

Theoretical principles of fluid management according to the physicochemical Stewart approach

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ABSTRACT

Interpreting acid base disturbances according to the physicochemical Stewart approach allows the cause of such abnormalities to be discovered. This method is based on three independent variables: SID (strong ion difference), mainly sodium and chloride; weak acids concentration — Atot, mainly albumins and phosphate; and carbon dioxide tension — $p\text{CO}_2$. These three independent variables are responsible for the change of water dissociation and for the change in H^+ concentration and, consequently, the change in serum pH value.

The SID value of the fluids administered to a patient is responsible for the change of serum SID value and therefore causes a change in the patient's acid base status. During the infusion of a given fluid, the SID value of the serum becomes closer to the SID value of that fluid; on the other hand, the infusion causes a decrease in Atot concentration. In order to avoid acid base disturbances connected with fluid administration, the SID value of fluids being administered should be greater than 0 and lower than the serum SID. It has been suggested that fluids should be given of which the SID value is as close as possible to the actual serum HCO_3^- concentration. Knowing the SID value of the fluid administered, and the serum HCO_3^- concentration, one can expect a change of serum pH after a fluid infusion. Administering a fluid with a SID greater than the HCO_3^- concentration causes a pH increase towards alkalosis. Likewise, administering a fluid with a SID lower than the HCO_3^- concentration causes a pH decrease towards acidosis. It seems that knowledge of the electrolyte concentration and the SID value of an administered fluid is an important factor regarding acid base disturbances.

Key words: fluid management, acid base status, Stewart approach

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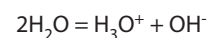
Physicians, including those working in intensive care units (ICUs), generally believe that pH of intravenous fluids affects the body's acid-base balance (ABB). Some of them even recommend infusions of pH-balanced fluids, i.e. of physiological or near physiological pH. It should be emphasized, however, that intravenous fluids of different pH values exert the same effects on ABB.

Professor Peter Stewart from Canada designed the physicochemical method, which explains body's acid-base changes differently than the traditional Henderson-Hasselbalch (H-H) approach.

In order to discuss the principles of fluid therapy based on the Stewart method, the basic assumptions of his approach should be recounted.

ESSENTIALS OF THE STEWART APPROACH

According to Stewart [1], water is the key molecule associated with acid-base disturbances. Pure water should be considered as the simplest acid-base system. Water is an inexhaustible source of H^+ ions (actually of H_3O^+ ions), which are formed during its dissociation:



To simplify the issues discussed, in the further part of the paper, H_3O^+ ions will be presented as H^+ .

A crucial element is the water dissociation constant - $K'w$, which depends on, among other things, the ionic strength of a solution plus temperature and equals 10^{-14} Eq L^{-1} .

$$\text{H}^+ \times \text{OH}^- = K'w = 10^{-14} \text{ Eq } \text{L}^{-1}$$

Under physiological conditions, pure water is neutral, i.e.

$$H^+ = OH^- = 10^{-7} \text{ Eq L}^{-1}$$

The acidic solution contains more H^+ ions whereas the basic one has more OH^- ions

$$\text{Acidic solution } [H^+] > \sqrt{K'w} > [OH^-]$$

$$\text{Basic solution } [OH^-] > \sqrt{K'w} > [H^+]$$

The essence of the Stewart approach can be explained using the simplified diagram. Figure 1 presents schematically the solution of sodium chloride (NaCl), which is neutral as the number of H^+ and OH^- is the same, i.e. $10^{-7} \text{ Eq L}^{-1}$ (Fig. 1A). When more Na^+ ions are added (Fig. 1B), the solution becomes basic, as more OH^- ions have to appear, according to the law of electroneutrality. By adding Na^+ cation, the pool of positive charges increases; therefore, more negative charges – anions (in this case OH^-) have to be formed for equilibrium. However, when Na^+ is given with an anion, e.g. NaOH, OH^- ions in water solution given with Na^+ react with H^+ , which diminishes H^+ concentration and OH^- ions outnumber H^+ ions. Clinically, such a situation is observed when the patient receives the solution of bicarbonate, $NaHCO_3$ to correct metabolic acidosis. We should be aware that plasma alkalinisation following the administration of $NaHCO_3$ is caused by the supply of Na^+ and not HCO_3^- ions. Bicarbonates are the accompanying ions. HCO_3^- ions react with H^+ forming $H_2O + CO_2$. CO_2 should be quickly excreted; otherwise, it will accumulate and diffuse to the cells. A similar alkalinising effect can be achieved by administering sodium acetate or sodium citrate. $NaHCO_3$ is *de facto* NaOH saturated with CO_2 .

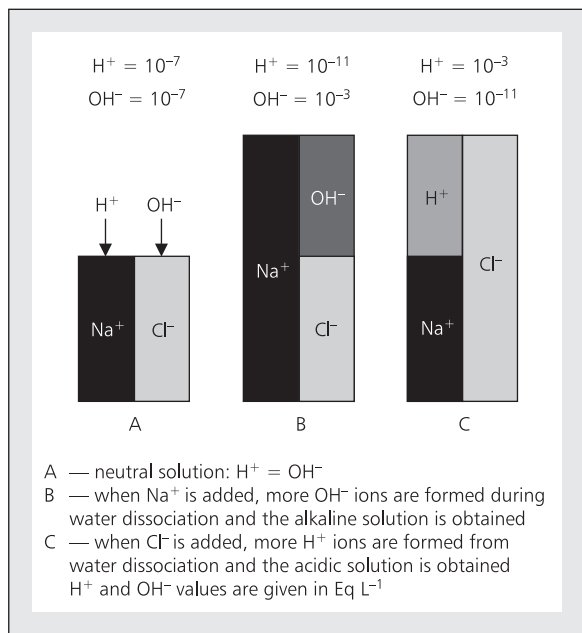


Figure 1. Effect of adding 1 mEq Na^+ (B) and 1 mEq Cl^- (C) on water dissociation

When more Cl^- ions are added (Fig. 1C), the solution becomes acidic, as, according to the law of electroneutrality, more H^+ ions have to appear. A similar status is caused by administration of HCl, and the changes are analogous to those described in Figure 1B [2].

Stewart described three mathematically independent variables that regulate the entire ABB:

1. pCO_2 — similarly to the H-H method, carbon dioxide is responsible for disorders of respiratory aetiology;
 2. strong ion difference (SID), with Na and Cl ions mainly responsible for it, followed by K, Mg, Ca ions and lactates;
 3. weak acids — $Atot$ — mostly albumins and phosphates in both dissociated (A⁻) and non-dissociated (AH) forms.
- „Strong ions” are those that are completely dissociated.

Changes in plasma pH are not induced by addition or elimination of free H^+ ions but by changes in the above-mentioned independent variables. Only a change in one or more independent variables alters water dissociation thereby changing H^+ concentration and subsequently pH [1]. In plasma (Fig. 2), strong cations, mainly Na^+ , outnumber strong anions, mostly Cl^- . The difference between them is called the SID. As the space with an electrical charge, the SID is expressed in mEq L^{-1} . The SID calculated from the difference in strong ion concentrations is called the apparent SID, (SIDa). Under physiological conditions, its value is about 40 mEq L^{-1} . Because SIDa is positive, it has to be counterbalanced by a negative charge. The negative charge filling this space is formed by weak acids — $Atot$ and HCO_3^- anions. The SID

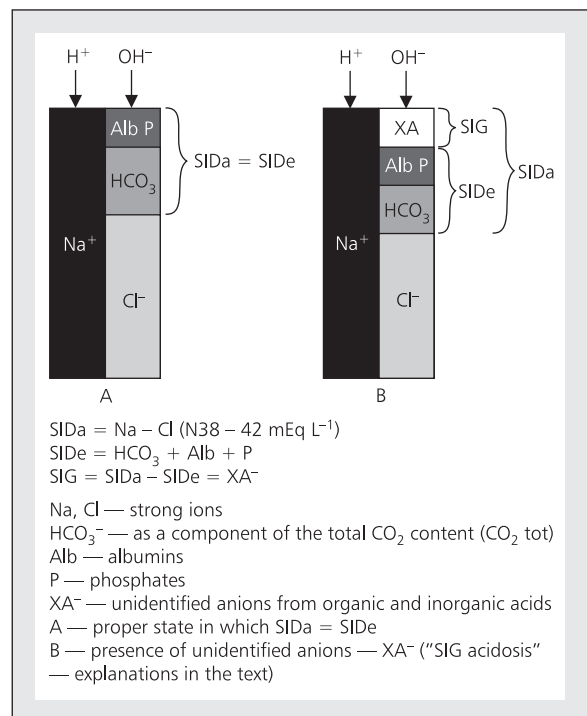
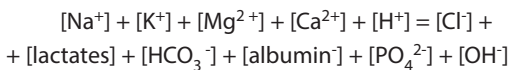


Figure 2. Independent variables according to the Stewart approach

calculated from the sum of Atot and HCO_3^- concentrations is named the effective SID (SIDe). In physiological conditions $\text{SIDa} = \text{SIDe}$ if Atot and HCO_3^- are the only additional anions besides Cl^- . When $\text{SIDa} \neq \text{SIDe}$, in fact when $\text{SIDa} > \text{SIDe}$, the unidentified anions — XA^- are present. In such a case, they fill the space at the expense of SIDe and the state is defined as a strong ion gap (SIG) [3, 4]. XA^- are anions from organic and inorganic acids formed during metabolic disturbances, which are secondary to those observed in severe sepsis, haemodynamic abnormalities or reduced tissue perfusion at the level of microcirculation. They include lactates formed in shock, ketone acidosis-attributable ketone bodies, such as acetoacetate, beta-hydroxybutyrate or intermediate derivatives of the Krebs cycle — sulphates, malates, acetates, citrates, and hippurates formed during kidney injury. Acidosis induced by them is called „SIG-acidosis” [3, 4]. It should be remembered that in aqueous solutions, which include plasma and extracellular fluid, H^+ and OH^- ions are always present yet their concentration is so low that they are invisible on diagrams.

According to the rules described, the regulation of ABB is mediated by interactions of three independent variables (SID, Atot , pCO_2) and their effects on water dissociation. The law of electroneutrality states that the sum of cations and anions has to be equal:



Using the following equations:

$$\text{SID} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{lactates}]$$

$$\text{Atot} = [\text{albumin}^-] + [\text{PO}_4^{2-}]$$

the equation transforms into:

$$\text{SID} + \text{H}^+ - \text{Atot} - \text{HCO}_3^- - \text{OH}^- = 0.$$

ACID-BASE DISTURBANCES ACCORDING TO STEWART

From the electrochemical point of view, the SID exerts significant effects on water dissociation (Fig. 3):

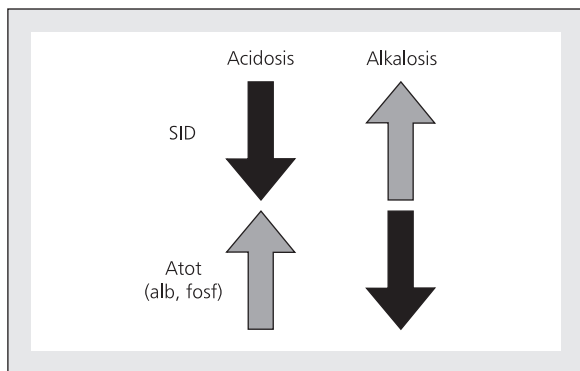


Figure 3. Effects of SID and Atot changes on acid-base balance (explanations in the text)

1. reduced SID, i.e. elevated Cl^- concentration (most common) or decreased Na^+ concentration (the anion concentration is higher) increases water dissociation; in accordance with the law of electroneutrality, more H^+ than OH^- are formed resulting in the development of metabolic acidosis;

2. increased SID, e.g. in hypernatraemia after NaHCO_3 supply or in hypochloreaemia in patients with abundant vomits, retention and loss of high volumes of gastric contents or those treated with loop diuretics, results in higher numbers of OH^- ions and the development of metabolic alkalosis;

Opposite effects are caused by weak acids — Atot :

1. elevated Atot concentration causes acidosis, which can be observed in renal injury when acidosis is induced by hyperphosphataemia in 30 % of cases;

2. reduced Atot concentration leads to the opposite effect; such a situation is observed in ICU patients. Over 90% of them have hypoalbuminaemia and metabolic alkalosis. Moreover, standard base excess (SBE) is often detected in them, which is attributable to the albumin deficit mentioned earlier and other things [5].

WHY DO PLASMA SID CHANGES INDUCE PH CHANGES?

The NaCl solution is a good example to discuss this issue [6]. SID in this case equals the difference in concentrations of Na^+ and Cl^- . The ions remaining in the solutions are H^+ and OH^- . To emphasise the importance of the issue, in Fig. 4, Atot and HCO_3^- were ignored and eliminated whereas H^+ and OH^- concentrations were overestimated. Under normal conditions, these concentrations are so low that they cannot be “seen”. According to the law of electroneutrality: $\text{Na}^+ + \text{H}^+ = \text{Cl}^- + \text{OH}^-$. Physiological plasma $\text{pH} = 7.4$, hence it is slightly alkaline, which means that the concentration of OH^- is slightly higher than that of H^+ .

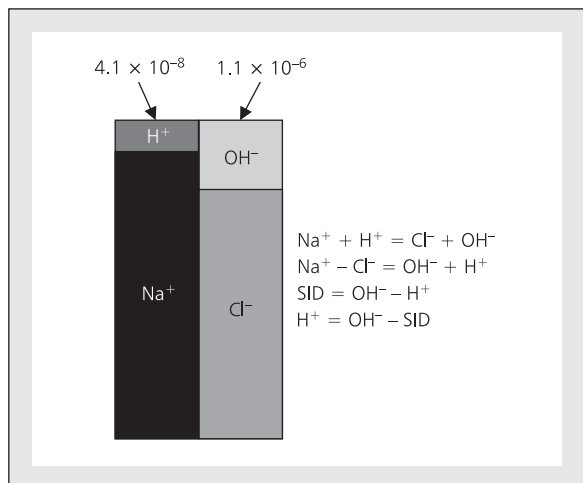


Figure 4. Relation between SID and H^+ ion concentration

After transformation, the formula is: $H^+ = OH^- - SID$, which means that when the SID is reduced (hyperchloraemia, hyponatraemia), the difference between OH^- and SID will increase and more H^+ ions will be released leading to acidosis. Otherwise, when the SID is increased (hypochloraemia, hypernatraemia), OH^- ions formed will be more numerous resulting in to the development of alkalosis.

Excluding the respiratory issues in which disorders are similar as in the H-H approach, high and low pCO_2 determine respiratory acidosis or alkalosis, respectively; all metabolic acid-base disturbances can be categorized as follows [7]:

- 1) metabolic acidoses:
 - a) „SIG acidosis“: acidosis caused by unidentified anions – ketone or lactate acidosis; in kidney injuries, diabetes mellitus, shock, intoxications,
 - b) acidosis with low SID, e.g. hyperchloraemic; after fluid infusions,
 - c) acidosis with elevated Atot due to hyperphosphataemia in kidney injury;
- 2) metabolic alkaloses:
 - a) alkalosis with high SID:
 - hypochloraemic – e.g. loss of gastric contents, treatment with loop diuretics,
 - hypernatraemia, e.g. excessive supply of nutritional Na, infusions of $NaHCO_3$,
 - b) alkalosis with low Atot, e.g. hypoalbuminaemia.

Noteworthy, patients can be affected by several different metabolic acid-base disturbances simultaneously, e.g. lactate and hyperchloraemic acidosis, simultaneous acidosis and alkalosis, which is difficult to diagnose using the traditional H-H method. The arterial blood gasometry findings will not explain the cause of the disorders observed; we do not know what a given SBE value means, for instance, when $SBE = +6$ and the concentration of lactates is 7 mmol L^{-1} .

FLUID THERAPY BASED ON THE STEWART APPROACH

High volumes of infused fluids can induce metabolic acidosis. The administration of the fluid in the form of water, glucose solution, mannitol, 0.9% sodium chloride solution or hypertonic solution of sodium chloride causes metabolic acidosis as in these fluids $SID = 0$, i.e. the number of strong ions is equal (NaCl solution) or they are absent (water, glucose). After infusion of such fluids, the plasma SID increases. For instance, administering 0.9% NaCl solution, which contains equal numbers of Na^+ and Cl^- ions, 154 mEq L^{-1} , each, the plasma concentration of Cl^- is relatively higher than that of Na^+ , which results in a new, lower value of plasma SID. This changes the extent of water dissociation and causes the development of metabolic acidosis.

The question is what rules cause plasma pH changes after fluid infusions. To answer this question, some earlier

concepts explaining the development of acidosis induced by fluid infusions should be mentioned [1]:

1. **pH of fluids:** it is not infrequently believed that acid-base disturbances after fluid infusions are caused by the excessive activity of protons, i.e. H^+ ions in the infused fluid. However, this is inconsistent with the rules described in the Stewart method. H^+ ions in the free state cannot be added or removed from the aqueous solution. H^+ ions appear when suitable conditions are provided, i.e. when water dissociation is enhanced due to independent variables mentioned earlier (pCO_2 , SID, Atot). In other words, pH of intravenous fluids has no substantial impact on plasma pH changes, thus is insignificant for induction of acid-base disturbances.
2. **dilution of HCO_3^- ions:** in many cases, it is said that acidosis after fluid infusions is caused by bicarbonate dilution. The law of electroneutrality states that HCO_3^- together with Atot (albumins, phosphates) fills the negatively charged space formed by strong ions (Fig. 2). The electrical neutrality of body fluids is characterized by the formula presented earlier:

$$SID + H^+ - Atot - HCO_3^- - OH^- = 0$$

After elimination of quantitatively irrelevant H^+ , OH^- , the formula can be simplified into:

$$SID - Atot = HCO_3^-.$$

What is the significance of the formula above? If the SID becomes lower due to increased Cl concentration (after infusion of 0.9% NaCl) or/and Atot increases (e.g. due to increased concentration of phosphates in kidney injury cases), the difference between the SID and Atot will decrease, which will reduce the concentration of HCO_3^- .

Otherwise, if the SID becomes higher, e.g. in hypernatraemia after $NaHCO_3$ treatment or hypochloraemia during vomiting and/or the Atot concentration becomes lower (in hypoalbuminaemia), the concentration of HCO_3^- will increase. In other words, the concentration of HCO_3^- changes depending on primary changes in independent variables, i.e. SID and Atot. Thus, the concept implicating that reduced concentration (dilution) of HCO_3^- in plasma is the cause of post-infusion acidosis is incorrect; HCO_3^- is the variable dependent on SID and Atot.

EFFECTS OF FLUID SUPPLY ON ACID-BASE BALANCE

Each intravenous fluid has its own electrolyte composition, hence SID. Prior to the infusion of a given fluid, its SID and Atot should be known. In crystalloids, $Atot = 0$, yet it does not regard some colloid preparations. The infusion of fluids causes the phenomenon of mixing of two different fluids- the fluid infused and plasma (extracellular fluid) of various values of SID and Atot.

Fluid administration induces acidosis as we dilute strong ions and decrease the plasma SID and, on the other hand, alkalosis by dilution of Atot and reduction in albumin concentration. During infusion, the plasma SID evolves towards the SID values of the infused fluid and as the plasma SID is the resultant of this process (Fig. 5).

What measures should be taken to avoid disturbances of acid-base balance induced by fluid therapy?

Let us consider a hypothetical situation, impossible in reality – we use an unlimited (infinite) infusion of a fluid of SID = 0 (e.g. 0.9% NaCl) [1, 6]. The unlimited infusion means complete replacement of extracellular fluid with 0.9% NaCl. Noteworthy, the physiological SID of extracellular fluid is about 40 mEq L⁻¹ whereas A⁻ (dissociated form of Atot) about 16 mEq L⁻¹, assuming that the albumin concentration range is 42 g L⁻¹ [8]. Once the plasma SID is completely replaced (eliminated), extremely severe metabolic acidosis will be induced with the SBE — 40 mEq L⁻¹ (excess/deficient SID can be used, SIDex — 40). The simultaneous dilution and

elimination of A⁻ (albumins) will induce metabolic alkalosis with the SBE +16 mEq L⁻¹ (SIDex +16). The combination of these two phenomena will still mean the presence of acidosis yet less severe with the SBE (SIDex) — 24 mEq L⁻¹. To restore normal acid-base balance and achieve electrical neutrality (SBE = 0), the SBE (SID) value should be increased by 24 mEq L⁻¹. Thus, according to the law of electroneutrality, when A⁻ is eliminated during the unlimited infusion, the entire space is filled with HCO₃⁻ (Fig. 6). To avoid acid-base disturbances after fluid infusions, their SID should be about 24 mEq L⁻¹, hence equal to the physiological HCO₃⁻ concentration in the patient's blood. The solutions of such SID values are called balanced solutions.

In everyday practice, the fluid supply to the patient induces the limited infusion in which A⁻ are still present but during fluid administration their blood concentration decreases. To prevent acid-base disturbances, the balance between a reduction in SID and a decrease in plasma A⁻ should be maintained. Numerous studies have confirmed that when fluids with SD = 24 mEq L⁻¹ are used, the SBE values are maintained at the proper level. The administration of fluids with SID < 24 mEq L⁻¹, hence lower than the plasma concentration of HCO₃⁻, induces metabolic acidosis; and otherwise, the administration of fluids with SID > 24, i.e. higher than the plasma concentration of HCO₃⁻, induces metabolic alkalosis. The above principles are used to prepare the composition of intravenous fluids [9–11].

Nevertheless, still another problem is faced: how to achieve the fluid SID of 24 mEq L⁻¹. The simplest way would be to replace 24 mEq Cl⁻ anions from the solution of 0.9% NaCl with other anions. Table 1 presents the balanced solutions — SID = 24 mEq L⁻¹. Cl⁻ anions were respectively replaced with OH⁻ anions (solution 1) and HCO₃⁻ anions (solution 3). When such solutions are kept in plastic bottles, which is the routine practice, they will become the solution 2 due to permanent equalisation of concentrations with atmosphe-

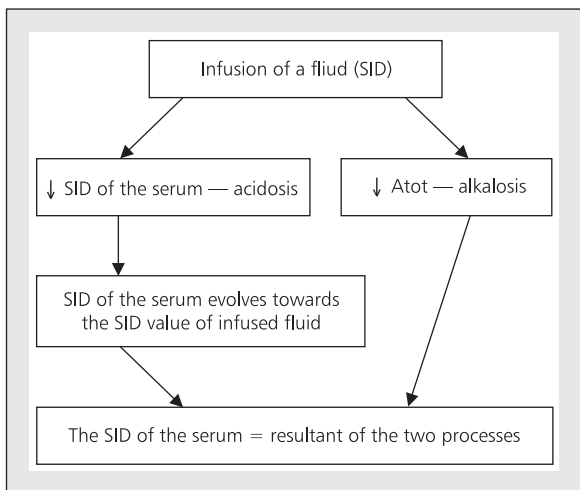


Figure 5. Effects of infused fluids on acid-base balance

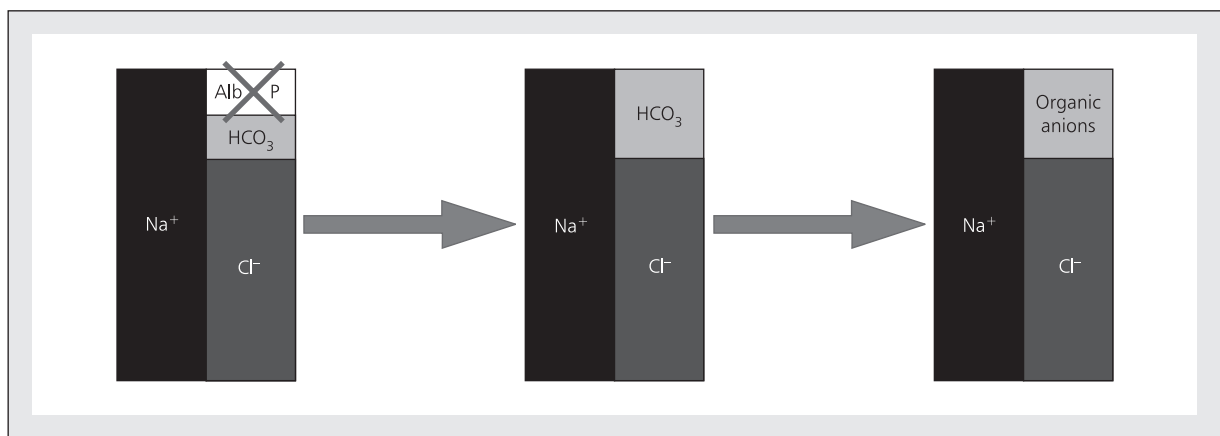


Figure 6. In an infinite infusion, Atot disappears and the entire space is filled with HCO₃⁻

Table 1. Balanced solutions

Solutions	no. 1	no. 2	no. 3	no. 4
Na	140	140	140	140
Cl	116	116	116	114
HCO ₃ ⁻		19.2	24	
CO ₃		4.8		
OH	24			
Lactate			26	
pCO ₂	0	0.3	760	0.3
pH	12.4	9.35	6.04	6.49
SID	24	24	24	24

ric CO₂. Let us highlight the pH value. The solution 1 has an extremely high pH > 12, which is unacceptable when we intend to administer larger volumes of the fluid and to use a high flow rate. However, when the solution 3 becomes the solution 2, its pH will increase > 9. As mentioned earlier, pH values of solutions do not affect acid-base balance but can be dangerous for the vascular endothelium and cause tissue necrosis. The infusion of each of the three solutions described above, despite various pH values, will produce the same effect on acid-base balance because all of them have the same value of SID, i.e. one of the independent variable [5].

To eliminate the harmful effects on blood vessels and the issue of equalization with atmospheric CO₂ and loss of CO₂, Cl⁻ ions are replaced with organic anions, such as lactates, malates, gluconates, citrates or others (Fig. 6). The solution 4 (Table 1) is an example of such an approach where Cl⁻ anions have been replaced with lactates. The *in vitro* SID of this solution is still 0; SID = 24 (effective SID) will appear when after fluid administration lactate has been quickly metabolised. Under physiological conditions, lactate is metabolised in the amount of 100 mmol h⁻¹, which equals the fluid infusion of about 4000 mL h⁻¹. When the patient suffers from liver failure and lactate has not been eliminated, the fluid will still have the SID near zero and its infusion will lead to the development of lactate acidosis [12].

Based on the baseline, pre-infusion concentration of HCO₃⁻ in the patient's plasma and the SID of the fluid (crystalloid, colloid), we can predict the direction of blood pH changes during fluid administration:

- shift towards more severe acidosis when the SID of the fluid infused is lower than the plasma HCO₃⁻ concentration;
- shift towards alkaline side when the SID of the fluid infused is higher than the plasma HCO₃⁻ concentration.

The same fluid infused with a defined SID, e.g. SID = 24, will have alkalisating effects in the patient with acidosis and low concentration of HCO₃⁻, about 20 mEq L⁻¹ or acidifying

effects in cases with primary alkalosis with higher values of HCO₃⁻, about 30 mEq L⁻¹ [13].

In everyday hospital practice, patients receive various crystalloid and colloid preparations of different SID values. The SID value is usually not provided by the manufacturer. To be aware of the consequences of acid-base disturbances, we should know the concentrations of strong ions in intravenous fluids, e.g. of Na, K or Cl and organic anions and calculate the SID of the fluids administered.

Prior to fluid infusion, the patient's acid-base balance is essential. If normal, fluids with the SID around 24 mEq L⁻¹ should be used, at least with SID values higher than 0 and lower than the plasma SID. When the patient is diagnosed with metabolic acidosis, the use of the fluid with SID higher than the plasma concentration of HCO₃⁻ exerts the therapeutic effect shifting acid-base balance towards the alkaline direction. The opposite relation is observed in the case of alkalosis. In some cases, such as ketone acidosis (SIG acidosis), the supply of the fluid with SID = 0 (0.9% NaCl) enhances acidosis by adding the hyperchloraemic component whereas the administration of the fluid with high SID, higher than plasma HCO₃⁻, is likely to lead to too quick equalisation of acidosis and development secondary breakthrough alkalosis, especially during causal treatment with insulin [10].

As in cases of crystalloids, the SID of colloids is a fundamental feature of rational fluid therapy. Before infusion, it should be known which of them are balanced. Moreover, fluid therapy with colloids is associated with elevated plasma oncotic pressure, which favours water redistribution to the intravascular compartment. This reduces the plasma SID and has possible slight alkalisating effects. Furthermore, some colloid preparations have their own activity of weak acids (Atot). This regards mainly albumins and gelatine solutions but not HES or dextran [8]. Therefore, while infusing larger amounts of albumins or gelatines, the development of higher Atot-induced acidosis can be anticipated (Fig. 3)[14].

Considering the above statements, it is pivotal to know the electrolyte composition and SID of intravenous fluids used in everyday practice.

Table 2 presents the parameters of the most commonly used intravenous fluids.

CONCLUSIONS:

1. The essence of the Stewart model is to understand that only three independent variables, pCO₂, SID and Atot, are relevant to determine the H⁺ concentration and pH values.
2. The relation between the SID of intravenous fluids infused vs. the direction and extent of plasma SID changes is linear.

Table 2. Composition of the most commonly used intravenous fluids

	Ringer's solution	Lactated Ringer's solution	Braun's Sterofundin solution	Sterofundin solution	Isotonic Polielectrolite solution	Tetraspan solution	0.9% NaCl
Na	147.2	130	140	140	141	140	152
K	4	4	4	4	5	4	
Cl	155.7	109	127	106	109	118	152
Ca	2.2	1.5	2.5	2.5	2	2.5	
Mg		1		1	1	1	
pH	5–7.5	6–7.5	4.6–5.4	4.5–7.5		5.6–6.4	
Lact		28		45			
Acetate			24		34	24	
Malate			5			5	
Citrate					3		
SID	Negative?	28	29	43	37	29	0

3. During fluid supply, the plasma SID is reduced, which equalizes the decrease in Atot concentration.
4. To avoid acid–base disturbances, the fluid SID should be > 0 and lower than the plasma SID; optimally, it should equal the baseline concentration of plasma HCO_3^- anions.
5. Study results confirm the hypothesis that changes in pH can be predicted on the basis of intravenous fluid SID and HCO_3^- concentration after infusion:
 - fluid SID > plasma HCO_3^- — plasma pH increases,
 - fluid SID < plasma HCO_3^- — plasma pH decreases.

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