there being an equilibrium. Indeed, experimental data have demonstrated that all body fluids, including erythrocytes (ICFV, ECFV), never show deviations in osmolality from a subject's plasma osmolality by more than 1 mosmol/kg H_2O [149].

The differences between osmolarity and osmolality and between theoretical and actual are now demonstrated on the example of plasma.

> The theoretical osmolarity of plasma of 291 mosmol/L can be calculated by adding all osmotically active species relative to 1 liter of plasma. Given a water content of 94%, this converts into a theoretical osmolality of 310 mosmol/kg H_2O. This value is greater because the available water space is 6% smaller. As electrolytes, especially sodium and chloride, are osmotically active only in part – 92.6% for sodium and chloride (osmotic coefficient, 0.926) [123] – the actual (real) osmolality is lower: 287 mosmol/kg H_2O. Comparison with the measured actual normal value of plasma of 288 mosmol/kg H_2O reveals the surprising finding that plasma osmolality and plasma osmolarity happen to be virtually identical by chance. This coincidence is presumably responsible for some of the confusion in the medical literature. Actual osmolality (rather than osmolarity) can be measured via freezing point depression (FPD).

This deduction is shown in Table 4 for plasma, along with a comparison with Ringer's acetate solution and 0.9% NaCl solution. Given its theoretical osmolarity of 308 mosmol/L (154 mosmol/L of sodium and 154 mosmol/L of chloride) and its osmotic coefficient of 0.926, NS has an osmolality of 286 mosmol/kg H_2O.

Osmolality is usually measured via freezing point depression (FPD), using two points of reference: distilled water (0 mosmol/kg H_2O) with an FPD of 0°C and 1 osmolal mannitol solution (1.000 mosmol/kg H_2O) with an FPD of –1.86°C.

Table 4:

Osmolarity vs. osmolality

	Plasma		Ringer's acetate (mmol/l)	0.9 % NaCl (mmol/l)
	Electrolytes (mmol/l)	Osmotically active species (mosmol/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	Σ = 291		Σ = 276	Σ = 308
Theoretical osmolarity (mosmol/l)	291		276	308
Water content (%)	94		99,7	99,7
Theoretical 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

* Because of protein binding

** Freezing point depression

5.2. Physiological Normal Value of Osmolality

The normal value of the actual osmolality of plasma is 288 ± 5 mosmol/kg H_2O with an SD of only 1.8%; the mean is a weighted mean of cryoscopic measurements obtained in a total of 181 subjects [126, 148, 291]. If, for practical considerations, whole blood osmolality is to be measured, the deviation from the plasma value is not more than 0.5% [399].

This normal value has been confirmed by a number of authors: the reported mean value is 286 ± 0.9 [27] or 290 ± 4.7 [313] or 289 mosmol/kg H_2O [54]. Moreover, a normal range of 285–295 mosmol/kg H_2O has been reported as well [140].

A change in osmolality as a function of age has been demonstrated [285]: It increases slightly from 288 (at age 20) to 298 mosmol/kg H_2O (at age 65), but early findings suggest that this has no clinical relevance.

5.3. *In vivo* Vs. *in vitro* Osmolality

There may be a difference between the osmolality of an IV fluid measured *in vitro* (laboratory) and its effect *in vivo* (patient). Some authors have used the term "tonicity" to describe this concept: A hypertonic solution causes water to leave a cell, while a hypotonic solution causes the cell to swell.

The simplest example is 5% glucose (dextrose) solution: Theoretically, it contains 278 mmol = mosmol per liter of solution. Its osmolarity is therefore 278 mosmol/L. Given a water content of 97% and an osmotic coefficient of 1.013 (clearly different from that of NaCl) [123], 5% glucose solution has an actual osmolality of 290 mosmol/kg H_2O, and therefore is a clearly isotonic solution, which has been determined *in vitro* on a number of occasions. Infusion of this solution, however, has the same effect as an infusion of pure water, since glucose is rapidly

metabolized inside tissue cells, leaving the water behind in the extracellular compartment.

If 5 mosmol/kg H_2O of glucose and 5 mosmol/kg H_2O of urea were added to an IV fluid, this would be equivalent to an additional osmolality of 5 mosmol/kg H_2O each, since plasma also contains both of these components, and both substances are in a concentration equilibrium with the intracellular compartment.

If an IV fluid contains 24 mmol/L of lactate or acetate as a bicarbonate substitute, osmolality will be unchanged because intracellular lactate or acetate metabolism results in the equimolar release of 24 mmol/L of bicarbonate. This means that the osmolality of this solution remains unchanged. In other words, the value measured *in vitro* is equal to the effect seen *in vivo.*

If, however, a solution contains, say, 5 mmol/L of malate as a bicarbonate substitute, its osmolality will be increased by 5 mosmol/L after the malate has been metabolized, since two moles of bicarbonate are released for each mole of malate.

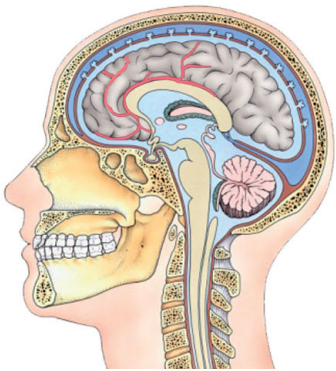
5.4. Hypotonic IV Fluids and Intracranial Pressure (ICP)

All body fluids have the same osmotic pressure as plasma, characterized by the value of osmolality. As a result, infusion of a hypertonic solution may cause water to move from the intracellular into the extracellular fluid compartment. Conversely, infusion of a hypotonic solution may move water into 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 and Ringer's acetate with an osmolality of 256 (rather than 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 – the blood and the cerebrospinal fluid (CSF) – can be partially shifted outside the skull: brain, 1340 mL (g); blood, 120 mL; CSF, 140 mL (see Figure 5).

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).



Brain	1,340 mL	+ 40 mL (3%)	
Blood	120 mL	– 40 mL (–33 %)	
		or	
CSF	140 mL	– 40 mL (–29 %)	
Total	1,600 mL		

Figure 5: Intracranial compartment responses to a change in plasma osmolality: A decrease in plasma osmolality by approximately 3%, say, from 288 to 280 mosmol/kg H_2O, invariably results in an increase in brain volume by 3%, causing a decrease in blood and/or CSF volume by as much as 30%.

The compliance of the CNS describes the change in blood and/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 quickly reach their limit.

The normal compliance of the CNS is approximately 0.5 mL/mmHg [335]. 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 [335].

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 [372], but this increase is less pronounced than that observed after infusion of larger volumes of D5W [20]. Another fact is that the osmolality of plasma may be reduced by infusing RL [315, 342]; this has also been demonstrated in healthy volunteers infused with 3.75 L of RL within 1 hour [407]. 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 [336].

This rough estimate still appears to be realistic, as demonstrated by the data in Figure 6: The mean (large scatter) ICP increase (mmHg) measured after reduction of plasma osmolality in animal model(s) [165, 177, 342, 392, 420, 421] 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 an 8.1 mmHg increase in ICP [421] 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.

Patients with a hypoosmolality of 240 mosmol/kg H_2O will fall into coma and show a mortality rate of 50% [13].

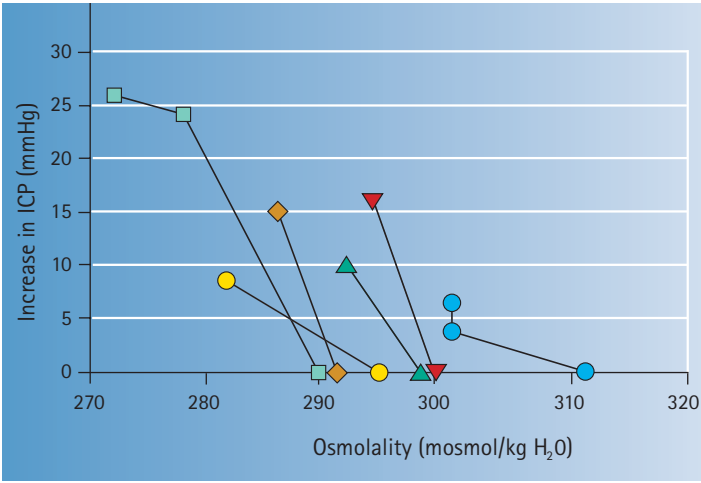


Figure 6: ICP increase in response to a change in plasma osmolality
increase in intracranial pressure (ICP, mmHg) measured in laboratory animals in response to reduction of plasma osmolality (mosmol/kg H_2O) induced by infusion of Ringer's lactate, as reported by various authors [165, 177, 342, 392, 420, 421].*
** This author most likely meant osmolarity rather than osmolality (●).*

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.

5.5. The Pathophysiology of Hyperosmolality

A number of classical clinical pictures are known to produce an occasionally dramatic increase in plasma osmolality with very high mortality.

Hyperosmolar hyperglycemic nonketotic syndrome (HHNS) in diabetics, which used to carry a mortality rate of almost 50% [12, 18], is thought to be due to excessive hyperglycemia, which produces a corresponding level of hyperosmolality. Clouding of consciousness begins at a glucose concentration of about 35–45 mmol/L, or a plasma osmolality of 325–335 mosmol/kg H_2O, and is due to hyperosmolality rather than to hyperglycemia [12, 350]. Substantial hyperosmolality is also observed in diabetic keto-acidosis (DKA), and loss of consciousness again is clearly correlated with plasma osmolality. In this condition, however, the hyperosmolality is rather due to an increase in lactate and ß-hydroxybutyrate than by an increase in glucose [102]. In both HHNS and DKA, mortality is clearly correlated with plasma osmolality – in children with the greatest predictive value [172].

Hypovolemic shock (acute hemorrhage with hypotension) also triggers hyperglycemia with hyperosmolality [37].

In an animal model, this has been found to be due to the release of epinephrine followed by hepatic glucose release [171]. Another hypothesis postulates that the increase in lactate leads to hyperglycemia via hepatic gluconeogenesis [183]. (In animal models) the hormone-induced increase in extracellular osmolality is proportional to blood loss [119], and detectable the sooner the greater the blood loss [45]. What remains a matter of debate, though, is whether hyperglycemia is responsible for hyperosmolality to a large [152] or rather small extent [183]. In patients with (multiple) injuries, mortality is clearly associated with hyperosmolality [180, 183]. In fact, survivors and nonsurvivors can be differentiated by their level of hyperosmolality: The difference between survivors and nonsurvivors is as little as 5 mosmol/kg H_2O in acute stroke patients [34], 15 mosmol/kg H_2O in multiple trauma patients [1], and as much as 25 mosmol/kg H_2O in ICU patients [160].

The repeatedly corroborated fact that hyperosmolality in shock patients has a not-insignificant role in restitution of the extracellular volume as well as plasma volume [37, 119, 171] will be revisited elsewhere in this Booklet.

Conclusion: Isotonic infusion fluids should be used as a matter of principle, especially in pre-existing hyperosmolality in shock patients. Hypotonic IV fluids should not be used because of the risk of cerebral edema. Hypertonic solutions should only be used – *e.g.*, in an effort to reduce ICP – as long as plasma osmolality is less than 320 mosmol/kg H_2O [161].

6. Effects of Infusion Fluids on a Patient's Acid-Base Balance

6.1. 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. It can be determined by titration in the laboratory or calculated from the composition.

The *base excess* (BE, mmol/L) of an infusion fluid, defined in analogy to blood [419], indicates the amount of HCO_3^- (mmol/L) needed to bring the pH of the solution to the patient's pH (7.40) under laboratory conditions (pCO_2 = 40 mmHg).

This means that any IV fluid without HCO_3^- automatically has a BE of –24 mmol/L or greater, depending on its titration acidity.

The *potential base excess* (BEpot, mmol/L) of an IV fluid indicates the amount of HCO_3^- that can potentially be consumed or released in the patient's body after infusion and metabolism of metabolizable anions (pCO_2 = 40 mmHg). This value is obtained by adding BE (with a minus 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 [146], BEpot was defined in 1993 [419] and, in 2002, applied to a large number of infusion fluids [418].

Conclusion: As with the calculated *in vivo* osmolality of 290 ± 10 mosmol/kg H_2O, basically the same demand is made here: Physicians are only fully informed about an infusion fluid if they are provided with the information they need to assess the impact of the IV fluid on their patient's acid-base status. In fact, doctors are rarely interested in bottle contents (pharmacy), and never in the amounts of ingredients that went into the solution (manufacture). The solution is ideal for them and their patients if BEpot is 0 ± 10 mmol/L.

6.2. What Does a BEpot of 0 mmol/L Mean for the Patient?

Any infusion fluid that does not contain the physiological buffer base HCO_3^- (BE –24 mmol/L) 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 with a TA of 10 mmol/l contains 24 mmol/L of acetate (monovalent anion) and 5 mmol/L of malate (bivalent anion), which between them release 34 mmol/L of bicarbonate. The BE of this solution is thus 34 mmol/L (TA + missing HCO_3^-), but this value reflects only the effect of the solution per se, in the absence of anion metabolism. However, as both acetate and malate are rapidly metabolized in the liver and muscle, the potential base excess of the solution is 0 mmol/L. This means that, after infusion and metabolism of acetate and malate, this solution can have no effect on the patient's acid-base balance and, therefore, will cause neither acidosis nor alkalosis. The requirement of a BEpot of 0 with a variation of ± 10 mmol/L is deduced from the fact that the solution will be diluted with 15 L of ECFV in the patient (75-kg individual) where it should produce a BE change of less than 1 mmol/L.

6.3. Base Excess and Mortality in Multiple Trauma Patients

The base deficit (BD, negative base excess) 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 [389].

Early observations from 1979 in 50 patients had suggested that BE might also be a good prognostic indicator for multiple trauma patients [288]. Since 1990, four clinical trials [80, 321, 326, 347] 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 BE) – referred to as BE clearance (see below) – from hospital to ICU admission is a valid estimate of subsequent risk [322, 356]. These results are summarized in Figure 7.

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:

"Commen 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" [151].

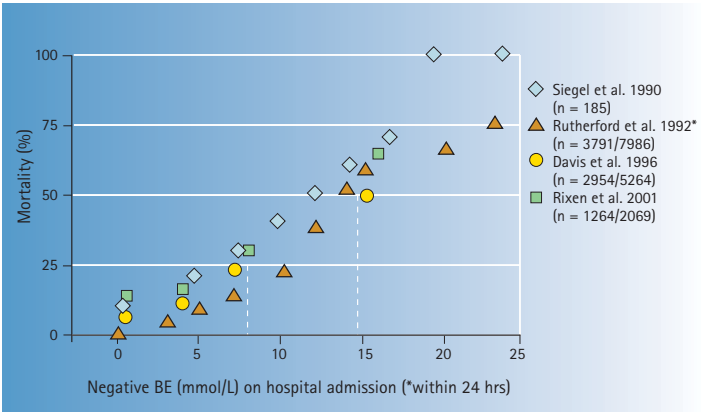


Figure 7: Mortality vs. base excess (BE) in multiple trauma patients: Correlation between mortality (%) and base excess (mmol/L) on hospital admission and 24 hours thereafter in a population of approximately 8,200 patients statistically selected from about 15,300 patients [80, 321, 326, 347].

It will be demonstrated under BE and Clotting below that there is indeed a causal relationship between BE and mortality.

In trauma patients, the baseline base deficit is a predictor of subsequent mortality as well as a strong indicator of later morbidity: A value greater than 6 mmol/L (BE < –6 mmol/L) suggests intraabdominal injury following blunt trauma [79], the development of acute pulmonary failure [94], or posttraumatic shock in pediatric patients [309].

6.4. BE Clearance and Mortality in Trauma Patients

Like lactate clearance, normalization of the base deficit can be used as an indicator of the clinical course in trauma patients:
Survivors normalized their BD from 7 or 15 to approximately 0 mmol/L within 24 hours, while nonsurvivors only showed a decrease in BD to 2–4 mmol/L [77]. Persistent BD above or below 4 mmol/L differentiates highly different mortality rates of 9% and 50%, respectively [185]. All surviving pediatric patients normalized their BD within two days [309]. The sole indicator of an unchanged or worsening prognosis in multiple trauma patients is whether their BD remains unchanged or increases in the interval between hospital admission and ICU admission [322].

6.5. Does Alcohol Interfere with BE Measurements?

There has been concern that the plasma lactate concentration might, as a result of oxidation of ethanol, cause BD to be misinterpreted in alcohol-intoxicated patients.
This suspected interference has not been confirmed in a very large number of trauma patients: The largest BE difference between individuals with 0 and over 2‰ blood alcohol concentration was as small as 1.3 mmol/L [78] or not greater than 2.8 mmol/L [91], depending on the patient population studied.

6.6. Why Is Metabolic Acidosis a Problem?

Metabolic (lactic) acidosis interferes substantially with blood clotting (see below) and intrahepatic gluconeogenesis (see above), which decreases significantly from a pH less than 7.1 (equivalent to a base deficit of 17.5 mmol/L) [31, 147]. In addition, metabolic (lactic) acidosis interferes with the cardiocirculatory system.

The concentrations of catecholamines epinephrine and norepinephrine increase substantially in the presence of lactic acidosis from a pH of 7.15, and the effect of exogenously administered norepinephrine is reduced [110]; the ventricular fibrillation threshold is significantly lowered, resulting in a correspondingly increased risk of arrhythmia, which, however, is never the case with respiratory acidosis and alkalosis (pH 7.0 to 7.7) [125]; acidosis has a direct negative inotropic effect on the myocardium, along with an indirect effect in that the myocardial response to circulating catecholamines is reduced [238].

The high mortality associated with lactic acidosis should be reiterated: In a large retrospectively analyzed population of 851 patients (from a total population of 9,800 ICU patients with a mortality rate of 26%), it was shown that mortality associated with lactic acidosis (56%) was substantially greater than mortality associated with acidosis with undetermined anion gap (39%) or hyperchloremic acidosis (29%) [132].

6.7. Base Excess and Clotting

There is a causal relationship between mortality and base excess in trauma patients, resulting in hemorrhagic shock with death from blood loss accounting for over 50% of clinical causes of death [331], being responsible for more than 80% of deaths in the OR [69, 136], and representing the most frequent cause of hemorrhage-related death with coagulopathy, acidosis, and hypothermia in the early postoperative period [226]. Aggressive management of the "lethal triad" – coagulopathy plus metabolic acidosis plus hypothermia – therefore appears to have the greatest potential of reducing mortality in severely injured patients [181].

This causal relationship is based on the fact that clotting activity is affected not only by temperature [175] but to a very large extent also by pH or BE, as is clearly demonstrated by numerous *in vitro* and *in vivo* studies:

Using three selected coagulation factors, experimental studies have shown that *in vitro* clotting factor activity is to a large extent determined by pH: Clotting (factor) activity was found to be halved at pH 7.20 (base deficit, 12.5 mmol/L) and doubled at pH 7.60 (base excess, 16.5 mmol/L) [248].

This observation has been corroborated in patients, as shown in Figure 8: a highly significant ($p<0.001$) correlation between prothrombin time (PT, Quick, %) and negative base excess was found in 4,066 out of a total of 20,815 severely injured (ISS $\geq$16) multiple trauma patients of the Trauma Registry of the German Society of Trauma Surgery *(Deutsche Gesellschaft für Unfallchirurgie)* receiving primary care [210].

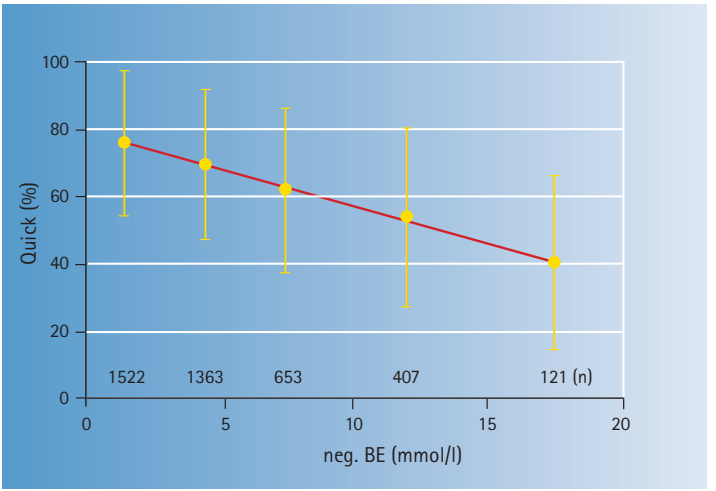


Figure 8: Clotting activity (prothrombin time, Quick, %) as a function of BE (mmol/L) in about 4,000 multiple trauma patients.

Apart from prothrombin time (PT), partial thromboplastin time (PTT) can also be matched with the base deficit of trauma patients on hospital admission: a larger BD will substantially increase both times [40], affecting as many as 25% of all trauma patients on admission [39]. In has been shown in large patient populations (7,683 out of 20,103) that PT and PTT are independent predictors of mortality in trauma patients [229], with PTT being even more predictive than BE [228].

These bench and bedside findings therefore suggest that a base deficit of approximately 15 mmol/L primarily reduces clotting activity to approximately 50%, which secondarily explains the reported mortality rate of approximately 50% in multiple trauma patients.

Numerous studies have looked at whether or not infusion fluids have an impact on coagulation *in vitro* or *in vivo;* the *in vitro* methods used in those studies will be commented on in another section below.

In vitro hemodilution with 0.9% NaCl, Ringer's lactate or electrolyte solution results in increased coagulation, or hypercoagulopathy [96, 167, 329, 331], as does *in vivo* hemodilution [239, 277, 278, 330]. Exactly why hemodilution should result in activation of the clotting system remains unclear [114], and the observed effects are presumably due to methodological problems [198]. Much more likely would be the observation of *reduced* clotting, or dilutional hypocoagulopathy, as described for HES, albumin or 0.9% NaCl solution following *in vitro* dilution [24, 371].

Hemodilution thus has general repercussions: Dilution means dilutional coagulopathy because the concentrations of coagulation factors are reduced. However, dilution also produces dilutional acidosis, which in turn may produce hypocoagulopathy. The latter should therefore always be avoided through the use of balanced solutions, while the use of conventional crystalloids, such as 0.9% NaCl, should be minimized [69].

In an animal model – uncontrolled bleeding from a liver incision – the use of 0.9% NaCl for volume replacement was observed to produce significant acidosis with hypocoagulopathy, resulting in major blood loss and hence the need for large volumes for blood pressure stabilization, while this effect was not observed with Ringer's lactate, known to produce (see below) hypercoagulopathy (TEG, PTT) without concomitant acidosis [186].

Experimentally induced acidosis (addition of HCl or lactic acid) produces hypocoagulopathy *in vitro* [10, 101]. This observation has been contested by other authors in that this effect was observed only in conjunction with hypothermia [84]. This effect of acidosis is reversible [100, 101].

It was not reversible, however, *in vivo* in 4 animal studies where coagulopathy persisted for another 12 to 18 hours despite treatment of acidosis: Both metabolic acidosis from hemorrhagic shock [327] and HCl infusion-induced acidosis [92, 241, 242] produced coagulopathy with decreases in platelet counts and in fibrinogen concentration to approximately 50–60% of normal, not reversible by treatment with HCO_3 or THAM (TRIS). Buffer therapy can only lessen the clotting disorder.

Conclusion: Because acidosis therapy is only effective if started during shock [327], and correction of acidosis takes several hours to exert a corrective action on a clotting disorder [241, 242], the following tenet applies: "Acidosis should be excluded" [92]. Or even more to the point: During the management of hemorrhage, any acidosis must be prevented through the use of a balanced solution, and exacerbation of acidosis, in the form of dilutional coagulopathy or dilutional acidosis, must be avoided.

6.7.1. BE and Measurement of Coagulation Status

The correlations established between acid-base status and coagulation and/or fibrinolysis should be extended to include diagnostics, most readily described on the example of thrombelastography (TEG).

The problems involved on the example of hypothermia are demonstrated first: The clotting activity of a patient with a body temperature of 32°C rather than 37°C is reduced by about 50% as a result of hypothermia alone [175]. If the patient's clotting status were determined, say, by TEG at 37°C, this would produce a misdiagnosis because the hypothermic patient's blood sample, brought to normal temperature in the thrombelastograph, would erroneously suggest a normal clotting status. This is why patient temperature can nowadays be set on point-of-care (POC) TEG instruments [193]. Given the significant temperature dependence, this had also been demanded for PT and PTT very early on [325].

The same applies to the patient's acid-base status, defined by the pH in conjunction with BE (mmol/L) and the pCO_2 (mmHg) of the blood. If clotting status is determined in such a way that changes in pH or BE are reversed by the diagnostic methods used – *e.g.*, by the use of buffered reagents – or that changes in pH are allowed – *e.g.*, the pH of a sample increases as a result of loss of CO_2 – leading to alkalosis – it is no longer possible to detect acidosis-related clotting disorders. All potential changes in pH, BE, and pCO_2 must be prevented to ensure the patient's momentary clotting status is captured correctly. This is not feasible as yet. For example, if samples are mixed with HCO_3^--free solutions, such as 0.9% NaCl in a ratio of 1 + 1, this will lead to dilutional acidosis, with pH decreasing from 7.40 to 7.10, erroneously suggesting a clotting disorder *in vitro*.

If it is currently claimed for TEG (see above) that *in vitro*–generated acidosis alone has no effect on clotting, but only synergistically in combination with hypothermia [84], then this test should be repeated with an optimized TEG method under reproducible conditions of the acid-base status of the samples.

6.7.2. Alleged Effects of Colloids on Coagulation

Given the methodological considerations discussed above (TEG), the following findings are included here only with reservations: Primary hemostasis *in vivo* has been claimed to be inhibited by gelatin [81] and to lead to dilutional coagulopathy in an animal model [113]; HES, gelatin, and albumin have been claimed to interfere with coagulation *in vitro* [96], and HES, depending on the author, has been claimed to cause hypercoagulopathy [328] or hypocoagulopathy *in vivo* [239].

6.7.3. Coagulation and Ionized Calcium

The normal plasma calcium concentration is approximately 2.5 mmol/L, and about half of plasma calcium is bound to proteins, mainly albumin. The calcium concentration that has an important role in clotting is the concentration of ionized (free) Ca^{2+} (1.25 mmol/L).

As protein binding depends greatly on pH – the Ca^{2+} concentration increases in acidosis – the concentration increases from 1.25 to 1.34 mmol/L at a BE of –15 mmol/L (pH 7.15). In other words, clotting activity is increased. In major blood loss, both albumin-bound Ca^{2+} and ionized Ca^{2+} are expected to decrease.

Severe hypocalcemia – seen in 10% of trauma patients – is defined as a Ca^{2+} concentration <0.9 mmol/L [388] which should be treated with calcium supplementation [337]. Ca^{2+} binding, or reduction in free calcium, has been described for lactate (chelation) and colloids. Lactate can be assumed to produce a linear decrease in Ca^{2+} concentrations by 0.05 mmol/L per 1 mmol/L of lactate [388, 415]. At a lactate concentration of 10 mmol/L, this means a reduction in ionized calcium from a normal concentration of 1.25 to 0.75 mmol/L, or hypocalcemia requiring therapy. Patients with lactic acidosis have been described to have substantially more pronounced hypocalcemia [65]. Among the colloids, only (negatively charged) gelatin has been reported to bind calcium.

The resultant decrease in Ca^{2+} concentration by 0.043 mmol/L at a gelatin concentration of 10% is, however, not clinically [388] significant, since gelatin solutions contain only 3–4% gelatin.

Conclusion: The use of lactate-containing infusion fluids (Ringer's lactate) and older packed red cell products should be avoided in acute hemorrhage because these are liable to produce or worsen hypocalcemia. Infusion fluids should contain at least the physiological Ca^{2+} concentration of 1.25 mmol/L; higher concentrations up to 2.5 mmol/L maintain the physiological pool of albumin-bound calcium.

7. Differentiation Between Colloid Volume Replacement and Crystalloid Fluid Replacement

Successful differential intravenous fluid management 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.

If, for the time being, there is no evidence from randomized controlled trials (RCTs) to establish that "fluid replacement" with colloid solutions is superior to fluid replacement with crystalloid solutions [323], the natural conclusion would and should be to initiate studies that differentiate strictly between crystalloid fluid replacement and colloid volume replacement with the exclusive use of balanced solutions.

7.1 The Clinical Physiology of Major Fluid Compartments

Typical volumes of the major fluid compartments in a 75-kg individual are as follows: intracellular fluid volume (ICFV), 30 L (40% of body weight); extracellular fluid volume (ECFV), 15 L (20% of body weight); intravascular blood (fluid) volume (IVFV), 5 L (plasma volume, 3 L); the plasma volume is part of the ECFV. The ratio of plasma (3 L) to ECFV (15 L) is thus 1:5, and the ratio of plasma volume (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 for the distribution of crystalloid fluids have been confirmed many times over by measurements performed in healthy volunteers or patients following the infusion of 0.9% NaCl or Ringer's lactate or Ringer's acetate.

Examples for 0.9% NaCl: 180 mL remained within the intravascular compartment (BV) after an infused volume of 1 L [205], 375 mL after 2 L [218], 483 mL after 2 L [315], 768 mL after 3.2 L [127], and 1,085 mL after 3.5 L [128]. All of these BV increases are equivalent to 18% to 31% of the infused volume. Examples for RL: 194 mL after 1 L [144] and 369 mL after 2 L [315]; example for RA: approximately 225 mL after 1.5 L [135]. These values are all in the same range as the 0.9% NaCl values. Similarly, the 4 intraoperative examples in Figure 1 [41, 367, 395, 406] clearly show for the distribution of chloride that crystalloid fluids distribute throughout the ECFV.

Only 20% of the infused volume of crystalloids used for intravascular volume replacement therapy will actually reach its target compartment.

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 [411].

Figure 9 illustrates available options for increasing the blood volume (BV, IVFV) by a total of 1 L with different IV fluids. This can be achieved by infusing the patient with either 9.4 L of D5W (*i.e.,* 5% dextrose solution in water, which behaves like pure water) or 5 L of 0.9% NaCl solution (isotonic crystalloid) or as little as 1 L of 6% HES solution (isooncotic colloid).

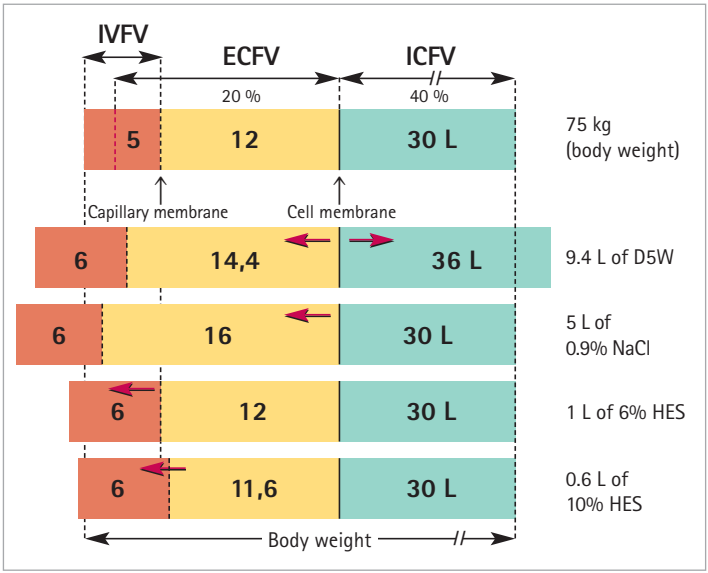


Figure 9: Options for increasing blood volume (IVFV) by1 L.

Hyperoncotic 10% HES solution is a unique fluid: 0.6 L of it has the same volume effect as 1 L of 6% HES because 0.4 L is shifted from the ECFV into the IVFV following the oncotic pressure gradient: Hyperoncotic 10% HES is ideal for one-off (!), rapid volume replacement therapy.

7.2. Would-Be Volume Replacement with Crystalloids

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." [312].

Numerous animal studies of isovolemic hemodilution have demonstrated that animals do survive substantial blood volume loss when infused with crystalloids (typically RL) 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 [26, 366]. At a hematocrit of 10% (two-thirds of blood volume removed), 50% of the animals survived when three times the removed volume was replaced [373, 374]. Animals even survived a hematocrit of 5.8% in one study replacing three times the removed blood volume [249].

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 more or less substantial. Overhydration (hyperhydration, intravenous fluid overload) has been defined as >10% weight gain [220] 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 (liters), 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 [134], weight gain is not limited by a pressure increase in the EVFV until extreme levels are reached.

- Volume replacement therapy with crystalloids requires about 5-fold greater volumes. The risk of dilutional acidosis from excessive fluid therapy with overhydration is therefore particularly great with crystalloids. Quantitative evidence in support of this is presented using 3 examples (Figure 10) showing intraoperative dilutional acidosis produced by infusion fluids with or without metabolizable anions (Ringer's lactate with 27 mmol/L of lactate or 0.9% NaCl solution).

  The first three cases [41, 367, 406] have already been commented on in Figure 1; in one case [367] only the bicarbonate changes rather than absolute values could be used; the fourth case mentioned in Figure 1 [395] could not be included because the lactate concentration had increased substantially as evidence of impaired metabolism.

The simple balance of the bicarbonate concentration of the ECFV (20% of body weight), starting with a normal value of 24 mmol/L, shows good agreement between the calculated concentration and the concentration measured by the authors.

Again, the following model calculation (mmol/L) is given as an example: 15 L of ECFV with 24 + 5 L with 0 (0.9% NaCl) gives 20 L with 18.0. This overhydration now produces dilutional acidosis which, however, shows lower mortality than lactic acidosis [38, 132].

After the chloride balance, now also the HCO_3^- balance adds to the clinical evidence in support of the distribution of crystalloid fluids throughout the entire ECFV.

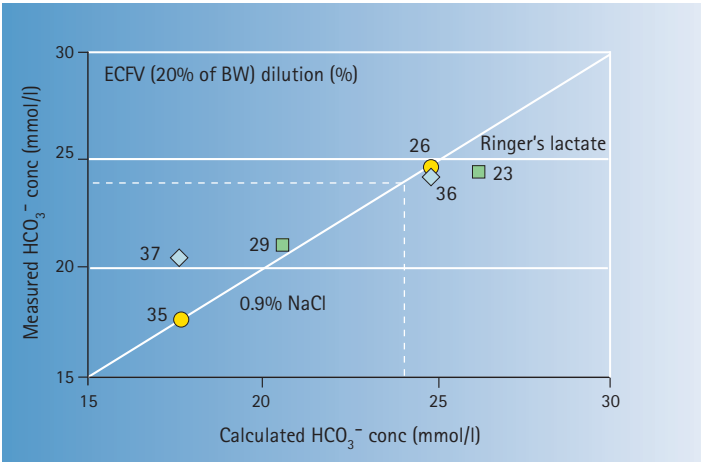


Figure 10: Dilutional acidosis as a result of overhydration intraoperatively produced by excessive fluid therapy [41, 367, 406] .

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. The correlation between mortality and colloid osmotic pressure in 99 ICU patients with cardiopulmonary diseases [266] and 128 critically ill patients [305] is shown in Figure 11: A reduction of COP to approximately 14-17 mmHg already results in a mortality rate of approximately 50%.

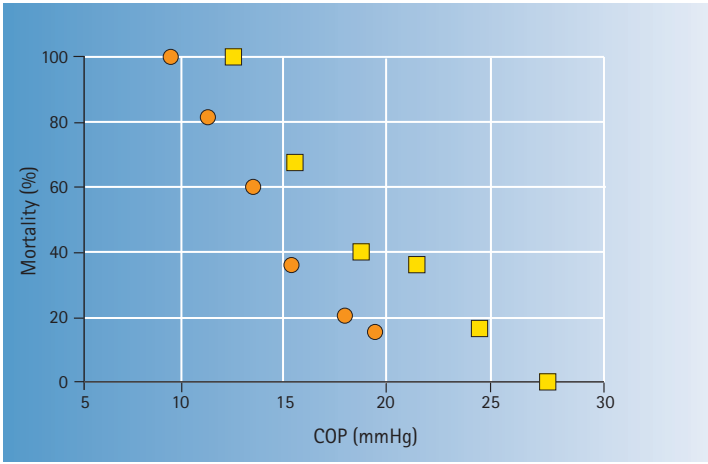


Figure 11: Mortality of ICU patients at reduced COP.

- Infused crystalloid volumes must be increased substantially to replace increasing blood losses: An estimate shows that 6 L of crystalloid must be infused to replace the first liter of blood lost, while as much as 7.3 L is needed to replace the second liter.

  The first liter of blood lost increases the PV/ECFV ratio from 1:5 to 1:6 because the blood loss entails greater plasma loss than RBC loss (2.4 L of PV : 14.4 L of ECFV). This ratio increases to 1:7.3 for the second liter of blood lost as a result of the preceding hemodilution. This phenomenon has been demonstrated in animal studies where the ratio of increasing blood loss to crystalloid replacement volume increases from 1:3 to as much as 1:12 [51, 52, 53].

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 [269].

- 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) [137]. The most likely explanation for this observation is that the increasing expansion of the EVFV expands the distribution space for albumin (this phenomenon has been referred to as "albumin hemodilution") [351], leading to extravasation of albumin [51, 269].
- 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 [351]. The following observation appears to be essential: Intravascular hypervolemia resulting from excessive infusion of crystalloids causes a shift of protein-containing fluid into the interstitial space [169].
- How best to monitor and control crystalloid-based volume replacement therapy is apparently still a matter of much debate all over the world: "It dose not make sense to titrate a fluid, most of which enters the interstitial space, against measurements taken of the intravascular space." [377]. This argument will be taken up again below in the "CVP Titration" section.

Three of the seven arguments mentioned will be discussed and assessed in more detail below.

7.3. Fluid Overload – Pulmonary Edema

As early as 1973 [33], 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 [133]: 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 promptly 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 [306, 386].

The need for this precaution is particularly evident in patients with septic or hypovolemic shock [306]: 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 (mean COP, 14.7 mmHg; mean PCWP, 12.7 mmHg). Following 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 RL did not develop pulmonary edema despite a COP drop to 12 mmHg if PCWP was maintained at 6 mmHg [345]. The teaching points of these studies are clear enough: Avoid a significant drop in COP, and avoid overhydrating your patients.

7.4. Fluid Overload – Increase in Body Weight

Weight gain from overhydration should not be taken lightly: "Weight gain and systemic edema are not benign problems" [312].

Here are a few extreme values to illustrate the issue: A patient with myocardial infarction of the right side of the heart within 24 hours received 14 L of normal saline and D5W, had a urinary output of 2.7 L and 17% weight gain [168]. An animal model simulating septic shock involved the infusion of 8.3 L of Ringer's

solution within 6 hours, resulting in a measured 37% weight gain [244]. Burn patients with a mean burned body surface area of 46% received up to 50 L of RL within 24 hours [157]; 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 approximately 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 [86, 87, 159, 218, 315, 352]. 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 RA were essentially unchanged [87]. 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) [352]. After 24 hours, as little as 17% of the infused 8.6 L of 0.9% NaCl solution was excreted [306].

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 [136]. This effect is no doubt driven by hyperchloremia (see above) limiting fluid elimination as a result of renin-aldosterone system suppression [89].

Moreover, the maximum daily urinary output appears to be limited to approximately 3 L (mean across 9 series, 3.1 $\pm$ 0.7 L/day) during excessive fluid therapy – *i.e.,* a fluid intake of 5–50 L/day – with isotonic or hypotonic hyperchloremic solutions (0.9% NaCl, RL) [15, 89, 158, 168, 201, 341, 386]. This is demonstrated particularly impressively on the following example [341]: Following intraoperative administration of a total volume of 12.5 L with 9.5 L of RL, urinary output is as low as 2.7 L on the day of surgery and 2.9 L on postoperative days 1 and 2.

Body weight gain from hyperhydration is thus inevitable.

Applied to patients in the intra and postoperative setting, these findings have the following consequences [15, 340, 341]: Intraoperative infusion of 9.5 L of RL (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 3.0 L. The increase in body weight, or ECFV overhydration, is still 8% on postoperative day 3 and 5% on postoperative day 4.

7.5. Fluid Overload – Compartment Syndrome

Overhydration (fluid overload) may lead to an abnormal increase in intraabdominal pressure with significant disruption of organ functions.

An international conference on critically ill adult patients has developed the following definitions of intraabdominal pressure (IAP) [230]: The normal IAP is 5–7 mmHg; intraabdominal hypertension (IAH) is defined as an IAP $\geq$12 mmHg; and an abdominal compartment syndrome (ACS) starts at an IAP >20 mmHg.

A review identified the "excessive use of crystalloids" as the primary determinant of the development of ACS, and deplores that "consensus regarding the optimal composition and volume of fluid required is lacking" [70].

Three typical patient populations are described in support of this:

A study in trauma patients compared normal (7 L/24 hrs) with supranormal (13 L/24 hrs) volume replacement therapy using Ringer's lactate. The percentage of IAH, ACS, and multiple organ failure doubled to 42%, 16%, and 22%, respectively, and mortality increased from 11% to 27% in those receiving supranormal volume replacement therapy [23]. In a study in medical patients with a mean positive fluid balance of 6.9 L, 85% had IAH and 25% ACS with organ dysfunction; the authors recommend IAP measurements in patients with a positive net fluid balance of >5 L in 24 hrs [57]. A study in burn patients with approximately 30% burned body surface area (BBSA) compared crystalloid with plasma therapy, and found that survivors (urine output as low as 1.4 L/day) had received 45 L and non-

survivors 61 L of crystalloid during treatment; the IAP increase among survivors was 24 mmHg versus 34 mmHg among nonsurvivors [284]; to ensure a urinary output of 1.8 L/day, burn patients must be infused with 15.6 L of Ringer's lactate; this produces an ACS (IAP >22 mmHg) within 24 hrs in 50% of patients [287].

7.6. Parameters Used for Control of Volume Replacement Therapy

Eighty five percent of the human blood volume (BV, IVFV) is in the low pressure system characterized by very great compliance ($\Delta V/\Delta P$) upstream of the right and left sides of the heart, and 15% is in the high pressure system characterized by low compliance downstream of the left side of the heart.

A basic distinction must be made between static and dynamic parameters:

1. Static parameters such as central venous pressure (CVP), systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial blood pressure (MAP) can be used to describe the volume status in the low pressure system upstream of the right side of the heart (CVP) or in the high pressure system (MAP) downstream of the left side of the heart. Hypovolemia causes low pressures on both sides (CVP, MAP).

2. Information about fluid responsiveness can be obtained from the dynamic response to a colloid volume bolus into the low pressure system upstream of the right side of the heart. The response can be diagnosed in the low or high pressure system. Hypovolemia exists if the response (ΔP) upstream of the right side of the heart is negative or the response downstream of the left side of the heart is positive. Given the differences in compliance, the dynamic response to a volume bolus upstream of the heart (low pressure system) tends to be small and that downstream of the heart (high-pressure system) tends to be large.

7.6.1. Central Venous Pressure (CVP)

Central venous pressure (CVP, mmHg), a classical static parameter for evaluating a patient's volume status, can be used to demonstrate how differently this parameter may be used in clinical practice. It is assumed that appropriate CVP measuring technique is used, including correct catheter placement, zero calibration, and elimination of intrathoracic (ventilation, PEEP) or intraabdominal pressure increases.

Arbitrarily selected examples are provided in Table 5.

Compared to 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 are obviously subject to exceedingly great variability, and this would appear to carry a high risk of failure to control much-dreaded hypovolemia.

If all groups of patients had a CVP of 12 mmHg recorded even before the planned volume replacement therapy for septic shock [42], the question arises what target CVP was used.

Table 5:

Arbitrary selection of typical CVP targets for various indications

Ref.	Indication	CVP target (mmHg)
Mittelstaedt et al. (2004)	Intraop. liver resection	0 – 3.7
Modig (1986)	Traumatic shock	> 4.4
Lowery et al. (1971)	Hemorrhagic shock	2 – 7
Sander et al. (2003)	Intraop. Gyn. surgery	> 4.4
Mythen et al. (1995)	Intraop. cardiac surgery[1]	5.5
Lucas et al. (1978)	Intraop. losses[2]	6.2 / 11.3
Kumle et al. (1999)	Intraop. abdominal surgery	10 – 14
Boldt et al. (2000)	Intraop. abdominal surgery	10 – 14
Wakeling et al. (2005)	Intraop. gut surgery	12 – 15
Gan et al. (1999)	Intraop. blood loss > 0.5 L	≥ 15
Riddez et al. (1997)	Acute hypovolemia[3]	5.7 ⟶ 3.2
Weiskopf et al. (1998)	Acute isovolemic anemia[4]	5.5 ± 4.5

[1] 200-mL boluses of 6% HES were infused 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 Hb concentration of 5 g/dL.

An earlier attempt [344] at establishing a correlation with CVP and additionally with CO and MAP in critically ill patients with a wide variety of conditions failed despite the availability of over 1,500 blood volume measurements.

A current conclusion would therefore appear to be justified [124]: There has never been a correlation between the static CVP and the circulating blood volume, and only extreme values, if any, might be a good indicator of a patient's hemodynamic status. Dynamic parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV) or respiratory variations in the pulse oxymeter plethysmogram should be used preferentially. The following conclusion can be drawn:

"Dynamic parameters should be used preferentially to static parameters to predict fluid responsiveness in ICU patients." [252].

7.6.2. CVP Dynamics (CVP Titration)

It was realized early on that CVP, basically a static parameter, can also be interpreted in dynamic terms: Hypovolemia is diagnosed by challenging the intravascular compartment into producing a CVP response through the administration of volume boluses, or *i.e.* volume titration of CVP until it responds with increasing pressures. However, the original suggestion [408] – CVP titration with 500–4,000 mL until an abrupt increase in CVP is produced – was doomed to failure because crystalloid fluids were used for titration, only 20% of which remains within the intravascular space.

Later suggestions invariably referred to the use of a colloid volume bolus of 200–250 mL (6% HES or 3.5% GEL) designed to produce an increase in CVP by 2–3 mmHg within approximately 10 minutes in the absence of hypovolemia [274, 296, 383, 389]. This intervention was to be repeated until a positive response would be obtained. If the CVP increase is greater than 5 mmHg, volume administration has to be stopped [383].

This approach essentially measures the compliance of the entire low pressure system; Table 6 shows the results of such measurements in humans. The fluids used included blood, albumin 5%, and colloid fluids. After elimination of one outlier [319], the values are surprisingly close to each other, the mean across 13 refs. being 168 mL/mmHg. The values obtained when using crystalloid solutions with 450–1,000 mL are substantially greater, as expected, *i.e.,* much larger volumes are needed to produce the same increase in CVP.

The following recommendation can be deduced for CVP titration, *i.e.* the dynamic interpretation of CVP: To do a hypovolemia challenge, a colloid bolus of 500 mL (3 x 168 mL) should be administered as many times as is necessary to produce a CVP increase by 3 mmHg. This is quite similar to the suggested use of a 200–250 mL bolus, but is based on a large number of measurements. "Challenging the intravascular compartment: Iteratively repeating a 200- to 500-ml fluid bolus in patients with oliguria, tachycardia, or hypotension." [236].

It also emerges from Table 6 that the same bolus of 500 mL of blood or colloid produces a 15-mmHg increase in MAP – making for rational volume titration of MAP.

Table 6:

Measurements of the compliance of the human low pressure system (ΔV/ΔP, ml/mmHg), rounded off to 5 or 0 – change in CVP (mmHg) following volume administration (mL) according to various authors. Where a differentiation was made between responders and nonresponders, only the responder values were used.

Author	Approach	Compliance (ml/mmHg)	Change MAP (%)
Blood			
Gauer (1956)	–6.5/+8.1 mL/kg	195	
Echt (1974)	+/–500 mL	175	
Cheung (1994)	–1.75 mL/kg	140	
(Riddez [1997]	–900 mL	360)	
Lattik (2002)	–211 mL	115	
	+176 mL	195	
Kramer (2004)	+500 mL	165	+20
Albumin 5%			
Calvin (1981)	+250 mL	250	
HES 6%/10%			
Michard (2000)	+500 mL 6%	165	+16
Lattik (2002)	+500 mL 10%	150	
Michard (2003)	+500 mL 6%	165	+17
Osman (2007)	+ 500 mL 6%	165	
GEL 3.5%			
Reuter (2002)	+580 mL 3.5%	155	+14
Preisman (2005)	+500 mL 3.5%	145	+13
	MW (n = 13)	168 (mL/mmHg)	+16% (~15 mmHg)
Crystalloids			
Rackow (1983)	+3.7 L 0.9% NaCl	845	
Riddez (1997)	+1.8 L RA	460	
Kumar (2004)	+3.0 L 0.9% NaCl	1,000	

Conclusion: Provided it is measured correctly, the CVP can provide the following diagnostic clues: If the CVP is less than the target value (of 5 mmHg), the presence of hypovolemia is safe to assume, but reaching the target (CVP >10 mmHg) is not a guarantee for an adequate preload. To verify hypovolemia (CVP <5 mmHg), a colloid bolus of 500 mL can be administered until a 3-mmHg increase in CVP is produced.

7.6.3. Dynamic Parameters Downstream of the Heart

Optimization of dynamic parameters such as stroke volume or cardiac output on the basis of measurements of dynamic parameters such as stroke volume variation (SVV) or pulse pressure variation (PPV), or respiratory variations in pulse pressure (pulse pressure difference, dPP) or in the pulse oxymeter plethysmogram is currently being discussed as a preferred approach. While some of these methods, such as PPV, show high sensitivity and specificity for fluid responsiveness [194], adequate validation during constant PEEP is still being questioned [28]. The future will show whether these methods find their way into clinical routine procedures.

7.7. Is There a Particular Level of Volume Loss That Should Trigger a Switch From Stop Gap Crystalloid Fluid Replacement to Genuine Volume Replacement with Colloids?

Animal studies have described the pathophysiological reactions to acute blood loss [45].

When splenectomized conscious dogs have 10%, 20% or 30% of their blood volume removed within 3 minutes, BV normalization within the next 24 hours is 100%, 75%, and 60%, respectively. The fluid shift from the intravascular into the extravascular compartment resulting from hormone-induced hyperosmolality causes the blood volume to be replenished with a concomitant decrease in COP. Normalization of the plasma protein concentration (the most essential response) and hence of COP is 80% complete within 24 hours after a blood loss of 30%.

This means that blood loss up to 15% of total blood volume is completely replaced within 24 hours even with no fluid intake or infusion.

Findings in humans are essentially identical.

> 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" [207, 225]. 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 [263]. 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 RL or RA 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) [301, 319]. The hormone-induced hyperosmolality in shock patients (see above) contributes toward restoration of extracellular and plasma volume [37, 119, 171].

The level of blood loss that should trigger the switch from *optional* crystalloid extracellular fluid delivery for volume replacement to actual colloid intravascular volume replacement can thus be put at approximately 15% of total blood volume, or approximately 750 mL: Blood loss up to 15% of BV (approximately 750 mL) *can optionally* still be replaced with crystalloid balanced solutions, while blood loss in excess of 15% of BV *should always* be replaced with colloid balanced solutions. Major blood loss *must always* be replaced with balanced colloids. Where true *volume* replacement is required, crystalloids should always be used with caution: "Crystalloids should be kept to a minimum, especially as the complications are now well recognized" [337].

8. Differentiation Between Volume Replacement Therapy and Blood Therapy

The limitation of any volume replacement therapy is reached once hemodilution has reduced the oxygen carrying capacity of the blood to the point where organs and tissues can no longer be adequately supplied with O_2. This limit is currently thought to be reached at an Hb concentration of approximately 7 g/dL in patients with no apparent heart disease. However, if strict normovolemia can be ensured during volume replacement therapy, Hb concentrations as low as 3 g/dL can be tolerated, especially with concomitant hyperoxia [417]. Examples include acute isovolemic hemodilution down to a cHb of 5 g/dL in healthy volunteers [402] or intraoperative normovolemic hemodilution with hyperoxia down to a cHb of 3 g/dL [109]. However, this requires the absence of any additional disruptions of the electrolyte or acid-base balance which might disrupt pure volume replacement therapy.
Numerous colloidal volume replacement fluids are nowadays available for the treatment of hypovolemia, including natural colloids (human albumin, HA) and synthetic colloids (dextran, DEX; gelatin, GEL; hydroxyethyl starch, HES). While there is a plethora of publications on this issue, the choice of the "optimal" colloid is more controversial than ever.

8.1. Volume Replacement Therapy with Natural Colloids (HA)

Of the commercially available human albumin solutions, only 5% isooncotic HA solutions can reasonably be considered for use in volume replacement therapy. Although they are obtained from pooled plasma, modern albumin preparations are considered "immunologically" safe because of the methods used in their manufacturing process. Even a recent large 28-day multicenter trial in 7,000 patients showed that HA 4% (Na 140, Cl 128, octanoate 6.4 mmol/L) and NaCl 0.9 % (normal saline, NS) were essentially equivalent; this means that no advantage

could be established for albumin [108]. Data analysis showed, however, that apparently neither the total volume infused over 4 days nor the relative proportions of HA or NS provided any clues as to the effectiveness of the volume effect of the two study solutions, since the total volumes infused were virtually identical and, therefore, both the proportions and differences in volumes of the study drugs were too small [411]. Apart from producing hyperchloremia, another important criticism leveled at current HA preparations in NaCl solution would appear to be the fact that the functionally important negative charge of HA is eliminated with relatively high concentrations of octanoate, caprylate or tryptophanate (metabolizable bases) for reasons of solution stability.

Conclusion: The use of HA for volume replacement cannot currently be recommended because albumin has no evidence-based advantages over the less expensive synthetic colloids; albumin, being limited by its high price, is therefore rendered expendable as a volume replacement fluid [411].

8.2. Volume Replacement Therapy with Synthetic Colloids (DEX, GEL, HES)

The usual synthetic colloid assessment criteria include the concentration (% (w/v) or g/L) of the colloid in solution; the synthetic colloid's molecular weight (MW); parameters of molar substitution; maximum (initial) volume effect (MVE) in percent of the volume infused; volume effect duration (VED), defined as the time during which the infused volume shows at least 100% intravascular effectiveness; and volume effect half-life (VEHL), defined as the time during which the infused volume shows at least 50% intravascular effectiveness [411].

DEX solutions are nowadays hardly used any longer in Europe, except in the Nordic countries. This unpopularity is mainly due to their high allergenic potency and substantial inhibition of platelet aggregation.

Among the HES products, the isooncotic 6% solution with a MW of 130 kD (degree of substitution (DS), 0.4) is nowadays preferred over higher MW HES preparations; 6% HES 130/0.4 in 0.9% NaCl solution has an MVE of 120%, a VED of 4 hours, and a VEHL of 7 hours [411]. Manufacturers of 6% HES preparations in balanced solution ideally manage to supply an essentially balanced solution. If this is not achieved, the use of such solutions is limited by the their more or less pronounced hypotension hypotonicity they produce and/or the absence of physiological calcium.

Two typical intraoperative studies are presented for HES in balanced solution: Patients assigned to two groups – one treated with HES in 0.9% NaCl solution and the other with HES in balanced solution – experienced dilutional acidosis (BE decrease, 7 mmol/L) with hyperchloremia (chloride concentration, 115 mmol/L) in the former group, but not in the latter group (BE increase, 1.2 mmol/L; chloride concentration, 108 mmol/L) [406]. When both the perioperative crystalloid fluid and colloid (HES) volume replacement regimen were completely switched from 0.9% NaCl to a balanced solution regimen, the latter prevented the development of any intraoperative and postoperative disruptions of the electrolyte and acid-base balance, and there was neither hyperchloremia (117 mmol/L) nor dilutional acidosis (BE –5 mmol/L) [35] – a significant benefit for the physician.

The currently most popular GEL preparation is 4% modified fluid gelatin solution (MW 30 kD) with an MVE of 100%, a VED of 1.5 hours, and a VEHL of 5 hours [411]. GEL preparations formulated in an NaCl carrier solution are clearly hypotonic. A recently introduced GEL preparation formulated in an almost balanced solution is, unfortunately, also clearly hypotonic. It would be desirable to have a GEL product formulated in an isotonic, balanced solution.

Over HES and DEX, GEL has the theoretical advantage of being a charged molecule (like albumin). This results in at least two benefits: (1) Gelatin can coat all blood cells with a thin film, affording them mechanical protection; and (2) the negative charge can be used to lower the chloride content of an IV fluid (replacement of 20 mmol/L of plasma proteinate anions).

The following limitations of the volume effectiveness of HES and GEL preparations merit consideration:

- Practically all experience with HES products is from studies of unbalanced, hyperchloremic preparations. This means that part of the colloid effect might be due to the antidiuretic effect of hyperchloremia.
- Most experience with current GEL preparations is based on unbalanced, hypotonic products which might be associated with increased diuresis and hence increased excretion.

8.2.1. Specific Indication for Use: Erythrocyte Protection

Whenever red blood cells come into contact with coarse surfaces, such as in the heart-lung machine, kidney replacement therapies (hemodialysis, hemofiltration) or automated intraoperative autotransfusion using cell savers, there is a risk of mechanically altering erythrocytes (and platelets) or even causing hemolysis. Experience has shown that a minimum concentration of approximately 1% albumin suffices to coat and adequately protect red blood cells. Highly effective protection of erythrocytes against mechanical stress is achieved very elegantly with gelatin preparations, while NS has quite the opposite effect, *i.e.,* it increases the hemolysis rate [363, 365].

8.2.2. Specific Indication for Use: Hyperoncotic Solutions

Hyperoncotic solutions, such as 10% HES (MW 130 kD) with an initial MVE of approximately 150%, are recommended for "one-off" use in emergency medicine. Such a hyperoncotic solution is required to achieve the fastest possible restoration of the IVFV in acute (rather than chronic), life-threatening hypovolemia, also drawing on interstitial fluid reserves. However, this approach is only viable if an adequate interstitial and/or intracellular fluid volume is available for fluid mobilization.

The advantage of this acute treatment of hypovolemia is that rapid physiological volume regulation is supported – *i.e.,* fluid is shifted from the extravascular compartment into the intravascular compartment with a fluid that has a physiological composition including HCO_3, except for albumin. Unlike the physiological response with COP reduction, infusion with a hyperoncotic IV fluid ensures that this volume shift is supported while maintaining COP. Use over several days – as reported in one study [42] – is, of course, contraindicated [412]. When using this hyperoncotic fluid, preparations in a balanced solution are obviously preferable to an NaCl-based solution.

8.2.3. Specific Limitation – Renal Function

Evidently at least 6% HES 200/0.62, compared with 3% GEL 30, had an adverse impact on renal function in patients with severe sepsis and septic shock [338]. The renal injury data generated in a recent study of 10% HES 200/0.5 in sepsis patients [42] cannot be used because that study substantially overdosed patients by infusing them with a hyperoncotic, higher MW HES in hyperchloremic solution for several days [412].

Still, these are clinically significant findings that merit further attention, and should be clarified in carefully designed studies of 6% HES 130/0.4 in balanced solution.

8.3. Hemotherapy Using Packed Red Cells or Whole Blood

A review of the current literature reveals that the transfusion of erythrocytes in the form of packed red cells (PRCs) is being viewed with an increasingly critical eye. This stance has been succinctly put in the title of a 2008 editorial: "New blood, old blood, or no blood?" [3].

This critical view arises from evidence suggesting a correlation between patient mortality and the number and age of transfused units of PRCs, and the arguments for or against the use of PRCs or whole blood.

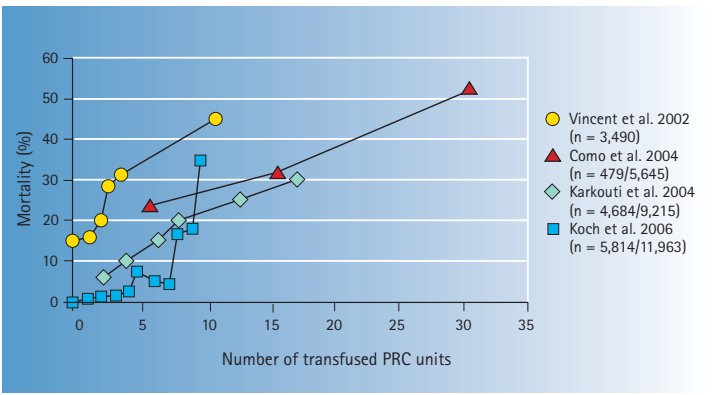


Figure 12: Mortality (%) in 14,467 patients from 4 studies [64, 178, 190, 384] following transfusion of PRC units.

The *number of transfused PRC units* shows a strong association with patient mortality, as demonstrated in Figure 12 for almost 15,000 patients from 4 studies, but no causal relationship can be deduced from this.

Indeed, many authors have claimed that transfusion is a strong independent predictor of mortality, and this applies to patients with blunt liver trauma [324] or trauma [231], heart surgery [273] or acute coronary syndrome patients [310], and those undergoing CABG surgery [99, 199].

The *age of transfused PRC units* was also shown to be strongly associated with patient mortality (Figure 13).

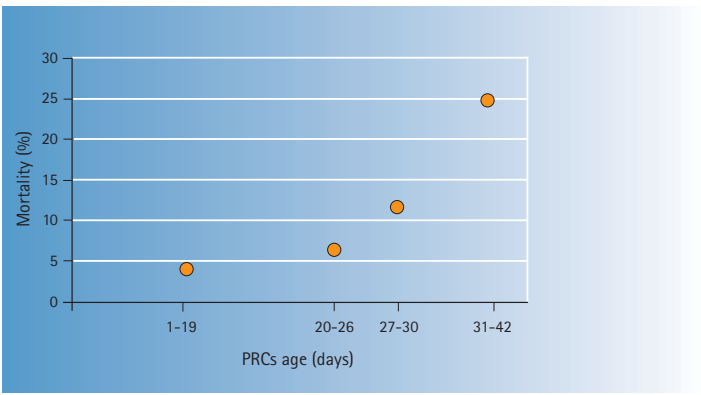


Figure 13: In-hospital mortality (%) among 321 reoperated cardiac surgery patients as a function of the age (days) of transfused PRCs (mean 5.2 ± 4.2 PRC units) [25].

The impact of PRC age on mortality has also been demonstrated for septic ICU [302] and critically ill patients [235, 369]. This finding has not been confirmed by other authors; the number of PRC units they transfused was probably too low to detect this effect: 2 [393, 394], 3 [410], 4 [379, 380] or max. 6 PCR units [209, 273]. If, for example, about 3,000 patients each are only given 2 units of PCRs after cardiac surgery, a difference in mortality is unlikely to be detected, since one-year mortality was 7.4% with 11-day-old PRCs vs. 11.0% with 20-day-old PRCs [191].

Die Frage, ob es sich hierbei um einen kausal begründbaren Zusammenhang handelt, soll wie folgt hinterfragt werden.

The question of whether a causal relationship can be established for the observed association will now be explored:

PRCs have long been known to show a base deficit even at the time of preparation, and theoretically this must be approximately 20 mmol/L, since the bicarbonate present in blood (20 mmol/L) is almost completely eliminated during the production process [364, 414].

During storage at 4°C for a maximum of 42 days (6 weeks), this base deficit increases again because the erythrocytes' anaerobic metabolism with the formation of lactic acid continues. Measurements [414] showing this are presented in Figure 14.

This rise in lactate levels in PRC units ranges from approximately 0.6 [339, 364] to 1 mmol/L/day [414] up to approximately 3 weeks (these data refer to mmol/L of total PRCs, rather than to the plasma of PRCs alone). Fresh PRCs therefore have a BD of 20 mmol/L, and 20-day-old PRCs a BD of 40 mmol/L.

20-day-old PRCs are considerd because this age is approximately the mean age of transfused PRCs for about 90,000 units from 3 studies (Western Europe, 16.2 ± 6.7; the Netherlands, 19.4 ± 7.0; United States, 21.2 ± 11.4) [67, 304, 384], or about half the maximum shelf life. This means that patients transfused with only 3 units of PRCs (approximately 1 L) are given 40 mmol of H^+ ions, or roughly the amount the kidneys

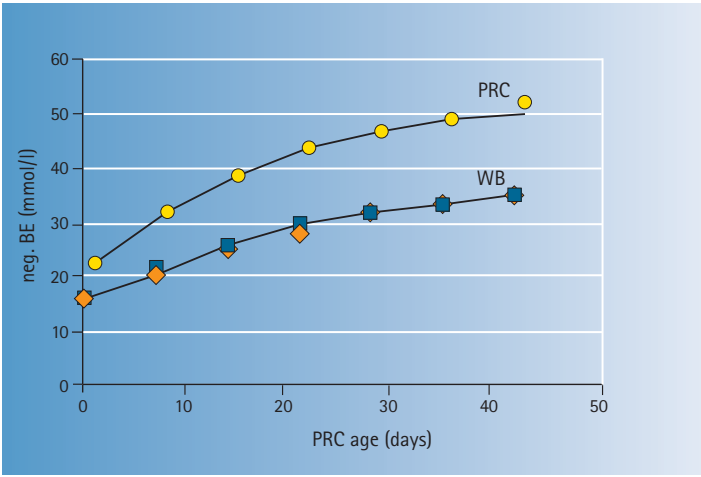


Figure 14: Negative base excess (mmol/L) during storage of packed red cell (PRC) or whole blood (WB) units with and without leukocyte depletion [414].

normally need to eliminate per day (50 mmol). If liver function is intact – which it rarely is in shock – half of this acid load can be converted hepatically. If it is not, a patient (75-kg individual, 15 L ECFV) transfused with, say, 7 units of PRCs has a base deficit of 6 mmol/L forced upon them, rather than as little as 1 mmol/L, as has been claimed [16].

The acid-base status of classical whole blood is described here for comparison:

Whole blood shows a baseline BE of approximately –15 mmol/L (see Figure 14) and, unlike PRCs, contains most of the alkalizing citrate (20 mmol/L) with a metabolic activity of 60 mmol/L. Fresh whole blood thus has a BEpot of +45 mmol/L, and, therefore, is a strongly alkalizing

blood product. During 3 weeks' storage, its BE increases, as a result of anaerobic metabolism, by approximately 0.7 mmol/L/day from 15 to –30 mmol/L [311, 414]. The resulting product is one that primarily causes acidosis in the patient (BE –30 mmol/L) and secondarily – if the patient's liver function is intact – alkalosis (BEpot +30 mmol/L).

This interpretation cogently explains published findings from the Vietnam War [63]. Fresh whole blood shows a base deficit of 20–25 mmol/L, which increases to 33–40 mmol/L after 15–22 days. Whole blood stored for the latter period of time is used most often: When a patient is transfused with approximately 10 units of whole blood in approximately 2 hours, their BE remains practically constant; it is about halved (*i.e.,* improved) only if the baseline BE was approximately –15 mmol/L; when a patient is infused with approximately 30 units of whole blood in approximately 8 hours, the BE remains practically constant; it is practically normalized only if the baseline BE was approximately –15 mmol/L.

It has thus been demonstrated that the alkalizing effect predominates in approximately 3-week-old whole blood samples, depending on the number and rate of the transfusions, and this is considered a definite advantage.

The debate in the 1970s about prophylactic bicarbonate buffering during transfusion can thus be plausibly explained: The acid-base status following transfusion of whole blood is extremely variable, as expected, and prophylactic administration of bicarbonate is a practice that should not be adopted [343] even when a transfusion must be administered very rapidly [255].

The balance between the acidifying BE (production process and formation of lactic acid) and the potentially alkalizing BEpot (effect of citrate) changes during storage of whole blood: A BE of –15 and a BEpot of +45 mmol/L on day 0 means a highly alkalizing preparation; a BE of –30 and a BEpot of +30 mmol/L on day 21 (3 weeks) means a mildly alkalizing product, depending on a patient's liver function.

The situation is a completely different one with PRCs because practically no alkalizing component is left, since as little as 3 mmol/L of citrate remains in the PRC unit.

The current debate about the potential merits of reintroduction of classical (leukocyte-depleted) whole blood tops off this interpretation ("Resuscitation with fresh whole blood and limited crystalloid" [156]):

Even though no advantages of autologous and fresh blood over cold stored blood could be demonstrated in heart surgery [314], there are a few publications that recommend the use of fresh, autologous whole blood, especially in pediatric cardiac surgery, because it is clearly superior to blood component therapy for correction of coagulopathy [115] and, therefore, significantly reduces blood loss [232]. Similar reports are available for adults: bleeding that could not be stopped even after many units of blood components (PRCs, platelet concentrate, FFP) ceased in nearly all cases after transfusing patients with uncooled, fresh whole blood [103].

In the military, fresh warm whole blood from "walking donors" has for decades been considered the best product for use in shock due to major blood loss [71], and the "walking donor pool" from volunteers has recently been used most rapidly [130, 286].

Conclusion: Unlike treatment with balanced colloids, the transfusion of PRCs has significant drawbacks because PRCs are liable to increase acidosis and hence coagulopathy, thus causally maintaining and perpetuating bleeding. The overriding goal in trauma patients is therefore to prevent coagulopathy from acidosis (and hypothermia) [16]; in battlefield medicine, prevention of acidosis is rightly given precedence over correction [153].

8.4. Infusion– and Hemotherapy in Massive Hemorrhage

Massive hemorrhage is defined as loss or exchange of one blood volume within 24 hours or transfusion of 4 PRC units within 1 hour. Massive hemorrhage is the greatest challenge in making the right infusion and blood therapy (hemotherapy) decision.

As in patients with multiple injuries, subsequent mortality shows a highly significant correlation with BE on hospitalization: In a subset of 3,275 patients (selected from a population of 14,240 patients), the nature of the trauma determined subsequent mortality [375]; blunt trauma and bullet wounds show similar values to multiple injuries, while stab or flesh wounds do not (Figure 15).

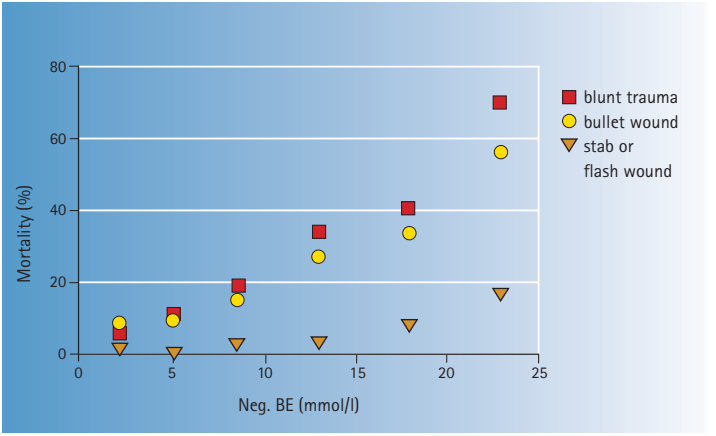


Figure 15: Mortality (%) of trauma patients with different causes of bleeding as a function of BE (mmol/L).

The "crux of coagulopathy" is frequently deplored in patients with massive injuries requiring massive transfusions [16].

The development of coagulopathy during massive transfusion in a trauma patient depends on their base deficit: In one series, patients with a BD of 15 mmol/L did not develop coagulopathy, while those with a BD of 21.2 mmol/L did [68]; in another series, trauma patients with a BD <14 mmol/L did not develop coagulopathy, while those with a BD >14 mmol/L did [262].

Among trauma patients requiring massive transfusions, survivors and nonsurvivors can be differentiated by their BD (mmol/L) alone: 9.0 vs. 16.0 [120], 12.5 vs. 17.1 [61], 13.4 vs. 20.3 [107], and <20 vs. >20 [44], *i.e.* BD between 12 and 18 mmol/L in a total population of over 300 patients.

Evident conclusion: The overriding goal in infusion and hemotherapy must be to avoid acidosis.

The currently accepted transfusion approach to major hemorrhage is as follows: first crystalloids, then colloids, then PRCs, and then plasma (FFP) [358]. This regimen merits revision and should be improved as follows:

- First line — Balanced colloids rather than crystalloids, aim for normovolemia (IVFV), maintain normal BE;
- Second line — Plasma for volume replacement plus clotting factors in case of dilutional coagulopathy despite normal BE;
- Third line — Transfusion of fresh PRCs if at all possible once the cHb falls below a critical level.

Clotting factors have the limitation that their effect depends on a normal BE. International recommendations for the use of recombinant factor VIIa (rFVIIa, NovoSeven) therefore define metabolic acidosis as an exclusion criterion [243, 357]. The limit is defined as a base deficit of 12.5 mmol/L (or pH 7.20). The recommendation even urges users to bring the pH "as near as possible to the physiological level" before using the product [357]. The recommendation to give this product "in conjunction with transfusion of 8–10 U of packed RBC," is conterproductive since PRCs in fact maintain acidosis. As clotting activity depends greatly on BE, there is reason to suspect that fibrinolysis and products modifying it, including aprotinin (Trasylol) or tranexamic acid, are also affected by BE. The fact that aprotinin had to be removed from the market [106] may, in part, have been due to BE being an efficacy-limiting factor.

Conclusion: The strategy of treating massive hemorrhage with massive transfusion evidently is a dead-end approach: The patient's metabolic acidosis causes coagulopathy, and massive transfusion with PRCs – which are typically 20 days old – increases acidosis and hence coagulopathy. The metabolic acidosis typically seen in trauma patients should be prevented rather than put up with or treated because, once it has developed, it is causally responsible for a risk of bleeding that persists for hours. The best-bet first-line approach to massive hemorrhage is therefore the use of balanced colloids.

9. Special Considerations in Pediatric Patients

Infants and toddlers have the following unique features setting them apart from school-age children and adults: their larger body surface area relative to their body weight results in greater insensible water loss and metabolic rates; their fluid turnover may be more than double; their renal plasma flow and GFR are substantially lower; renal sodium excretion is limited in the first few months of life; their urine may be diluted to 30–50 mosmol/kg H_2O, but it can only be concentrated to approximately 800 mosmol/kg H_2O; their glycogen reserves are smaller; and their gluconeogenesis (mainly from lactate) capacity is insufficient.

These features translate into the following requirements for fluid management in infants and toddlers: Close monitoring of the fluid balance (by regular weighing) and the sodium and glucose concentrations is necessary; the latter should be corrected with IV glucose once the glucose concentration falls below 70 mg/dL (4 mmol/L).

Starting in 1992, there have been numerous reports of deaths from hyponatremic encephalopathy [11] – estimated at 15,000 per year in the United States alone [14]. Investigator interest therefore soon focused on the corresponding perioperative infusion regimen. When treatment of a specific form of viral encephalitis was associated with a large percentage of hyponatremic children (sodium concentration <132 mmol/L, osmolality <275 mosmol/kg H_2O) with symptoms of intracranial pressure increase and herniation [246], it was suspected that these events might in fact be cases of iatrogenic hyponatremia arising from the (routine) use of hypotonic infusion fluids: "the routine use of hypotonic fluids in hospitalized children can be dangerous" [268]. A high percentage of acute infusion-related hyponatremia was also diagnosed retrospectively in Canada; the criterion used was a decrease in the sodium concentration to <136 mmol/L within 48 hours resulting in brain swelling and herniation [138]. The teaching point of

this is that all hypotonic solutions should be replaced with isotonic solutions in this clinical setting.

Subsequently, various authors came out in favor of using isotonic 0.9% NaCl solution [267, 368]. This solution should have 5% glucose added to it [90] although it had been demonstrated in infants long ago that the addition of 2% glucose is quite sufficient to rule out any perioperative hyperglycemia or hypoglycemia and increased lipolysis [279].

The observation of a high incidence of hyperchloremic acidosis in children, presumably due to impaired renal chloride elimination, demonstrated that, apart from sodium, chloride may also be a problematic factor to reckon with [281].

Other authors favored restricting the infused volume over raising the sodium concentration of infusion fluids [142, 143].

A different solution was preferred in France: Polyionique B66 contains 120 mmol/L of sodium and, therefore, has an osmolarity of as little as 256 mosmol/L which, with a glucose concentration of 50.5 mosmol/L, is raised to a physiological level of 306.5 mosmol/L *in vitro*; the solution also contains 20.7 mmol/L of lactate [30].

As recently as 2006, a survey among UK anesthesiologists revealed that a huge majority perioperatively keep using the usual 4% glucose solution in 0.18% NaCl [397] – a solution claimed to be responsible for the death of children in Northern Ireland in a 2007 TV documentary [360].

The debate about the optimal isotonic infusion fluid for pediatric patients was concluded for the time being in a 2007 editorial [219] demanding an isotonic solution with a sodium concentration very close to the plasma level and the addition of glucose. The editorial closes with the following appeal: "Medical companies, please provide us with this special perioperative infusion fluid as it will definitely have the potential of saving lives!" The recommended "golden compromise solution" with 0.9% glucose and 120 mmol/L of NaCl is, however, not

accepted; a "fool proof" solution has been suggested instead [362]: an isotonic solution with an electrolyte pattern that is as physiological as possible, has acetate rather than lactate added to it, and has a glucose concentration of 1%.

10. Summary & Conclusion

A balanced intravenous fluid with the attributes described in this booklet, either as a **colloid isotonic solution for volume replacement** or a **crystalloid isotonic solution for fluid replacement,** evidently renders the following rather pessimistic opinion from 1999 [60] obsolete: "Despite >20 years of animal and human studies, the optimal fluid for resuscitation in a clinical situation remains unclear."

A balanced solution that 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, 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.
- Infusion of such a balanced solution will – except in terms of volume – produce no iatrogenic disruptions of the electrolyte balance, in particular no hyperchloremia with renal vasoconstriction and decreased diuresis, and hence no overhydration with compartment syndrome and weight gain for several days.
- After infusion and anion metabolism, a solution with a BEpot of 0 ± 10 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.
- Acetate has a number of significant advantages over other metabolizable anions, 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, and this should be borne in mind in pediatric patients in particular.
- Blood loss up to 15% of BV (approximately 750 mL) can optionally still be replaced with crystalloid balanced solutions, while blood loss in excess of 15% of BV should always be replaced with colloid balanced solutions.
- Colloids can maintain a physiological COP to prevent any edema, especially pulmonary edema. Synthetic colloids such as gelatin and HES are preferable to human albumin.
- Balanced fluid or volume management prevents the development of acidosis and hence coagulopathy, which, along with hypothermia, forms the lethal triad.
- Because of the risk of exacerbation of acidosis, the transfusion of PRCs has significant drawbacks over the use of balanced colloids because PRCs increase acidosis and hence coagulopathy and may causally maintain hemorrhage.
- The overriding goal of infusion and blood hemotherapy must be to avoid acidosis.

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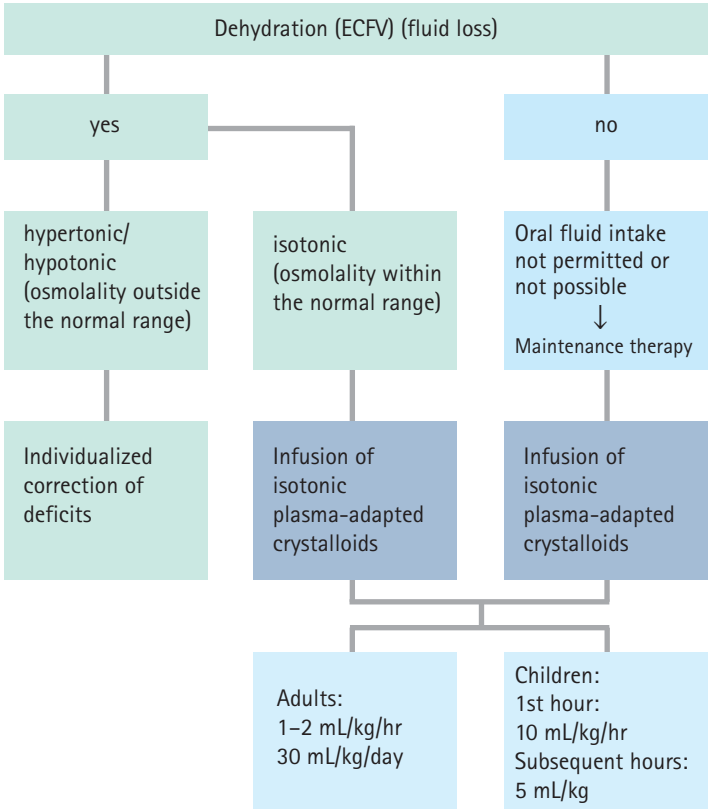
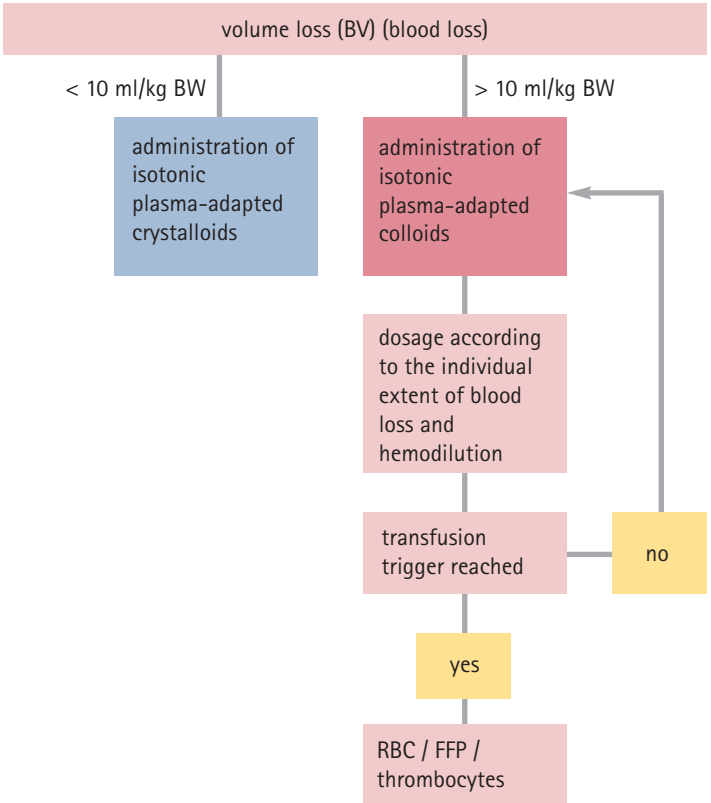
Acronyms & Abbreviations

BBSA	Burned body surface area
BE	Base excess (base deficit BD)
BEpot	Potential base excess
BV	Blood volume (IVFV)
BW	Body weight
CNS	Central nervous system
COP	Colloid osmotic pressure
CVP	Central venous pressure
D5W	5% dextrose (glucose) solution in water
DBP	Diastolic blood pressure
ECFV	Extracellular fluid volume
ECS	Extracellular space
EVFV	Extravascular fluid volume
FFP	Fresh frozen plasma
FPD	Freezing point depression
GFR	Glomerular filtration rate
HA	Human albumin
HES	Hydroxyethyl starch
IAP	Intraabdominal pressure
ICFV	Intracellular fluid volume
ICP	Intracranial pressure
IVFV	Intravascular fluid volume (BV)
MAP	Mean arterial blood pressure
MFG	Modified fluid gelatin
MW	Molecular weight
PCP	Pulmonary capillary pressure
PCWP	Pulmonary capillary wedge pressure
PRC	Packed red cells
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Plasma volume
RA	Ringer's acetate
RL	Ringer's lactate
RQ	Respiratory quotient
SBP	Systolic blood pressure
TA	Titration acidity
TBFV	Total body fluid volume
WB	Whole blood

Intravenous fluid management
= infusion of crystalloids and colloids

IV fluids are used to replace fluid loss.
The nature and composition of the solution to be used depends on the target fluid compartment.





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

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Fluid Management

Second expanded edition