Designing 'Balanced' Crystalloids

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ABSTRACT

Objective: *To present a rationale for the design of balanced resuscitation and renal replacement crystalloids based on Stewart's physical chemical approach to acid-base.*

Data sources: *Articles and published abstracts on acid-base physiology, crystalloid infusions and renal replacement therapy.*

Summary of review: *Although it is uncertain that crystalloid-induced metabolic acidosis causes significant harm, Stewart's approach assists in designing balanced fluids without this side effect. In his analysis, the three independent variables determining acid-base balance are PCO_2, the total concentration of non-volatile weak acid (A_{TOT}) and the strong ion difference (SID). Raising and lowering A_{TOT} while holding SID constant cause a metabolic acidosis and alkalosis respectively. Lowering and raising plasma SID while clamping A_{TOT} cause a metabolic acidosis and alkalosis respectively.*

The SID of a crystalloid is its [HCO_3^-], or that part of an organic bicarbonate surrogate which is metabolised on infusion. Rapid infusion alters plasma SID towards crystalloid SID, but also lowers A_{TOT} by haemodilution. We have shown that the SID of a balanced infusion crystalloid is 24 mEq/L. This generates a fall in plasma SID precisely counteracting the A_{TOT} dilutional alkalosis. In contrast, a balanced renal replacement crystalloid must generate a higher plasma SID appropriate for the existing A_{TOT}, since there is no dilution. If A_{TOT} is low, as in hypoalbuminaemia, the balanced dialysis SID falls correspondingly. A further SID reduction is needed to counteract Donnan effects within the filter.

Conclusions: *A crystalloid SID of 24 mEq/L is 'balanced' for rapid intravenous administration. The 'balanced' SID of renal replacement fluids is likely to be significantly higher, although less than the normal plasma SID of 42 mEq/L.* (**Critical Care and Resuscitation 2003; 5: 284-291**)

Key words: Balanced crystalloid, fluid resuscitation, metabolic acidosis, renal replacement therapy, Stewart's approach

Large volumes of intravenous saline tend to cause a metabolic acidosis.[1-3] To counteract this side effect, a number of commercial crystalloids have been designed to be more 'physiologic' or 'balanced'. They contain stable organic anions such as lactate, gluconate and acetate (Table 1). These are replaced by HCO_3^- after metabolism, so that they are in effect HCO_3^- surrogates.

What becomes apparent from inspection of Table 1 is that the composition of these 'balanced' crystalloids is highly variable. In each, the surrogate [HCO_3^-] exceeds that of normal plasma (24 mmol/L), in some cases greatly so. If the intention of the higher concentrations is to accelerate correction of metabolic acidosis, a [HCO_3^-] of 55 mmol/L (Plasmalyte-R, Table 1) seems excessive on first inspection, and perhaps prone to over-shoot. However, it is difficult to be certain, because the underlying rationale driving the various compositions is not obvious.

The challenge is to find a logical basis on which to predict the acid-base effects of this disparate group of fluids. Such a rationale should enable us to select from the available 'balanced' crystalloids in an informed manner, and to design resuscitation fluids with specific acid-base effects. We argue here that such a framework is provided by incorporating Stewart's physical chemical analysis of acid-base into the existing conventional concepts, and that the same

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Table 1. Three 'balanced' salt solutions (electrolyte concentrations in mmol/L)

	Hartmann's[a]	Plasmalyte[a]	Plasmalyte-R[a]
Sodium	129	140	140
Chloride	109	98	103
Potassium	5	5	10
Calcium	2		5
Magnesium		1.5	3
Lactate	29		8
Acetate		27	47
Gluconate		23	
Effective SID[b]	27	50	53

SID = strong ion difference
[a] Baxter, Australia
[b] SID values are in mEq/L, and assume stable plasma lactate concentrations of 2 mmol/L.

principles can be applied when designing balanced renal replacement fluids. We begin by reviewing some important principles of acid-base analysis with an emphasis on the physical chemical approach.

Acid-base analysis – conventional approach

As a rule the first step in the laboratory evaluation of acid-base status is to measure the arterial blood PCO_2 and plasma pH. The PCO_2/pH relationship then allows clinicians to identify primary acid-base disturbances and to distinguish respiratory from metabolic (non-respiratory) perturbations. Traditionally, we use offsets in $[HCO_3^-]$ (the Boston school),[4,5] or standard base excess (the Copenhagen school)[6-8] to quantify metabolic acid-base status (Figure 1).

In acute respiratory acid-base disturbances, PCO_2 is abnormal but the PCO_2/pH curve is not shifted (Figure 1). The $[HCO_3]$ is appropriate for the abnormal PCO_2, and standard base excess is in the normal range. If the PCO_2/pH relationship is shifted to the left (Figure 1), there is a metabolic acidosis (either primary or compensatory), in which case $[HCO_3^-]$ is low for the prevailing PCO_2, and standard base excess is reduced. If the PCO_2/pH relationship is shifted to the right, there is a metabolic alkalosis (Figure 1), and $[HCO_3^-]$ and standard base excess are elevated.

The Stewart approach

The late Peter Stewart looked at acid-base balance from the perspective of physical chemistry.[9-11] In his analysis, $[HCO_3^-]$ and pH in body fluids are dependent variables determined by the state of three independent variables, PCO_2, strong ion difference (SID), and the total concentration of non-volatile weak acid (A_{TOT}). Arterial PCO_2 is regarded as independent because it is an equilibrium value set by alveolar minute ventilation and CO_2 production. In plasma, A_{TOT} is albumin and to a lesser extent inorganic phosphate, whereas in erythrocytes the predominant contributor to A_{TOT} is haemoglobin. Although both albumin and haemoglobin influence acid-base balance, neither is controlled by the acid-base status. A_{TOT} thus qualifies as an independent variable.

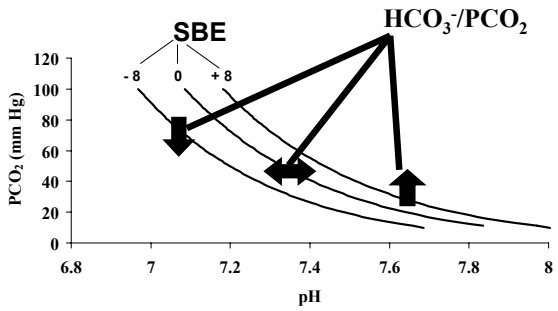

Figure 1. $PaCO_2$/pH relationships *in vivo*. SBE is standard base excess (mmol/L). The middle curve illustrates the normal metabolic acid-base status, where $[HCO_3^-]$ is appropriate for any PCO_2, and SBE is zero. The left-shifted curve illustrates metabolic acidosis, where $[HCO_3^-]$ is low at any PCO_2, and SBE is reduced. The right-shifted curve illustrates metabolic alkalosis, where $[HCO_3^-]$ is high at any PCO_2, and SBE is increased. Curve shifts arise either from primary metabolic acid-base disturbances or as compensation for respiratory acid-base disturbances.

The SID concept grew from the observation that certain ions in body fluids such as Na^+, K^+, Ca^{++}, Mg^{++} and Cl^- as well as organic anions like lactate and beta-hydroxybutyrate remain essentially completely ionised under all physiologic acid-base conditions. Stewart therefore termed them 'strong ions'. In body fluids there is always a surfeit of strong cations, quantified by SID. In other words, SID = [strong cations] – [strong anions]. Being a 'charge' space rather than a molar space, SID is expressed in mEq/L.

SID in normal plasma is 42 mEq/L. The overall SID in whole blood is harder to quantify, but can be derived using plasma/erythrocyte distribution equations and expressions for intra-erythrocytic buffering.[12,13]

In the Stewart analysis, as in the traditional 'schools' of acid-base analysis, respiratory acid-base disturbances arise from primary alterations in PCO_2. What differs is the contention that metabolic acid-base derangements are caused solely by alterations in either or both SID and A_{TOT}. To improve our understanding of this idea, we first need to explore the concept of 'buffer base'.

Buffer base

The SID space is filled passively by weak ions to preserve electrical neutrality (Figure 2). Unlike strong ions, their concentrations change with pH by variable dissociation of their respective conjugate bases. They include protons, OH^-, HCO_3^-, carbonate, and the negative charge on non-volatile weak acids, such as albumin in plasma. The latter is the A^- component of A_{TOT}, where $A_{TOT} = [HA] + [A^-]$. However, in a numerical analysis there are only two weak ions of quantitative significance, HCO_3^- and A^-, collectively termed the 'buffer base'. The rest are present in such minute concentrations, measured in either µmol/L or in the case of protons in nmol/L, that the buffer base concentration ($[A^-] + [HCO_3^-]$) is virtually the same as SID.[14] (This is *not* to say that they lack biological impact). The distribution and total concentration of the buffer base anions have major effects on pH, because the proton concentration in biological fluids must satisfy simultaneously the dissociation constants of HA and H_2CO_3 in Equations 1 and 2 below (as well as those of water dissociation and HCO_3^-):

$$H^+ + A^- \leftrightarrow HA \qquad \text{Equation 1}$$

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \qquad \text{Equation 2}$$

Thus although SID dictates the buffer space available, the buffer base anions within that space have a crucial influence on metabolic acid-base status. Equation 2 is especially important from a clinician's perspective, since it deals directly with the pH/PCO_2 relationship (Figure 1).

Metabolic acid-base disturbances and buffer base

Peter Stewart concluded that metabolic acid-base changes can only arise from alterations in SID or A_{TOT}. We will now link these changes to the PCO_2/pH relationship, since this is the acid-base 'window' used by clinicians.

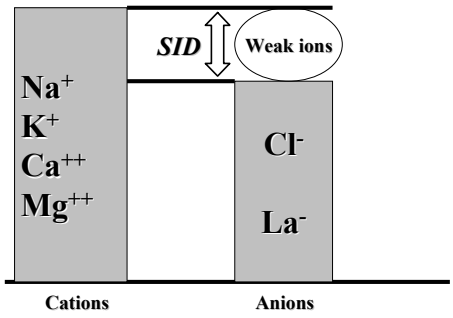

Figure 2. Illustration of the mirror image relationship between SID and weak ions. The only numerically significant weak ions are the buffer base anions A^- and HCO_3^- (see text). In order to maintain electroneutrality, the total concentration of buffer base anions ($[A^-] + [HCO_3^-]$) is the same as SID. La^- is the lactate anion.

SID changes

SID reductions are encountered when strong anions such as lactate or beta-hydroxybutyrate appear in the plasma without an equivalent rise in strong cations, or when $[Cl^-]$ and $[Na^+]$ simply move closer together. An isolated reduction in SID by either mechanism contracts the available buffer space, reducing the total buffer base concentration. Both $[HCO_3^-]$ and $[A^-]$ must participate in this reduction by titrating protons, shifting Equations 1 and 2 to the right. Carbon dioxide generated by the right shift of Equation 2 stimulates increased alveolar minute ventilation as necessary to control PCO_2. The end result is that for any given PCO_2, the $[HCO_3^-]$ and therefore the pH are now lower than previously (Equation 2). In other words, the fundamental PCO_2/pH relationship is shifted to the left (Figure 1), indicating a metabolic acidosis. Thus isolated SID reductions cause a metabolic acidosis. By a similar mechanism, isolated SID elevations shift the PCO_2/pH relationship to the right and cause a metabolic alkalosis.

A_{TOT} changes

A_{TOT} changes have the opposite effect. Isolated A_{TOT} elevations cause a metabolic acidosis, and reductions cause a metabolic alkalosis.[15] The mechanism can be thought of as follows: An isolated increase in A_{TOT} increases the A^- component of buffer base. However the total buffer base concentration ($[A^-] + [HCO_3^-]$) cannot alter since it is constrained by SID. As a result $[HCO_3^-]$ must titrate protons to be reduced by an amount equal to the rise in $[A^-]$. Equation 2 is shifted to the right, again with homeostatic control of the generated CO_2. The fall in $[HCO_3^-]$ moves the

PCO_2/pH relationship to the left and creates a metabolic acidosis (Figure 1). In similar manner an isolated fall in A_{TOT} creates a metabolic alkalosis.

In summary, isolated decreases in SID or increases in A_{TOT} cause a metabolic acidosis, whereas increases in SID or decreases in A_{TOT} cause a metabolic alkalosis. All such disturbances are mediated by alterations in either the total concentration of the buffer base anions or their ratio, both of which impact on the PCO_2/pH relationship via Equation 2.

Physical chemical properties of crystalloids

Because fluids are administered into a physiological milieu, their *in vivo* properties can be described in Stewart's physical chemical terms. Firstly, no pure crystalloid contains A_{TOT}, so that rapid intravenous administration dilutes plasma A_{TOT}. The second consideration is the crystalloid SID itself, and its effect on plasma SID. All saline solutions have a zero SID, since Na^+ and Cl^- are present in equivalent concentrations. The SID of water, dextrose solutions and mannitol is also zero, since these fluids contain no strong ions at all. Infusion of large volumes of zero SID fluids will reduce plasma SID by admixture and equilibration, forcing acid-base balance in the direction of a metabolic acidosis.[16,17] Importantly, although this acidosis is commonly hyperchloremic, it can also occur with a reduction in plasma [Cl^-], depending on the fluid employed.[18]

To prevent acidosis during rapid intravenous infusions, it is necessary to lessen but not eliminate the fall in plasma SID, as will be discussed below. This can only be done by increasing crystalloid SID, which means replacing some Cl^- ions in the crystalloid with HCO_3^-. However, HCO_3^- ions in aqueous solution are in equilibrium with dissolved CO_2, a highly diffusible gas, making them unstable in plastic bags. Such fluids must be stored in glass and infused promptly to prevent CO_2 loss to the atmosphere. This is why commercial balanced salt solutions contain organic anions (lactate, acetate, or gluconate) as stable surrogates for HCO_3^- (Table 1). Although these are actually strong ions with pKa values at least 2 below physiological pH, they are metabolised following infusion. Provided their metabolic clearance is rapid, organic anions removed in this way can be regarded as weak ions (Table 1).

The *in vivo* or 'effective' SID of crystalloids can thus be calculated from the component subject to metabolic 'disappearance'. For example Hartmann's solution contains L-lactate at a concentration of 29 mmol/L. Unless there is severe liver dysfunction, L-lactate can be metabolised at rates of 100 mmol/hr or more by oxidation or gluconeogenesis.[19,20] If the baseline plasma lactate concentration remains at 2 mmol/L during infusion, the effective SID of Hartmann's solution is 27 mEq/L. Only with severe impairment of lactate metabolism, such as in liver failure coupled with rapid infusion, is the effective SID of Hartmann's solution likely to be significantly reduced.

Intravenous infusion acidosis

The conventional explanation of infusion associated acidosis is that there is dilution of plasma HCO_3^- by large volumes of non - HCO_3^- containing fluid.[21-24] However, from the perspective of physical chemistry, crystalloid infusions exert two separate influences on acid-base. There is always a reduction in A_{TOT} by simple dilution. The result is a metabolic alkalosis as discussed.[15] However, there is a simultaneous effect on plasma SID by admixture and equilibration, the specifics of which depend on the crystalloid SID.[25] The end result represents the final plasma SID balanced against the metabolic alkalosis of A_{TOT} dilution. If the crystalloid SID is lower than plasma SID, plasma SID will be reduced. This creates a metabolic acidosis which opposes the alkalosis of A_{TOT} dilution. Conversely, fluids with high SID (such as sodium bicarbonate solutions) increase plasma SID, compounding the effect of A_{TOT} dilution.

Determining the 'balanced' intravenous crystalloid strong ion difference

To avoid acid-base disturbances, some plasma SID reduction is necessary to offset the A_{TOT} dilution effect, but the two processes must balance exactly. Theoretical determination of the crystalloid SID which achieves this balance is not straightforward, because infused strong ions distribute amongst plasma, erythrocytes and interstitial fluid in proportions governed by Gibbs-Donnan equilibria and the laws of electroneutrality and of chemical equilibrium. Meanwhile A_{TOT} remains concentrated maximally in the intravascular space throughout the dilution.

A useful exercise is to consider the most extreme haemodilution possible, which is complete replacement of extracellular fluid by crystalloid. At this point, the A^- component of plasma buffer base (albumin and phosphate ions) disappears, and HCO_3^- occupies the entire SID space. In other words crystalloid SID = plasma SID = plasma [HCO_3^-]. With no erythrocytes left to participate in Cl^- and HCO_3^- exchange, the chloride shift is eliminated. Without the chloride shift, plasma SID and therefore plasma [HCO_3^-] no longer alter with changes in PCO_2. To maintain normal metabolic acid-base balance, the plasma [HCO_3^-] and thus the crystalloid SID must be

chosen so that pH = 7.4 when PCO_2 = 40 mm Hg. By definition this value is 24.4 mmol/L.

The more practical question is whether this same crystalloid SID maintains normal metabolic acid-base balance during finite haemodilution, where plasma A_{TOT} and thus $[A^-]$ remain quantitatively important, and where red cells are still present. A relatively simple bench experiment demonstrated that this is true *in vitro*,[26] and we have now confirmed in one animal model that the rule also holds *in vivo*.[27] Thus it is likely that the SID of a balanced crystalloid is 24 mEq/L, for all degrees of dilution from mild to extreme.

Judging by our data, commercial 'balanced' salt solutions with a much higher effective SID than 24 mEq/L should be significantly alkalinising. For example, the effective SID of Plasmalyte (Baxter, Sydney, Australia) is 50 mEq/L after complete metabolism of infused acetate and gluconate anions (Table 1). Although measured data concerning this fluid are limited, it has been shown that if Plasmalyte is used to prime cardiopulmonary bypass circuits, arterial base excess increases by the end of bypass.[28] If there is a pre-existing metabolic acidosis, high SID fluids such as Plasmalyte will accelerate the correction process. They will also counteract ongoing acidosis generation more effectively. These may be advantages when resuscitating shocked patients, although over-correction is a potential drawback. Similarly, a crystalloid SID < 24 mEq/L more rapidly corrects a pre-existing metabolic alkalosis, with a similar tendency to over-correction.

Renal replacement therapy

Renal replacement is another area where crystalloids impact significantly on acid-base balance. As with resuscitation fluids, there is considerable variation in the effective SID of dialysis and replacement crystalloids in common use. For conventional intermittent haemodialysis, the preferred mode in the USA,[29] a dialysate $[HCO_3^-]$ (and thus SID) of 35 mmol/L has been recommended.[30] When intermittent haemodialysis is performed in Australia, $[HCO_3^-]$ values in on-line fluids vary considerably, and appear to have been derived empirically. For example, in two Brisbane tertiary hospitals, on-line $[HCO_3^-]$ values range from 32 mmol/L to 40 mmol/L (personal communication, J. Burke, Princess Alexandra Hospital, and Z. Endre, Royal Brisbane Hospital). However, in most Australian and New Zealand intensive care units, continuous renal replacement therapy (CRRT) is preferred over intermittent techniques.[31] Here again there is wide variation in the effective SID values of fluids designed for CRRT.[20] (Table 2).

Table 2. Two fluids used for continuous renal replacement therapy (electrolyte concentrations in mmol/L)

	Haemofiltration replacement fluid[a]	Hemosol®[c]
Sodium	140	140
Chloride	100	109.5
Potassium	1	
Calcium	1.6	1.75
Magnesium	0.8	0.5
Lactate	46	3
Acetate		
Gluconate		
Bicarbonate		32
Glucose	10.8	
Effective SID[b]	44	33

SID = strong ion difference
[a] Baxter, Australia
[b] SID values are in mEq/L, and assume stable plasma lactate concentrations of 2 mmol/L.
[c] Hospal Ltd, Rugby, UK

By applying Stewart's principles, a more logical approach should be possible. Firstly, renal replacement is not a diluting process. For this reason alone our findings concerning haemodilution cannot apply to renal replacement. If replacement crystalloids match the normal plasma $[HCO_3^-]$ of 24 mmol/L, an immediate metabolic acidosis will result [20] (unless the plasma albumin concentration is extremely low). This is despite the fact that such crystalloids are ideal 'balanced' resuscitation fluids. The fundamental difference is that crystalloid fluid loading reduces A_{TOT}, whereas renal replacement does not (although elimination of hyperphosphataemia does reduce A_{TOT} to a small extent).

The primary acid-base effect of dialysis fluids is thus on plasma SID. If there were no other considerations, dialysis fluid SID would need to match or slightly exceed the normal plasma SID (42 mEq/L). However, there are a number of other factors. First, hypo-albuminaemia is almost universal in critical illness, which in Stewart's terms translates as low plasma A_{TOT}. Dialysis fluid SID needs to be reduced correspondingly to counteract the resultant alkalosis.

Secondly, whether the dialysis mechanism is diffusive or convective, albumin does not cross the dialysis membrane and thus acts as a non-exchangeable anion. Chloride transfer from plasma to dialysate/ultrafiltrate is therefore increased by the Donnan effect,[32] while sodium transfer is reduced. If there is significant ultrafiltration, the Donnan effect is

magnified as albumin concentrates progressively along the filter pathway. Furthermore if PCO_2 falls significantly within the filter by diffusive loss, chloride will exit the erythrocytes (via the chloride shift, itself a variant of the Donnan effect), entering the plasma and thus the ultrafiltrate or dialysate, further increasing chloride loss. All of these factors raise plasma SID. This necessitates an additional reduction in the dialysate/replacement fluid SID below normal plasma SID to prevent metabolic alkalosis. Donnan effects and hypo-albuminaemia are the likely reasons for the metabolic alkalosis seen during CRRT when replacement fluids match the normal plasma SID.[33] There is evidence that pre-dilution affects Na^+ and Cl^- mass balances differently compared with post-dilution.[32] As a result, post-dilution is likely to generate a higher plasma SID, and is thus more alkalinising than pre-dilution.

Finally, CRRT using high lactate fluids can deliver L-lactate at 100 mmol/hr or more, so that even mildly impaired lactate metabolism results in elevated plasma lactate concentrations.[34,35] High volume haemofiltration can increase L-lactate delivery to over 270 mmol/hr, overwhelming the healthiest lactate-handling mechanisms.[36] Hyperlactaemia during CRRT with high lactate fluids is thus common, and might be expected to cause a metabolic acidosis by reducing plasma SID. However, the high effective SID of standard lactate replacement/dialysis crystalloids combined with the prevalence of hypo-albuminaemia usually suffices to prevent metabolic acidosis until severe hyperlactaemia supervenes.[33,36]

Does crystalloid-related metabolic acidosis really matter?

This is an important question. If the answer is 'no', designing resuscitation or renal replacement fluids to avoid metabolic acidosis is unnecessary or even counter-productive. *Severe* acidaemia certainly has important cardiovascular effects. They include reduced myocardial contractility, tachy- and brady-dysrhyth-mias, systemic arteriolar dilatation, venoconstriction and pulmonary vasoconstriction.[37] Undoubtedly, both global and regional oxygen delivery can suffer as a result. However, the acidaemia attributable to crystalloid infusions is seldom of this severity, and evidence for milder metabolic acidosis causing genuine harm is inconclusive.[38] For a start, intracellular pH is relatively stable during metabolic acidosis, in contrast to respiratory acidosis.[37]

There are even theoretical benefits. The Bohr effect increases tissue oxygen availability,[39] although this is rapidly counter-acted by a pH-induced fall in 2,3-diphosphoglycerate levels.[40] There is evidence that lowering pH is protective against hypoxic stress. A cell culture experiment [41] and a model of liver ischaemia/reperfusion injury [42] demonstrated apparent acidaemic protection against hypoxaemia. Leverve has argued that lactic acidosis is a protective adaptation.[43] Respiratory acidosis may also be protective in a range of scenarios.[44] In human studies of saline versus 'balanced' resuscitation, either with or without additional colloid, there have been no consistent differences in morbidity or mortality, apart from a predictable metabolic acidosis in patients receiving saline.[2,45-48] However none of these studies was powered to detect small mortality differences.

Nevertheless, the appearance of a normal anion gap metabolic acidosis in the context of fluid resuscitation has potential drawbacks. One is the risk of misinterpretation. A new or persistent metabolic acidosis during resuscitation might be attributed to unresolved tissue dysoxia. Such an error could lead to excessive fluid loading, or even an unnecessary laparotomy.[49] There is also a possible association with an increased gastric CO_2 gap,[48] and with post operative bleeding.[45] Human volunteers given 50 mL/kg normal saline over 1 hour experienced mental changes, abdominal discomfort and relative oliguria, but not when the same volume of Hartmann's solution was administered.[50] In one animal model, hyperchloremia reduced renal blood flow and glomerular filtration rate.[51] In another, HCl infusion caused NO production, hypotension and acute lung injury.[52] In two experimental models of severe haemorrhagic shock, Ringer's lactate outperformed saline in morbidity and survival.[53,54]

On balance it remains to be determined whether fluids with neutral acid-base effects produce the best results in terms of tissue oxygenation, organ function or survival.

Conclusion

By applying the principles of physical chemistry to traditional acid-base concepts it should be possible to design resuscitation and renal replacement crystalloids with specific acid-base effects. Our *in vitro* and *in vivo* evidence suggests that a crystalloid SID of 24 mEq/L is 'balanced' for rapid intravenous administration from an acid-base perspective. The exact 'balanced' SID value in renal replacement fluids is likely to be significantly higher than this, although less than the normal plasma SID. It remains to be established with certainty that crystalloid-induced metabolic acidosis causes significant harm.

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