DOI: 10.1111/sdi.12716

TREATMENT CONSIDERATIONS IN CONVENTIONAL HD – WHAT WE KNOW

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WILEY Seminars in Dialysis

Dialysate bicarbonate concentration: Too much of a good thing?

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Abstract

Acid-base equilibrium is a complex and vital system whose regulation is impaired in chronic kidney disease (CKD). Metabolic acidosis is a common complication of CKD. It is typically due to the accumulation of sulfate, phosphorus, and organic anions. Metabolic acidosis is correlated with several adverse outcomes, such as morbidity, hospitalization and mortality. In patients undergoing hemodialysis, acid-base homeostasis depends on many factors: net acid production, amount of alkali given by the dialysate bath, duration of interdialytic period, as well as residual diuresis, if any. Recent literature data suggest that the development of postdialysis metabolic alkalosis may contribute to adverse clinical outcomes. Unfortunately, no randomized studies exist about the effect of different dialysate bicarbonate concentrations on hard outcomes, such as mortality. Like everything else in dialysis, the quest for the "ideal" dialysate bicarbonate concentration is far from over. The Latin aphorism "*ne quid nimis*" ie "nothing in excess" (excess of neither acid nor base) probably best summarizes our current state of knowledge in this field. For the present, the clinician should understand that target values for predialysis serum bicarbonate concentrations have been established primarily based on observational studies and expert opinion. On the basis of this information, we should keep predialysis serum bicarbonate concentrations at least at 22 mEq/L. Furthermore, a specific focus should be addressed to the clinical and nutritional status of the major outliers on both the acid and alkaline sides of the curve.

1 | INTRODUCTION

The physiologic approach to assessing acid-base status views blood pH as being determined by the prevailing levels of carbonic acid (that is, PCO_2, the respiratory component) and HCO_3^- (the metabolic component, further indicated as BIC).[1,2] The standard blood gas analyzer measures pH and PCO_2, from which BIC is calculated using the Henderson Hasselbalch equation.[1] Attributable to convenience and wide availability, directly measured serum total CO_2 (TCO_2) in venous blood is routinely used in screening for acid-base disorders in patients undergoing hemodialysis (HD).[2] The underlying rationale is that both metabolic and respiratory disorders (the latter by virtue of the secondary responses of BIC to changes in PCO_2) are associated with abnormalities in BIC.

Although the measured TCO_2 is almost always termed BIC, the two are not equivalent. Serum TCO_2 includes both BIC and dissolved CO_2 ($TCO_2 = [HCO_3^-] + 0.03 \times PCO_2$). Under most conditions TCO_2 is approximately 1 mEq/L higher than BIC when measured in the same blood sample.[3]

Ideally, assessment of acid-base status in any patient should include blood pH and PCO_2, with calculation of BIC. Unfortunately, the additional time (and cost) for this measurement in all our HD

patients is not feasible. Predialysis serum TCO_2, bundled into the current Medicare payment for HD, remains the standard marker for assessing acid-base contribution to morbidity and mortality in the United States.[3]

2 | ACID-BASE BALANCE IN PATIENTS UNDERGOING HD

Proteins in contemporary Western diet generate predominantly acidic products including hydrogen chloride, sulfuric acid, and phosphoric acids, leading to an endogenous acid production of ~1 mEq/kg/day, i.e., ~ 70 mEq/day in an average adult. These acids are nonvolatile and rely on the kidneys for excretion. In a steady state renal net acid excretion is equal to net endogenous acid production. In patients affected by chronic kidney disease (CKD) renal acid excretion becomes insufficient, leading to metabolic acidosis.[4] The latter is a common complication of CKD; acidosis generally is mild to moderate in degree, with serum BIC ranging from 12 to 22 mEq/L, and it is rare to see values less than 12 mEq/L, in the absence of an increased acid load. Degree of acidosis approximately correlates with severity of renal failure and usually is more severe at a lower glomerular filtration rate. Metabolic acidosis is correlated with several adverse outcomes, such as morbidity, hospitalization, and mortality. Thus, correction of metabolic acidosis is fundamental for an adequate management of many systemic complications of CKD.[5]

At present, the control of metabolic acidosis in patients undergoing HD is mainly focused on the supply of BIC during dialysis sessions. There is a wide variation in the dialysate BIC concentration (D_{BIC}) among countries with values ranging from 32.2 ± 2.3 mEq/L in Germany to 37.0 ± 2.6 mEq/L in the United States.[6] The correction of acidosis during dialysis is achieved by the transfer of D_{BIC} to the blood compartment, following a steep concentration gradient.[5] Sodium BIC is the main buffer used during maintenance HD, and patients who undergo this procedure receive high doses of sodium BIC for their life span. The optimal D_{BIC} is one that prevents acidosis at the beginning of the next HD session while avoiding postdialysis alkalosis.[7] New BICs are primarily added directly from the bath, although a small amount is also generated from the addition and metabolism of acetate, citrate, and/or acetic acid (Figure 1).

With D_{BIC} set around 35 mEq/L, the average predialysis serum BIC at the beginning of the week is highly variable, ranging from less than 17 mEq/L to more than 27 mEq/L.[7] Serum BICs typically increase rapidly during the first 2 hours of treatment to subsequently level off and, by the end of the session, serum BICs are about 4-7 mEq below D_{BIC}.[7,8] The reason postdialysis serum BIC is below D_{BIC}, and not at the same level as it would be expected for a small molecule, is likely due to stimulation of organic acid production associated with BIC transfer from dialysate to plasma, thus minimizing further increases in serum BIC.[7] The amount of organic acid produced is difficult to quantitate and may vary considerably from patient to patient.[7]

In patients undergoing HD, acid-base homeostasis depends on many factors: net acid production, amount of alkali given by the dialysate bath, duration of interdialytic period, as well as residual diuresis, if any. The mass of BIC added during dialysis is a function of its dialysance and the integral over the time of treatment of its transmembrane concentration gradient [9] (Figure 1). When measured at a blood flow rate of 200 mL/min and a dialysate flow rate of 400 mL/min using a regenerated cellulose membrane with a surface area of 1.8 m^2, dialysance is 131 mL/min or about 65% of blood flow rate.[10] When comparing bicarbonate kinetics and acid-base status in high-flux HD and on-line postdilution hemodiafiltration (D_{BIC} was 38 mmol/L in both treatments; the mean reinjected volume was 21 L in hemodiafiltration), no significant differences were observed between acid-base parameters at the end of HD and hemodiafiltration sessions. An unexpected result was the continuous decay of BIC dialysance both in HD and hemodiafiltration runs.[11] These data confirm the in vitro data obtained by the same group.[12] Thus, BIC dialysance behaves very differently from urea clearance, even though both solutes have a similar molecular weight.[11,12]

In the interval between treatments serum BIC gradually decreases because of both the production of endogenous acids and the retention of fluid.[13] Fluid retention without added alkali dilutes the existing alkali and thereby reduces serum BIC (Figure 1).[13] Patients undergoing HD consume their body alkali stores primarily by endogenous acid production. Higher animal protein intake is associated with a higher dietary acid generation that, in turn, is associated with lower predialysis serum BICs.[13] There is an inverse relationship between serum BICs and normalized protein catabolic rate, suggesting that more acidotic patients have a greater protein intake.[14]

Although oral base therapy could be a solution for correcting acidosis in patients undergoing HD, it increases their already enormous medication load and sodium intake. Therefore, we need to rely more on correcting acidosis during the HD procedure, which is difficult to achieve, in part because HD is an intermittent therapy. The currently used fixed D_{BIC} is associated with predialysis acidosis and intra-dialysis alkalosis.

3 | PRE- AND POSTDIALYSIS SERUM BIC AND MORTALITY IN PATIENTS UNDERGOING HD

Predialysis serum BICs have progressively increased in the last years: among 12,099 patients undergoing HD in the United States in 1987-1988, the mean serum BIC was 19.2 mEq/L[15]; in contrast, the mean serum BIC was 21.4 mEq/L in 4,515 patients undergoing HD in the United States in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996 to 2001,[16] and was 21.9 mEq/L among 56,385 patients who underwent HD from 2001 to 2003.[14] In 2000 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommended maintaining predialysis serum BIC

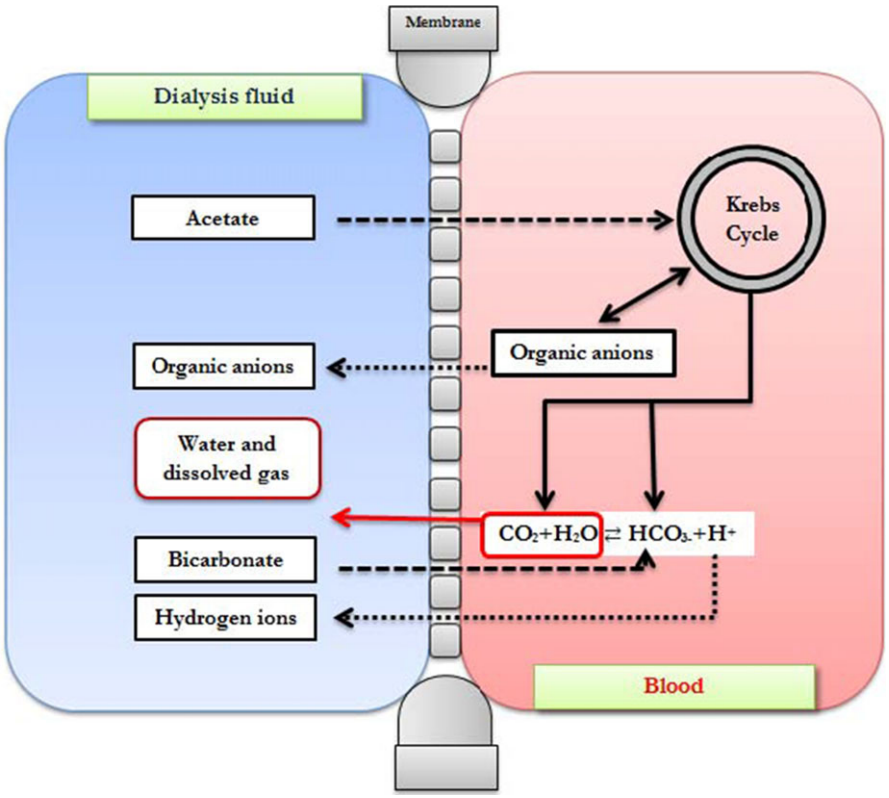

FIGURE 1 The events governing blood pH and serum BIC changes occurring during a dialysis session. A small acetate dialysis is also performed during BIC dialysis due to the 2-7 mEq/L acetate, citrate, and/or acetic acid usually present in BIC dialysis fluids. No ultrafiltration occurs in this simplified model [Color figure can be viewed at wileyonlinelibrary.com]

at ≥22 mEq/L.[17] Despite these changes, a substantial proportion of patients do not meet the KDOQI target. From 2001 to 2006 at one large dialysis provider, 40% of 110,951 patients undergoing HD had a time-averaged predialysis serum BIC <22 mEq/L.[18] Only 5% had serum BIC ≥27 mEq/L.[18]

In general, patients being dialyzed against a high D_{BIC} have higher predialysis serum BIC.[18-20] However, there are clearly other important determinants of predialysis serum BIC, namely:

1. *Acid generation rate*: differences in endogenous acid production, largely determined by dietary protein intake, account for some of the interindividual variability in serum BIC[13,14,21];
2. *Inter-dialysis weight gain*: it lowers serum BIC by expanding the bicarbonate space[13,22,23];
3. *Time since last dialysis* (ie, long vs short interval): serum BIC is approximately 1 mEq/L lower after the long interval than after the short interval[16,24];
4. *Phosphorus binder use*: sevelamer hydrochloride reduces serum BIC, whereas phosphate binders containing alkali precursors do the opposite[25,26];
5. *Postdialysis serum BIC*: the factors that determine the magnitude of the intra-dialytic increase in serum BIC are also determinants of the predialysis serum BIC, as they determine the starting point for the progressive decline in serum BIC that typically occurs between HD treatments.

The main determinants of postdialysis serum BIC are the following:

1. *High D_{BIC}*;
2. *Dialysate nonbicarbonate anion concentration* (eg, acetate, citrate, lactate);
3. *Determinants of dialysis adequacy* (eg, treatment time; blood flow rate, dialysate flow rate);
4. *Dialysance of bicarbonate and nonbicarbonate anions*;
5. *Ultrafiltration rate*;
6. *Organic anion generation during dialysis*;
7. *Predialysis serum BIC*.

Acid-base status and its association with mortality in patients on dialysis has been the subject of several epidemiological studies[6,14-16,18,27] (Table 1). In 1990, Lowrie and Lew reported in a retrospective analysis of more than 12,000 patients a U-shaped relationship between baseline serum BIC and all-cause-mortality, with a higher risk of death when serum BIC was <17.5 or was >25 mEq/L.[15] As documented by the DOPPS, there is a U-shaped relationship between cardiovascular mortality and predialysis serum BIC, with increased risk of death in patients with predialysis BIC less than or equal to 17 mEq/L and greater than 27 mEq/L.[16] It is important to emphasize that these values represent mid-week sampling, and the mid-week value is approximately 1 mEq/L higher than the value obtained after the long interval between treatments.[16] The lowest mortality risk in this cohort was in patients

TABLE 1 Summary of epidemiological studies evaluating the impact of acid-base status on mortality in HD patients

Study Authors (Ref.)	Study design—Countries—Number of patients	Effects on mortality	Main results
Lowrie et al[15]	Observational retrospective multicentric (United States; n = 12,099)	YES	U-shaped relationship between serum BIC and all-cause mortality, with a higher risk for serum BIC <17.5 mEq/L or >25 mEq/L
Bommer et al[16]	Observational prospective multicentric Database: DOPPS I[a] (n = 7,140)	YES	U-shaped relationship between serum BIC and mortality, with a higher risk for patients with predialysis serum BIC in a mid-week session <18 mEq/L or ≥27 mEq/L
Wu et al[14]	Observational retrospective multicentric Database: DaVita (United States; n = 56,385)	YES	15%-35% increase in mortality risk for patients with predialysis serum BIC <19 mEq/L
Vashistha et al[18]	Observational retrospective multicentric Database: DaVita (United States; n = 110,951)	YES	15%-35% increase in mortality risk for patients with predialysis serum BIC <22 mEq/L
Tentori et al[6]	Observational prospective multicentric Database: DOPPS II-III-IV[b] (n = 17,031)	YES	Positive association between D_{BIC} and mortality (9% higher mortality per each 4 mEq/L increase in D_{BIC})
Yamamoto et al[27]	Observational retrospective multicentric Database: Japanese Renal Data Registry (Japan; n = 15,132)	NOT	36% increase in mortality risk for patients with predialysis pH >7.40. No association between serum BIC before or after dialysis with mortality

[a]DOPPS I: France, Germany, Italy, Spain, Japan, UK, United States.
[b]DOPPS II-III-IV: Australia, Belgium, Canada, France, Germany, Italy, New Zealand, Spain, Sweden, UK, United States.

with a predialysis serum TCO_2 between 19 and 24 mEq/L (equivalent to 18-23 mEq/L of serum BIC after the long interval between treatments). A later article based on the DOPPS database in a larger group of patients also showed a significant (25%) increase in mortality risk when the serum TCO_2 was 17 mEq/L or lower.[6] Two other studies using the DaVita database have shown a significant increase in mortality risk for predialysis serum BICs less than 20 mEq/L in some populations and less than 22 mEq/L in others.[14,18]

In addition to D_{BIC}, other factors like protein intake, respiratory function and residual kidney function may have also an impact on postdialysis BICs. Nutritional status and inflammation have been known to confound the association between serum BICs and mortality. Wu et al[14] found that the lowest mortality occurred with predialysis serum BICs in the 17-23 mEq/L range. Better nutritional status was associated with mild predialysis acidosis in the 17-23 mEq/L range. After adjusting for variables of malnutrition-inflammation complex syndrome such as protein intake, serum albumin, blood urea nitrogen, and phosphorus, this association reversed so that serum BICs greater than 22 mEq/L produced lower death rates.[14]

Two recent studies deserve an in-depth analysis. The first study is an observational one including cross-sectional and 1-year analyses of data from the Japanese Society of Dialysis Therapy (2008-2009), which enrolled 15,132 dialysis patients 16 years or older.[26,27] Outcomes were all-cause and cardiovascular mortality during the 1-year follow-up. The major finding was that pH greater than or equal to 7.4 was the only predialysis value associated with significantly elevated risk of all-cause and cardiovascular mortality.[27] Neither very low nor very high serum BICs had an independent association with mortality, although high values (>26 mEq/L) almost reached statistical significance ($P = .07$).[27]

The second study is that of Tentori et al.[6] The authors, using DOPPS data, published an international prospective cohort study. It included 17,031 patients receiving thrice-weekly in-center HD from 11 DOPPS countries (2002-2011). It showed a positive association between D_{BIC} and mortality (9% higher mortality per each 4 mEq/L increase in D_{BIC}). The authors postulated that high D_{BIC} may contribute to rapid electrolyte shifts during the HD session and to the development of postdialysis metabolic alkalosis and thus contribute to adverse clinical outcomes.[6] This is the first study to report higher mortality in patients treated with higher D_{BIC}.[6] However, this study has some important weaknesses, as stressed by Basile and Lomonte.[28]

To summarize, very few studies have assessed so far mortality risk of patients treated with different D_{BIC}. A recent report concluded that there were insufficient data for a meta-analysis.[29]

4 | POTENTIAL ADVERSE EFFECTS ASSOCIATED WITH A HIGH D_{BIC}

The main potential adverse effects associated with a high D_{BIC} are the following:

1. *Excess generation of CO_2*, requiring an increase in ventilation to maintain acid-base balance.[30] The latter is hard to cope with in chronic respiratory failure patients;
2. *Electrolyte imbalances*. During the HD session, the rise in serum BICs cause a fall in ionized calcium (Ca^{2+}) concentration. This phenomenon is primarily caused by an alkalosis-induced change in electric charge of proteins, which increases the amount of complexed calcium. A correction of metabolic acidosis that is too rapid can then compromise cardiovascular reactivity because of decreased Ca^{2+} levels.[31] Furthermore, Fissell and Hakim underlined that dialysis treatment lowers plasma potassium (K^+), both by removal of K^+ with dialysate and by rapid shift of K^+ from the

extracellular to the intracellular space as metabolic acidosis is treated.[32] A randomized controlled trial showed an association between higher D_{BIC} and a faster decrease in intradialysis plasma K^+ concentration.[33] The true challenge in patients undergoing HD is to avoid both life-threatening predialysis hyperkalemia (plasma K^+ level >6 mmol/L) and postdialysis relative hypokalemia (or at least very rapid decrease in plasma K^+ level, and the related risk of lethal arrhythmias)[34];

3. *Arrhythmias and prolongation of the QT interval*. The QT interval is a recognized electrocardiographic marker of the ventricular repolarization and its prolongation has been associated with increased risk of sudden death in both pathological and healthy populations.[35] Electrolyte disorders are one of the main HD-related factors that can cause QT interval alterations and cardiac arrhythmias, because of their involvement in the genesis, duration, morphology and propagation of the cellular action potential. The electrolytes that mostly influence the ventricular repolarization are K^+ and Ca^{2+}.[35] A randomized controlled crossover trial found a prolongation of the QTc interval in association with a high D_{BIC}, low dialysate K^+ and low dialysate Ca^{2+}.[36] This association was an independent predictor of the QTc interval[36];
4. *Hemodynamic instability*. Gabutti et al found that a high D_{BIC} was associated with symptomatic hypotension, which may be mediated by hypocalcemia secondary to metabolic alkalosis or by rapid decrease in serum K^+ concentrations causing decrease in peripheral resistance.[37-39] Higher D_{BIC} has also been associated with lower cardiac performance at the end of HD session.[40] Other mechanisms described are reduced cerebral blood flow and respiratory suppression or calcium phosphate precipitation in vessels.[41]

5 | PRACTICAL RECOMMENDATIONS FOR THE DAILY PRACTICE

Metabolic alkalosis is as harmful as metabolic acidosis with both increasing the mortality risk.[14] A key question to be answered before embarking on manipulating D_{BIC} is whether the level (eg, metabolic acidosis or alkalosis) is in itself the cause of variations in morbidity and mortality or is simply a marker of other factors that are responsible for these outcomes.[7] For example, predialysis serum BICs correlated inversely with serum albumin, phosphorus, and protein nitrogen appearance, suggesting that high BICs may just be a marker for protein malnutrition, which in itself can increase mortality risk.[14,16] A key finding in the latter studies was that the "ideal" level for predialysis serum BICs is somewhere between 18 and 23 mEq/L.[14,16] Although this range of values likely represents the presence of metabolic acidosis, albeit mild, we must recall that the predialysis serum BIC is a nadir value and that it is higher at all other times.[7]

Improvement in this field requires that attention be focused on patients with:

1. *Very low predialysis serum BICs* (<18 mEq/L): measure blood pH and PCO_2 to characterize acid-base disorders; evaluate other factors related to metabolic acidosis (high protein intake, ketoacidosis, lactic acidosis, diarrhea, etc.) or compensatory state of respiratory alkalosis; assure that alkali delivery during dialysis is effective (measure postdialysis serum BICs). If serum BICs increase normally during HD, the patient's diet and fluid intake should be assessed, as excessive protein ingestion and/or fluid retention could result in a low predialysis serum BIC. If predialysis serum BIC remains low after attempting to address these issues, D_{BIC} should be increased sufficiently to achieve a predialysis serum BIC of 20 mEq/L or higher on a consistent basis.[7] If they have a mixed respiratory alkalosis and metabolic acidosis, then increasing their serum BIC is not likely to be beneficial[3]; If they have a mixed respiratory and metabolic acidosis, the indication to increase their serum BIC may be more urgent.[3]
2. *Very high predialysis serum BICs* (>27 mEq/L): measure blood pH and PCO_2 to characterize acid-base disorders; malnutrition with poor dietary protein intake is one of the causes of predialysis metabolic alkalosis; check other factors related to metabolic alkalosis or compensatory state of respiratory acidosis (in the latter case, attention should be focused on the patient's pulmonary problem); decrease D_{BIC} according to acid-base state and correct the cause of metabolic alkalosis or compensatory state of respiratory acidosis.
3. *High postdialysis serum BICs* (>28 mEq/L): measure blood pH and PCO_2 to characterize acid-base disorders; check factors related to metabolic alkalosis or compensatory state of respiratory acidosis; in metabolic alkalosis, reduce alkali administration by individualizing D_{BIC}; in compensatory state of respiratory acidosis, carefully adjust D_{BIC} according to blood pH.

As a final comment, it must be said that most of the published information about acid-base status has been limited to measurements of serum TCO_2. Respiratory acid-base disorders are important components of the acid-base abnormalities of dialysis patients and are not identified by measuring serum TCO_2. The latter do not provide any insight into systemic pH nor into the ventilatory response to the prevailing systemic pH. Blood pH is directly and predictably related to systemic and cell pH, and the latter is critical for enzyme function and cell metabolism.[24] A recent study has provided evidence that blood pH may be the key for assessing mortality risk in dialysis patients.[27]

6 | CONCLUSIONS

Acid-base equilibrium is a complex and vital system whose regulation is impaired in CKD. Unfortunately, no randomized studies exist about the effect of different D_{BIC} on hard outcomes, such as mortality. We await further studies in order to assess the extent to which it is a major determinant of overall survival. Like everything else in dialysis, the quest for the "ideal" D_{BIC} is far from over. The Latin

aphorism "*ne quid nimis*" ie, "nothing in excess" (excess of neither acid nor base) probably best summarizes our current state of knowledge in this field.[42] For the present, the clinician should understand that target values for predialysis serum BIC have been established primarily based on observational studies and expert opinion. Based on this information, we should keep predialysis serum BIC at least at 22 mEq/L. Furthermore, a specific focus should be addressed by attending nephrologists to the clinical and nutritional status of the major outliers on both acid and alkaline sides of the curve.

CONFLICT OF INTERESTS

The authors have no interest to disclose.

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How to cite this article: Basile C, Rossi L, Lomonte C. Dialysate bicarbonate concentration: Too much of a good thing? *Semin Dial*. 2018;31:576–582. https://doi.org/10.1111/sdi.12716