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Crystalloid fluid choice in the critically ill

Current knowledge and critical appraisal

Carmen A. Pfortmueller · Barbara Kabon · Joerg C. Schefold · Edith Fleischmann

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Summary Intravenous infusion of crystalloid solutions is one of the most frequently administered medications worldwide. Available crystalloid infusion solutions have a variety of compositions and have a major impact on body systems; however, administration of crystalloid fluids currently follows a "one fluid for all" approach than a patient-centered fluid prescription. Normal saline is associated with hyperchloremic metabolic acidosis, increased rates of acute kidney injury, increased hemodynamic instability and potentially mortality. Regarding balanced infusates, evidence remains less clear since most studies compared normal saline to buffered infusion solutes.; however, buffered solutes are not homogeneous. The term "buffered solutes" only refers to the concept of acid-buffering in infusion fluids but this does not necessarily imply that the solutes have similar physiological impacts. The currently available data indicate that balanced infusates might have some advantages; however, evidence still is inconclusive. Taking the available evidence together, there is no single fluid that is superior for all patients and settings, because all currently available infusates have distinct differences, advantages and disadvantages; therefore, it seems inevitable to abandon the "one fluid for all" strategy towards a more differentiated and patient-centered approach to fluid therapy in the critically ill.

Keywords Normal saline · Balanced crystalloids · Acetate · Chloride load

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C. A. Pfortmueller, MD (✉) · B. Kabon, MD · E. Fleischmann, MD
Clinic for General Anesthesiology, Intensive Care and Pain Management, Medical University of Vienna, Vienna, Austria
cpfortmueller@gmail.com

B. Kabon, MD
barbara.kabon@meduniwien.ac.at

E. Fleischmann, MD
edith.fleischmann@meduniwien.ac.at

C. A. Pfortmueller, MD · J. C. Schefold, MD
Department of Intensive Care, Inselspital, Bern University Hospital, Bern, Switzerland
joerg.schefold@insel.ch

Introduction

Intravenous fluids are among the most commonly used medications in daily medical practice [1]. Currently available crystalloid infusion solutions have a variety of compositions and may therefore influence acid-base balance, body water content, the volume of body water compartments and plasma electrolyte composition [2] and may thus have a major impact on organ (dys)function and clinical outcome when used for fluid resuscitation purposes [3]. This may be of special importance in critically ill patients as they typically receive large quantities of intravenous fluids in order to maintain vital organ functions. The choice of crystalloid fluid may therefore profoundly impact on morbidity and mortality in affected patients [2–4]. A further characteristic of critically ill patients is that their vulnerability for fluid overload is high, e.g., in sepsis patients with concomitant capillary leakage. Fluid overload is not a benign occurrence, despite the general perception. For many years so the so-called goal-directed approach was a mainstay of fluid therapy, especially in patients with sepsis or septic shock [11, 12]; however, mounting evidence shows that goal-directed therapy does not result in better clinical out-

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Table 1 Composition of the most commonly used infusion solutions (all values in mmol/l)

	Isotonic saline	Lactated Ringer's	Acetated Ringer's	Plasma-lyte-A[a]
Theoretical osmolarity	308	277	302	295
Potential base excess	–24	0	0	–
Na^+	154	131	140	140
Cl^-	154	112	108	97.93
K^+	–	5.4	5	4.96
Ca^{++}	–	1.8	2.5	–
Mg^{++}	–	–	1.5	1.48
Lactate	–	28	–	–
Acetate	–	–	45	27.05
Malate	–	–	–	–
Gluconate	–	–	–	23.01

[a]Plasmalyte-A: Baxter, Switzerland

comes in patients with shock [11–14] and that fluid overload is itself related to increased mortality and morbidity [15–24]. It seems therefore of paramount importance to further investigate crystalloid fluids that are used for volume replacement in the critically ill patient as well as to minimize fluid overload.

The aim of this review is to provide an overview on currently used crystalloid fluids and to investigate respective risk-benefit profiles.

Crystalloid fluids

Several types of infusates are currently available for fluid resuscitation in the critical ill. The available solutes have variable salt-acid compositions (details depicted in Table 1).

Isotonic 0.9% saline is probably the best known and studied infusion solution in clinical practice [5–10]. In recent years, several drawbacks of normal saline were identified [11–16]; however, normal saline still remains among the most commonly used infusates worldwide [2, 11, 12, 15, 17, 18]. The benefit of balanced infusion solutions may be the ability to compensate the ion fluctuations better and buffering of the physiological acid-base status when compared to normal saline [2, 4, 19]. Nevertheless, despite continuing evaluation, no superiority of one particular type of infusion fluid has so far been shown [4, 15, 20, 21].

Normal saline (0.9% NaCl)

The most frequently used infusion solution worldwide is 0.9% saline [11, 12, 17, 18]. Interestingly, 0.9% saline was initially invented for physiological experiments [22], and not for infusion purposes. Isotonic saline has a sodium and chloride content of 154 mmol/l. In reality isotonic saline solution, often referred to as "physiological" saline, is thus slightly hypernatremic and markedly hyperchloremic [22]. In contrast to buffered infusions, isotonic saline does not contain potassium. Studies evaluating hypertonic saline showed a tendency to hyperchloremia and concurrent metabolic acidosis in patients receiving normal saline [11–14]. Additionally, the infusion of isotonic saline, as all non-buffered solutions, produces metabolic acidosis by plasma dilution. Through infusion of non-bicarbonate containing isotonic saline, the bicarbonate concentration of the plasma is diluted resulting in dilutional acidosis. Dilutional acidosis can either be produced by infusion of chloride-rich isotonic saline, non-buffered solutes, 5% glucose or mannitol solutions [23, 24]. Furthermore, the use of normal saline is most likely associated with an increased incidence of acute kidney injury, coagulation disturbances, hemodynamic instability and mortality [1, 12, 25, 26]. Physiological consequences of normal saline are shown in Fig. 1.

Buffered or balanced crystalloids

Balanced infusates were first introduced in 1931 by Alexis Hartmann with the aim to create an infusion solution with a reduced chloride content [27]. The search for a chloride-reduced solute was problematic; however, as electroneutrality within fluids needs to be ensured, a reduction in chloride will automatically lead to a cation excess. Chloride is the main extracellular anion of the human body; therefore, at first sight it seems an ideal anion for intravenous fluids. Nevertheless, hyperchloremia may result in triggering hyperchloremic metabolic acidosis [11–14]. The combination of bicarbonate with chloride might be a good choice regarding anions in infusion solutes and may result in a stable acid-base homeostasis and avoidance of dilutional acidosis. Nevertheless, bicarbonate has a short shelf life and is therefore unsuitable. This problem was solved by adding weak acids or so-called metabolizable anions, such as lactate, gluconate, malate or acetate to respective solutes [28, 29]. These anions are metabolized to bicarbonate leading to a more balanced acid-base homeostasis and avoidance of dilution at the same time [13, 30–33]. This may explain why they are called buffered infusates. Balanced infusion solutions contain, in contrast to isotonic saline, calcium, potassium and magnesium. One of the fears of physicians using balanced crystalloids is the respective potassium content; however, even though balanced infusates contain potassium they do not augment plasma potassium levels when compared to 0.9% saline [28, 34] and are thus not suitable for substitution of potassium. Currently, there is no evidence that balanced infusates increase plasma potassium concentrations even in patients with acute kidney injury [29]. Balanced infusates are supplemented with calcium and magnesium as cations in order to reduce sodium content and to maintain electroneutrality. Calcium-containing infusions might be problematic because of increased coagulation activity

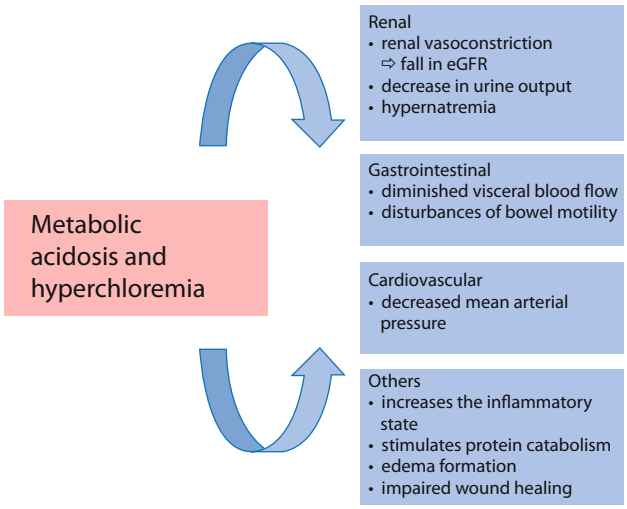

Fig. 1 Overview of physiological impacts of 0.9% saline. *eGFR* estimated glomerular filtration rate

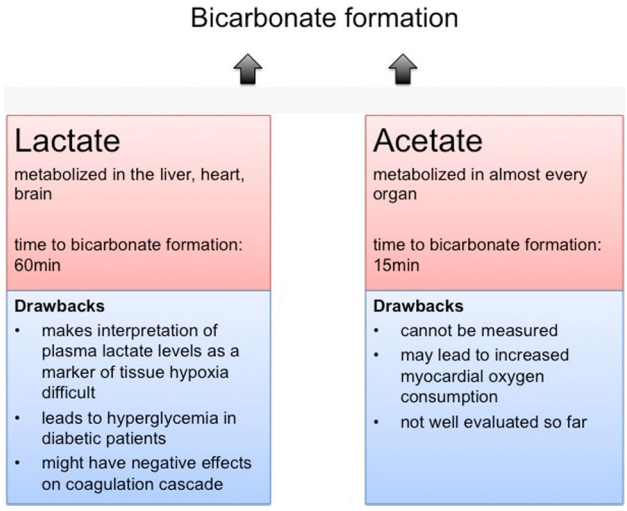

Fig. 2 Comparison between lactate and acetate

when concomitantly infused with blood products [28, 35]; however, some controversy on this topic exists.

Lactate versus acetate-buffered infusion solutions

Lactate and acetate are the most commonly used metabolizable anions in infusion solutes. Lactate and acetate-buffered crystalloids have some marked differences and advantages or disadvantages that may favor lactate over acetate-buffered crystalloids. When compared to lactate, acetate acts differently as a buffering substance in infusion solutions. Under normal circumstances, generation of bicarbonate from acetate would take approximately 15 min, as compared to 1 h for lactate [36–40]. Moreover, bicarbonate can be generated from acetate in almost all organs [19, 41, 42]. Lactate is a physiological intermediate, meaning it can cause acidemia and alkalemia and is metabolized at an extremely high rate in the liver but to a little extent in other organs, such as the heart or the brain [3].

The most feared side effect of acetate infusion is its vasodilatory effect; however, this issue remains controversial. While some studies reported reduced blood pressures after sodium acetate infusions [40, 43–45], others showed stable [46, 47] or even increased blood pressures [48]. Additionally, there is some uncertainty with respect to whether vasodilatory side effects of acetate-containing infusates would be dose-dependent [49, 50]. In general, balanced crystalloids are more often associated with alkalemic states but factors leading to alkalemia are as yet unknown. One could assume that this may vastly depend on renal, hepatological and respiratory functions but clinical trials in this area are needed.

Metabolic alkalosis was associated with acetate-containing infusates; however, infusion therapy with acetate-buffered crystalloid infusates may lead to increased bicarbonate levels [19, 21, 51, 52] but changes in pH and concurrent metabolic alkalosis seem less frequent than changes in bicarbonate after infusion of an acetate-buffered crystalloid solute due to slower metabolizing rates [19, 21]. Metabolic alkalosis may even be more detrimental than mild metabolic acidosis; however, the optimal mount of organic base has not yet been defined.

Use of lactate-buffered infusions may have additional problems: infusion of a solution containing lactate was shown to increase serum lactate levels and therefore theoretically impair use of lactate as a marker of tissue hypoxia [3, 19, 21, 53–56].

In patients suffering, e. g., from diabetes, lactate can theoretically lead to hyperglycemia via increased hepatic gluconeogenesis [36, 37, 57]. Lactate acidosis was associated with lowered levels of ionized calcium [58, 59], it is however, unclear whether this is also true for lactate-buffered infusates as the respective solutes do not induce lactic acidosis. Furthermore, it is unknown whether this effect is clinically relevant with respect to coagulation cascades. For comparison of the metabolic properties of lactate and acetate, please refer to Fig. 2.

Normal saline or balanced infusates: what is the current evidence?

Metabolic acidosis and hyperchloremia

Mounting data show that infusion of chloride-rich infusates results in metabolic acidosis in critically ill patients when compared to buffered infusates [1, 11–16, 29, 34, 60–64]. Many studies have shown that even moderate infusion volumes (≥2 l per 24 h) of isotonic saline induces metabolic acidosis [65–68]. Earlier, the clinical relevance of hyperchloremic metabolic acidosis was controversially discussed [69] but recently, a growing number of studies have shown that hyperchloremic metabolic acidosis is related to morbidity

and increased mortality in the critically ill [10, 12, 70]. Metabolic hyperchloremic acidosis following infusion of normal saline has a marked impact on excitable tissue [71, 72] and cellular function [73]. Studies showed that in comparison to 0.9% saline, the occurrence of acidosis and electrolyte disturbances is significantly lower in patients receiving lactated Ringer's solution [2, 16, 28, 29, 52, 53, 68, 74–79].

Renal function

In the 1980s it was first shown that infusion of hyperchloremic solutions leads to renal vasoconstriction and a fall in the glomerular filtration rate (GFR; [80, 81]). Additionally, in animals and humans, it was shown that infusion of normal saline is associated with markedly decreased renal perfusion pressures [11, 12, 61, 68]; however, with respect to patient-centered outcomes, such as occurrence of acute kidney injury (AKI) and the need for renal replacement therapy (RRT), the discussion remains controversial [5, 12, 26, 29, 62, 70, 82–87]. Whereas some trials did not observe a change in creatinine or an increased rate of AKI under chloride-rich infusates in both general intensive care unit (ICU) patients and in patients with sepsis [5, 83, 86], others demonstrated a markedly increased incidence of AKI and need for RRT under infusion of normal saline [12, 26, 29, 82, 87]. This effect remained significant after adjusting for confounders such as illness severity, operative status, mechanical ventilation, and type of admission [26, 29, 82]. A recently published meta-analysis concluded that the use of chloride-rich infusates is associated with a significant high risk to develop AKI [62].

Generally, the body of available literature varies widely with respect to methodology, total fluid volumes, AKI definition, as well as RRT initiation [5, 12, 29, 82]. For example, the recently published SPLIT trial compared the effects of normal saline to an acetate-buffered crystalloid solution on RRT did not find a difference in relation to RRT; however this trial only included low risk intensive care populations (as defined by relatively low APACHE scores) and patients only received very small fluid amounts [5]. Thus, the results of this trial may hardly be generalizable.

In conclusion, hyperchloremia and AKI after infusion of chloride-rich infusate may be dose dependent [88]. The volume of chloride-rich infusate infused as well as prior kidney function are major contributors to AKI.

Fluid overload

Volume overload is a considerable problem in the critically ill. Lowell et al. observed that 40% of patients admitted to a surgical ICU had an excessive increase in total body water of more than 10% from preoperative weight [89]. In patients with sepsis, extracellular volume overload exceeded 10l after 2 days of resuscitation, resulting in approximately 3 weeks until the respective fluid was excreted [90]. Generally, an increase in postoperative complications and adverse outcomes was associated with administration of excess sodium and water in the perioperative period by promoting interstitial edema [14, 91–98]. It was also shown that restrictive fluid and salt infusion was associated with significantly fewer cardiopulmonary events [14, 99, 100], increased bowel motility [100, 101], improved wound and surgical site healing [14, 99, 100] and reduced hospital stay [100, 101].

Several studies showed that normal saline (due to its high sodium content) may result in more fluid overload [102, 103]. Lindner et al. showed that normal saline use in the ICU is one of the main reasons for a positive sodium balance and hypernatremic hyperosmolarity in the critically ill [103]. In addition, it was shown that normal saline takes significantly longer to be eliminated via urine than other infusion solutes; however, use of hypertonic saline has resulted in decreased perioperative weight gain, negative fluid balance, and increased diuresis after major surgical procedures [104–107]. Fluid overload may not be uniquely a result of normal saline, it may also occur following infusion of balanced infusates and in cases of decreased renal function. Nevertheless, whether the type of crystalloid fluid influences the incidence rate and extent of volume overload needs to be investigated.

Cardiovascular function

Recent evidence suggests that the type of crystalloid infusate used for fluid resuscitation may impact on baseline blood pressures, cardiac performance, and need for catecholamines support. In 2014, Kellum et al. performed a rodent study with experimental sepsis where they found significantly decreased mean arterial pressures in the normal saline group [61]. Another experimental study showed that infusion of normal saline and ensuing metabolic acidosis may induce a time dependent decrease in mean arterial blood pressures, cardiac index, and cardiac work in rodents with abdominal sepsis [108]. In humans, use of normal saline was significantly associated with increased catecholamine needs and worsened hemodynamics [34, 109, 110]. A recently published prospective randomized-controlled double blind clinical trial in patients undergoing major abdominal surgery showed that patients in the normal saline group more often needed vasoactive agents in a higher dose [110]. In addition, in this trial patients receiving saline had worsening hemodynamics with ongoing time, which was associated to the amount of fluid infused and higher doses of vasoactive medication [110].

The underlying physiological changes related to increased hemodynamic instability in patients receiving normal saline when compared to acetate-buffered crystalloid still remain elusive. Several po-

Table 2 Pros and cons of acetate on the cardiocirculatory system

Positive effects	Negative effects	Unclear effects
– Increase in cardiac output – Coronary vasodilatation – Increased blood flow to the kidneys and gastrointestinal tract	– Increase in myocardial oxygen consumption	– Effects on peripheral vascular resistance? – Dose dependency?

tential contributors are discussed: first, metabolic acidosis (attributed to normal saline) reduces cardiac activity [71, 72], as well as vascular tone [111–113] and inhibits endogenous catecholamine production [114]. This was also seen in the KATECHOL trial [110]. Second, acetate may influence cardiovascular function. In 1978 Liang and Lowenstein infused acetate and pyruvate into anesthetized dogs to assess the impact on the circulation [115]. They found that increased acetate levels were associated with a significant increase in cardiac output [115]. Even though myocardial oxygen consumption increased during acetate infusion, the decrease in myocardial oxygen extraction and the increase in coronary sinus blood oxygen saturation suggest that an active coronary vasodilation takes place that does not result in increased cardiac work [115]. Acetate infusion also increases blood flow to the gastrointestinal tract, the renal system, intercostal muscles, and the diaphragm [115]. Another experimental study found similar results in healthy volunteers [48] and three other studies showed a positive effect on cardiac output with acetate-rich infusates, while peripheral vascular resistance was decreased [116–118]. Several other studies also reported a declined blood pressures after acetate infusion [40, 43–45]. In summary, use of acetate-buffered solutions could be harmful to patients with decreased myocardial reserve as evidence points to the fact that it increases myocardial contractility and oxygen consumption.

An overview on the risks and benefits of acetate on the cardiocirculatory system is shown in Table 2.

So far, no study has compared the effects of a lactate-based to an acetate-based crystalloid infusate on the cardiovascular system. Whether there is a difference between acetate-buffered and lactate-buffered crystalloids with respect to hemodynamic stability in the critically ill is currently under investigation [88].

Inflammation and coagulation

Inflammatory makers were found to be increased in animals receiving chloride-rich infusates in experimental sepsis [28, 61, 119, 120] and in trauma [121]. In humans, use of normal saline was associated with increased neutrophil activation [122, 123], effects on coagulation cascades [121, 124, 125] and increased transfusion needs [12].

Mortality

Whether use of normal saline is associated with increased mortality is controversially discussed. In a large observational study, Shaw et al. detected increased mortality rates in patients undergoing major abdominal surgery when treated with normal saline [12]. In fact, use of normal saline resulted in an approximately 50% absolute increase in mortality (2.9% versus 5.6% mortality) when compared to buffered crystalloids [12]. Additionally, patients treated with normal saline had higher rates of postoperative infections, blood transfusions and AKI [12].

Several other large-scale studies in various settings of critically ill patients found increased mortality rates for patients treated with normal saline, when compared to chloride-depleted infusates. This effect remained significant after adjusting for important confounders [10, 12, 63, 64, 126]; however, the results in the published literature remain controversial. A recent meta-analysis failed to confirm an association between chloride-rich infusions and mortality [62]. In addition, several large recently published randomized controlled trial, such as the SPLIT and LICRA trials did not find any difference in mortality between the groups [5, 29, 62, 86]. In a further large trial (SALT) a composite outcome of death, dialysis and persistent renal failure was not significantly different between the saline and the balanced infusion group in the general ICU population [8]. Studies investigating mortality with respect to crystalloid choice are depicted in Table 3.

A critical appraisals: what fluid should we choose in the critically ill?

Currently available crystalloid infusion solutions have multiple physiological effects; however, it seems important to remember that infusion solutes are among the most frequently used medications prescribed. In contrast to the usual choice of medications, the current approach to fluid therapy is mostly not patient-centered and generally follows a “one fluid for all” principle. Medical doctors are most often not aware of the importance of the fluids administered and knowledge on risks and benefits is most often sparse; however, the effects of infusion solutions on organ functions are not negligable, especially in the postoperative setting when patients have already received large volumes before being admitted to an ICU. In addition, with declined use of colloid solutions [127–132], choice of correct crystalloid solutes may even become more important.

The currently available data indicate that balanced infusates might have some advantages but evidence is still inconclusive. Normal saline is still among the most widely used iv fluids. In fact, media reports reveal that as many as 740 units of 0.9% saline are used each minute in the USA. [133].

Table 3 Studies investigating mortality with respect to crystalloid choice

Author (year)	Design	Study population	Total study population	Study intervention	Primary outcome	Mortality	Reference
Studies indicating increased mortality							
Shaw et al. (2012)	Prospective observational study	Major abdominal surgery	31,920	0.9% saline vs balanced crystalloids[a]	Mortality and morbidity	5.6% NS and 2.9% BG $p = 0.001$	[12]
Shaw et al. (2014)	Retrospective observational study	Patients with SIRS	109,836	0.9% saline vs balanced crystalloids[a]	Mortality	3.7% with stable chloride, 7.2% with 10–20 mmol/l increase in chloride, 9.2% with >20 mmol/l increase in chloride, $p = 0.001$	[63]
Shaw et al. (2015)	Propensity-matched cohort study	Patients with SIRS	3116	0.9% saline vs balanced crystalloids[a]	Mortality and morbidity	3.27% NS vs 1.03% BG , $p = 0.001$	[64]
Raghunathan et al. (2015)	Retrospective cohort study	Patients with septic shock	60,734	0.9% saline vs balanced crystalloids	Mortality and morbidity	24.2% NS vs 17.7% BG, RR 0.79, $p = 0.001$	[126]
Raghunathan et al. (2014)	Retrospective cohort study	Patients with sepsis	6730	0.9% saline vs Ringer's lactate	Mortality and morbidity	22.8% NS vs 19.6% BG, RR 0.86, $p = 0.001$	[10]
Studies indicating no difference in mortality							
Young et al. (2015)	Double-blind, cluster randomized, double-cross over trial	General ICU population	2278	0.9% saline vs Plasma-lyte-148	Acute renal failure, need for renal replacement therapy	8.6% NS vs 7.5% BG, RR 0.88, $p = 0.40$	[5]
Yunos et al. (2012)	Open-label, sequential period pilot study	General ICU population	760	Chloride-rich infusates[a] vs balanced crystalloids[a]	Acute renal failure, need for renal replacement therapy	9% NS vs 9% BG, $p = 0.42$	[29]
Krajewski et al. (2015)	Meta-analysis	Perioperative and ICU population	6253	Chloride-rich infusates[a] vs balanced crystalloids[a]	Mortality and morbidity	RR 1.13 increase NS vs BG, $p = 0.23$	[62]
McIlroy et al. (2017)	Prospective, open label, four-period sequential study	Perioperative, patients undergoing cardiac surgery	1136	Chloride-rich infusates[a] vs balanced crystalloids[a]	Acute renal failure	5.6% NS vs 5.3% BG, $p = 0.78$	[86]

NS normal saline group; *BG* balanced group
[a] Any type

Current evidence shows that normal saline can be used safely when some caution towards its negative side effects is applied and it is only used in patients requiring smaller fluid volumes with reduced illness severity scores. With respect to balanced infusates, the evidence remains less clear as most studies compare normal saline to a buffered infusion solute. Studies comparing the different buffered solutes are much less common but it seems important that buffered solutes should not be regarded as a homogeneous group. The term "buffered solutes" refers to the concept of acid-buffering in infusion fluids but does not imply that respective solutes have similar physiological impact. Nevertheless, different buffered solutes should be characterized more clearly in the future. Taking the available evidence together there is no single fluid that is superior for all patients and settings, because all of the currently available infusates have distinct differences, advantages and disadvantages; therefore, it seems inevitable to abandon the "one fluid for all" strategy towards a more differentiated and patient-centered approach to fluid therapy in critical illness.

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Conflict of interest C.A. Pfortmueller, B. Kabon, J.C. Schefold, and E. Fleischmann declare that they have no competing interests.

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