The choice of dialysate bicarbonate: do different concentrations make a difference?

Carlo Basile[1], Luigi Rossi[1] and Carlo Lomonte[1]

[1]Division of Nephrology, Miulli General Hospital, Acquaviva delle Fonti, Italy

Metabolic acidosis is a common complication of chronic kidney disease; it is typically caused by the accumulation of sulfate, phosphorus, and organic anions. Metabolic acidosis is correlated with several adverse outcomes, such as morbidity, hospitalization, and mortality. Thus, correction of metabolic acidosis is fundamental for the adequate management of many systemic complications of chronic kidney disease. In patients undergoing hemodialysis, acid-base homeostasis depends on many factors including the following: net acid production, amount of alkali given by the dialysate bath, duration of the interdialytic period, and residual diuresis, if any. Recent literature data suggest that the development of metabolic alkalosis after dialysis may contribute to adverse clinical outcomes. Our review is focused on the potential effects of different dialysate bicarbonate concentrations on hard outcomes such as mortality. Unfortunately, no randomized studies exist about this issue. Acid-base equilibrium is a complex and vital system whose regulation is impaired in chronic kidney disease. We await further studies to assess the extent to which acid-base status is a major determinant of overall survival in patients undergoing hemodialysis. For the present, the clinician should understand that target values for predialysis serum bicarbonate concentration have been established primarily based on observational studies and expert opinion. Based on this, we should keep the predialysis serum bicarbonate level at least at 22 mmol/l. Furthermore, a specific focus should be addressed by the attending nephrologist to the clinical and nutritional status of the major outliers on both the acid and alkaline sides of the curve.

Kidney International (2016) **89,** 1008–1015; http://dx.doi.org/10.1016/j.kint.2016.01.010

KEYWORDS: dialysate bicarbonate; hemodialysis; metabolic acidosis; metabolic alkalosis

Correspondence: *Carlo Basile, Division of Nephrology, Miulli General Hospital, Strada Provinciale per Santeramo km 4.1, 70021 Acquaviva delle Fonti, Italy. E-mail: basile.miulli@libero.it*

Received 11 November 2015; revised 7 January 2016; accepted 13 January 2016; published online 26 February 2016

Metabolic acidosis is present in the majority of patients with chronic kidney disease (CKD) when the glomerular filtration rate decreases to less than 20% to 25% of normal, although as many as 20% of individuals can have acid-base parameters close to or within the normal range. Acidosis generally is mild to moderate in degree, with plasma bicarbonate (BIC) concentrations ranging from 12 to 22 mmol/l, and it is rare to see values less than 12 mmol/l in the absence of an increased acid load. The degree of acidosis approximately correlates with the severity of renal failure and usually is more severe at a lower glomerular filtration rate. The metabolic acidosis can be of the high anion gap variety, although the anion gap can be normal or only moderately increased even with stage 4 to 5 CKD. Several adverse consequences have been associated with metabolic acidosis, including muscle wasting, bone disease, impaired growth, abnormalities in growth hormone and thyroid hormone secretion, impaired insulin sensitivity, progression of renal failure, and exacerbation of β_2-microglobulin accumulation.[1] Metabolic acidosis results from the imbalance between the whole-body net production of acid and acid removal by the kidney.[2] Endogenous acid production depends primarily on diet. It has the most important effect in the development of acidosis: animal proteins contain greater amounts of sulfate and phosphorus than do vegetable proteins, which conversely increase alkali production. Metabolic acidosis in severe CKD is typically caused by the accumulation of sulfate, phosphorus, and organic anions; thus, normochloremic acidosis with a high anion gap is a common picture in advanced CKD.[1]

Acid-base balance in patients undergoing hemodialysis

Hemodialysis (HD) has historically used acetate buffer in dialysate. High concentrations, up to 40 mmol/l, result in BIC generation after liver metabolization. Nonetheless, at such concentrations, acetate is a potent vasodilator and myocardial depressor and can cause intradialytic hypotension. Acetate has been replaced over time by BIC. Many centers use BIC concentrations in the dialysate (D_{BIC}) on the order of 32 to 39 mmol/l. Such levels are often obtained with a 3-stream method using a proportioning dual-concentrate system that mixes water with a "base concentrate" containing liquid or powder sodium and an "acid concentrate" in either a liquid or solid form and containing sodium chloride, calcium chloride, magnesium chloride, potassium chloride, glucose monohydrate, and an organic acid. The latter is necessary because the mix of BIC and calcium requires a small amount of acid

to avoid insoluble precipitation of calcium carbonate. The organic acid can be in the form of glacial acetic acid, sodium diacetate, lactic acid, or citric acid.[3] Sodium diacetate is composed of approximately 50% acetic acid and 50% sodium acetate. Should one choose to use sodium diacetate as the organic acid and to aim for the presence of 4 mmol/l of acetic acid in the final dialysate, one needs to provide 4 mmol/l of sodium diacetate (containing 4 mmol/l of acetic acid and 4 mmol/l of sodium acetate) to the final dialysate by way of the acid concentrate. The acetate in the sodium acetate will increase the total amount of buffer base (the sum of BIC and BIC precursors [acetate in this case]) in the final dialysate. When using sodium diacetate, the additional source of buffer base should be kept in mind.[3] It should also be kept in mind that a potential risk of hypervolemia and hypertension may exist because of the increased total amount of sodium in the final dialysate. Even these small amounts of acetate in the dialysate have been shown to cause hemodynamic instability.[4] Finally, a recent registry-based study has shown an improved survival associated with acetate-free HD in patients aged 70 years and older.[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.

New BICs are primarily added directly from the bath, although a small amount is also generated from the addition and metabolism of acetate, citrate, or acetic acid (or a combination) (Figure 1). With D_{BIC} set at 35 mmol/l, average predialysis serum BIC at the beginning of the week ranges from 20 to 24 mmol/l; individual values, however, range from less than 17 mmol/l to more than 27 mmol/l.[6] Serum BICs normally increase rapidly during the first 2 hours of treatment and then level off, ending the treatment at a level about 4 to 7 mmol less than D_{BIC}.[7] The reason postdialysis serum BIC does not approach D_{BIC} likely results from stimulation of organic acid production by the added BIC, an event that consumes this alkali and minimizes further increases in serum BIC. The amount of organic acid produced is difficult to quantitate and may vary considerably from patient to patient.[6] In patients undergoing HD, acid-base homeostasis depends on many factors: net acid production, amount of alkali given by the dialysate bath, duration of the 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[8]:

$$\text{BICs added} = \text{dialysance} \times \int_{o}^{t} (D_{BIC} - \text{blood [BIC]})$$

where dialysance is a measure of the rate of movement of BIC across the dialysis membrane, expressed in ml/min, and is dependent on the surface area and permeability of the membrane used as well as on blood and dialysate flow rates[8] (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.[9] 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.[10] These data confirm the *in vitro* data obtained by the same group.[11] Thus, BIC dialysance behaves very differently from urea clearance, even though both solutes have a similar molecular weight.[10,11] Because predialysis serum BICs are a function of endogenous acid production in the interdialysis period, alkali addition is by definition equal to endogenous acid production. Because the membrane characteristics, dialysis duration, and bath solution are all

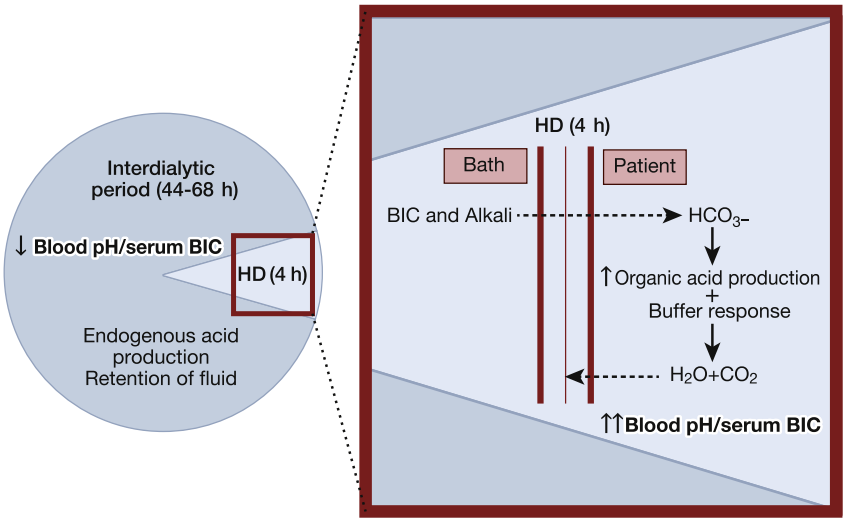

Figure 1 | The events governing blood pH and serum bicarbonate (BIC) changes occurring during an entire cycle (intra- and interdialysis periods). No ultrafiltration occurs in this simplified model. HD, hemodialysis.

fixed for any given patient, the only factor that varies is the transmembrane concentration gradient. As a result, the key variable for the process of alkali exchange is the serum BIC. Net alkali addition during dialysis is inversely related to serum BICs, creating a new artificial equilibrium in which bath alkali concentration and serum BICs interact to "regulate" body alkali stores.[8] The great problem when dealing with BIC kinetics is to calculate the apparent BIC space and BIC mass (apparent BIC space × plasma concentration) at the beginning and end of the dialysis session. BIC equilibrates easily between the extracellular fluid compartments. A Gibbs-Donnan effect forces some of it out of the intravascular compartment (thus having, e.g., 24 mmol/l of BIC in the intravascular fluid and 28 mmol/l of BIC in the interstitial fluid, in which no negatively charged proteins are present). BIC is easily converted by carbonic anhydrase to CO_2, which is highly lipid soluble and thus diffuses effortlessly in and out of cells. BIC itself finds it difficult to traverse the cell membrane, which is essentially impermeable to it (thus, BIC intracellular concentration is about 10 mmol/l).[12] It is known that pH may influence the apparent BIC space.[13] In an experimental study, the calculated mean apparent BIC space was equivalent to 88% of body weight in acidotic dogs, as opposed to 50% and 44% in normal and alkalotic dogs, respectively.[14] These data show an inverse correlation between initial plasma BICs and the apparent space of distribution.[14] There is also a positive relationship between the interdialytic water gain and the apparent BIC space.[15] It is known that patients with a high interdialytic weight gain may require higher D_{BIC} to achieve normal acid-base status, whereas patients with lower interdialytic weight gains may require lower D_{BIC} to prevent alkalemia at the end of dialysis.[16] Finally, the continuous decay of dialysance should also be taken into account.[10,11] New computational studies are needed to help us to know the optimal D_{BIC}.[17]

The artificial homeostasis achieved by HD treatment, however, is much coarser than the balance achieved by our kidneys. As a result, serum BICs show a much greater intraindividual and interindividual variability in patients undergoing HD than in individuals with normal renal function.[8] In the interval between treatments, serum BIC gradually decreases because of both the production of endogenous acids and the retention of fluid.[18] Fluid retention without added alkali dilutes the existing alkali and thereby reduces serum BIC (Figure 1).[18] Patients undergoing HD consume their body alkali stores, just as do individuals with normal renal function, 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.[18] There is an inverse relationship between serum BICs and normalized protein catabolic rate, suggesting that more acidotic patients have a greater protein intake.[19] In contrast to individuals with normal renal function, however, no homeostatic feedback loop exists to link acid production to acid excretion, thereby maintaining acid-base equilibrium.[8] 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 intradialytic alkalosis. Recently, Tovbin and Sherman[20] suggested that a decreasing D_{BIC} from an initially high concentration be considered as a means of correcting acidosis with a limited intradialytic alkalosis. Some evidence, as well as theoretical considerations, supports such an approach.

Risk of death and D_{BIC}

The lower limit of the ideal predialysis serum BICs changes among different studies. As documented by the Dialysis Outcomes and Practice Patterns Study (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 mmol/l and greater than 27 mmol/l.[21] Two other studies using DaVita data have shown a significant increase in mortality risk for predialysis serum BICs less than 20 mmol/l in some populations and less than 22 mmol/l in others.[19,22] Furthermore, 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.*[19] found that the lowest mortality occurred with predialysis serum BICs in the 17 to 23 mmol/l range. Better nutritional status was associated with mild predialysis acidosis in the 17 to 23 mmol/l range. After adjusting for variables of the 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 mmol/l produced lower death rates.[19] Thus, in routine clinical practice, maintaining predialysis serum BICs at less than 22 mmol/l without consideration of nutritional status may contribute to adverse cardiovascular outcomes because a low serum BIC may reflect higher protein intake and prolong survival.

Short-term studies in which predialysis total CO_2 level was increased by increasing D_{BIC} demonstrated that this maneuver decreased muscle catabolism and improved bone responsiveness to parathyroid hormone.[23,24] These studies led to National Kidney Foundation Kidney Disease Outcomes Quality Initiative nutrition and bone disease guidelines[25,26] as well as to European guidelines[27] recommending that treatment prescriptions be adjusted to achieve a predialysis BIC greater than or equal to 22 mmol/l in all patients receiving intermittent HD. By 2013, dialysis programs in the United States had worked to achieve this goal by increasing D_{BIC} to greater than or equal to 38 mmol/l in almost 50% of treatments.[28] The prescribed concentration of HD buffers progressively increased over time among Fresenius Medical Care North America facilities. On 4 November 2011,

Fresenius Medical Care North America sent an internal memo to Fresenius Medical Care dialysis units in the United States, including 4 statements: (i) the total buffer that patients receive could be underestimated, (ii) the predialysis serum BICs increased over time (22.9 versus 24.1 mmol/l comparing 2004 to 2011, with 25% ≥26.0, 15% ≥28.0, and 3% ≥30.0 mmol/l), (iii) an internal case-control study evaluated risk factors in patients undergoing HD with cardiopulmonary arrest (941 patients from 667 facilities) compared with other patients undergoing HD (80,516) in the same facilities between 1 January and 31 December 2010. Logistic regression analysis indicated an unadjusted odds ratio for cardiopulmonary arrest of 6.3 with predialysis serum BICs ≥ 28.0 mmol/l; and (iv) reducing D_{BIC} in patients with predialysis serum BICs > 24 mmol/l was recommended.[29] In 2012, the Food and Drug Administration issued a safety communication notifying health care providers to consider the presence and quantity of acetate, citrate, or acetic acid (or a combination) in dialysate concentrates (these substances typically are found in acid concentrate in amounts ranging from 1.5 to 8 mmol/l) when determining patients' dialysate prescription. When metabolized, these potential sources of alkali can contribute to elevated serum BIC in patients undergoing HD and then to metabolic alkalosis, which is a significant risk factor associated with cardiopulmonary arrest, low blood pressure, hypokalemia, hypoxemia, hypercapnia, and cardiac arrhythmias.[30] Studies have examined peridialytic sudden cardiac death risk factors, but only 1 study considered the association of cardiopulmonary arrest (fatal and nonfatal events including cardiac and respiratory causes). It found that lower albumin and hemoglobin levels and body mass index, a higher erythropoietin-stimulating–agent dose, and more missed sessions had the strongest associations with outcome.[31]

Two recent studies deserve an in-depth analysis. The first is that of Tentori *et al.*[28] 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 mmol/l increase in D_{BIC}). The association was stronger in patients with longer dialysis vintage.[28] 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. This is the first study to report higher mortality in patients treated with higher D_{BIC}.[28] However, this study has some important weaknesses[32]: (i) the correlations should have been calculated using total base and not only BICs, (ii) postdialysis serum BICs were not available, and (iii) DOPPS data from Japan were not included in the analysis because there was minimal overlap of Japanese D_{BIC} distribution with worldwide data (83% of Japanese D_{BIC} was ≤30 mmol/l compared with only 3% in other DOPPS countries).[28] Is the potential reduction in the risk of postdialysis alkalosis caused by the reduction in D_{BIC} 1 of the causes of the higher life expectancy reported in Japanese patients undergoing HD compared with other countries?[32] By extending this concept, the following question can be raised: is the difference in the usual D_{BIC} in the United States (38 mmol/l, with 5–7 mmol/l of acetate), Japan (lowest D_{BIC} and lowest mortality), and Europe (~34 mmol/l) a potential explanation of the statistically significant difference in this patient population intermediate mortality?

The second 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 patients 16 years or older who were undergoing dialysis.[33] 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 a significantly elevated risk of all-cause and cardiovascular mortality.[33] Neither very low nor very high serum BICs had an independent association with mortality, although high values (>26 mmol/l) almost reached significance ($P = 0.07$).[33] The study by Yamamoto *et al.*[33] adds a new level of information to our current understanding of the relationship between acid-base status and survival while also raising new questions about what our goal should be. Should we take monthly measurements of pH and P_{CO_2} in our patients to more reliably assess acid-base status? This is an expensive and labor-intensive step, and more studies are needed to determine whether it is cost-effective. Should we make any change in managing patients undergoing HD based on this new information?[34] Actually, few studies have so far assessed mortality risk in patients treated with different D_{BIC}s. A recent report concluded that there were insufficient data for a meta-analysis.[35]

Risk factors

The main risk factors associated with a high predialysis blood pH/serum BIC leading to an increased risk of death in patients undergoing HD are summarized in Table 1. A unifying pathophysiological hypothesis outlining their strict interplay is being formulated (Figure 2).

Respiratory changes. At a D_{BIC} of 35 mmol/l, the rapid intradialytic transfer of BICs from the dialysate to the patient generates excess CO_2 and requires an increase in ventilation to maintain acid-base balance.[36] In patients with chronic obstructive pulmonary disease undergoing HD with a D_{BIC} of

Table 1 | Main risk factors associated with high predialysis blood pH/serum bicarbonate leading to an increased risk of death in patients undergoing hemodialysis

Hypercapnia
Ionized hypocalcemia
Hypokalemia
Arrhythmias and prolongation of the QTc interval
Hemodynamic instability
Calcium phosphate precipitation
Infection risk

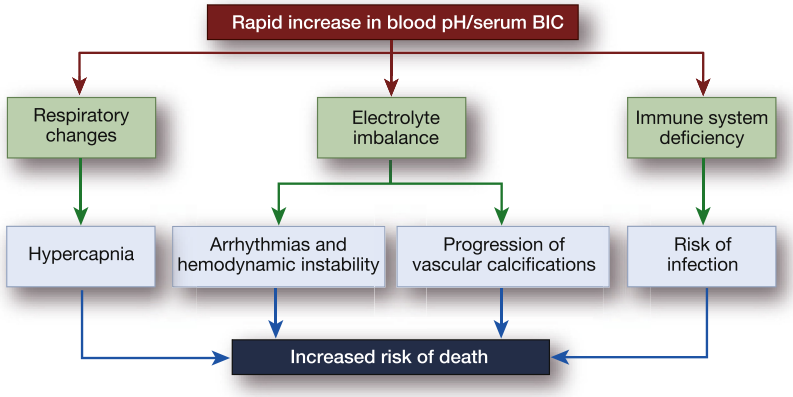

Figure 2 | The strict interplay of the main risk factors associated with a high predialysis blood pH/serum bicarbonate (BIC) leading to an increased risk of death in patients undergoing hemodialysis.

37 mmol/l, the increase in arterial P_{CO_2} was greater than in control participants, although both experienced a rise in P_{CO_2}.[37]

Electrolyte imbalances. In HD therapy, the rise in serum BICs causes a fall in ionized calcium (Ca^{2+}) concentration. This phenomenon is primarily caused by an alkalosis-induced change in the electric charge of proteins, which increases the amount of complexed calcium. A correction of metabolic acidosis that is too rapid can then compromise vascular and cardiac contraction because of a decreased amount in Ca^{2+}.[38]

Fissell and Hakim[39] underlined that dialysis treatment lowers plasma potassium (K^+), both by removal of K^+ with dialysate and by a rapid shift of K^+ from the extracellular to the intracellular space as metabolic acidosis is treated. Unlike the extracellular K^+, which can pass freely across the dialysis membrane, the intracellular K^+ is slow to move into the extracellular space. Alkalosis causes a shift of K^+ into cells, and acidosis results in a K^+ efflux from cells. Introduction of buffer base into blood during dialysis promotes cellular uptake of K^+ and thereby attenuates the dialytic removal of K^+ (this is more evident in an acidotic patient). There are case reports describing that dialysis succeeded in reducing plasma K^+ concentrations even though the dialysate K^+ levels were higher than the predialysis plasma K^+ values. The decline in plasma K^+ concentration was associated with a corresponding dialysis-induced rise in blood pH.[40,41] A randomized controlled trial showed an association between higher D_{BIC} and a faster decrease in intradialytic plasma K^+ concentration. Three different D_{BICs} were used, 27, 35, and 39 mmol/l with the same dialysate K^+ (2.0 mmol/l).[42] The pre- and postdialysis serum K^+ were 5.40 ± 0.26 mmol/l and 4.24 ± 0.15 mmol/l, respectively, with a D_{BIC} of 27 mmol/l; 5.38 ± 0.21 mmol/l and 3.80 ± 0.19 mmol/l respectively, with a D_{BIC} of 35 mmol/l; 5.45 ± 0.25 mmol/l and 3.34 ± 0.11 mmol/l respectively, with a D_{BIC} of 39 mmol/l.[42] 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 a very rapid decrease of plasma K^+ level, and the related risk of lethal arrhythmias).[43]

Arrhythmias and prolongation of the QTc interval. Cardiovascular diseases account for 38% to 40% of all deaths in patients undergoing dialysis, with a large proportion (about 25%) attributed to sudden cardiac death.[44–47] The QT interval is a recognized electrocardiographic marker of the ventricular repolarization, and its prolongation has been associated with an increased risk of sudden death in both pathologic and healthy populations.[48] Electrolyte disorders are 1 of the main HD-related factors that can cause QT-interval alterations and cardiac arrhythmias because of their involvement in the genesis, duration, morphologic characteristics, and propagation of the cellular action potential. The electrolytes that mostly influence the ventricular repolarization are K^+ and Ca^{2+}.[48] 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+}.[49] This association (high D_{BIC}, low dialysate K^+, and low dialysate Ca^{2+}) was an independent predictor of the QTc interval. Prolongation of the QTc interval persisted a long time after the end of the dialysis session.

Hemodynamic instability. Intradialysis or immediate postdialysis hemodynamic instability is a complex situation resulting from the following multiple mechanisms: cardiac arrhythmias, reduced contraction of cardiac muscle, imbalance of blood pressure regulation, and reduced cerebral perfusion.[50–54] Gabutti *et al.*[50–52] found that a high D_{BIC} was associated with symptomatic hypotension, which may be mediated by hypocalcemia secondary to metabolic alkalosis or by a rapid decrease in serum K^+ concentrations causing decrease in peripheral resistance. Higher D_{BIC} has also been associated with lower cardiac performance at the end of the HD session.[53] Other mechanisms described are reduced cerebral blood flow and respiratory suppression or calcium phosphate precipitation in vessels.[54] In a randomized controlled trial with a single blind crossover design, Gabutti *et al.*[50–52] demonstrated that when dialyzing with D_{BIC} of

32 mmol/l, compared with a D_{BIC} of 26 mmol/l, the following occurs: (i) the nadir of systolic blood pressure, the mean systolic blood pressure, and the mean diastolic blood pressure were significantly lower; (ii) the incidence of symptomatic or silent hypotensive episodes was significantly higher; and (iii) the need to use extra isotonic saline or hypertonic glucose infusions, or both, was significantly greater.[50] Similar results were obtained comparing a D_{BIC} of 40 mmol/l with a D_{BIC} of 30 mmol/l.[55]

Calcium phosphate precipitation. Cardiovascular disease is the leading cause of morbidity, hospitalization, and mortality in both patients with CKD and those undergoing dialysis.[56] The high incidence of cardiovascular disease in patients with CKD is caused primarily by both intimal and medial arterial calcifications that provoke atherosclerosis and increased arterial stiffness, respectively, with subsequent higher pulse pressure and decreased myocardial perfusion during diastole.[57] Patients undergoing dialysis have a higher risk of coronary artery calcification than do age-matched patients not undergoing dialysis.[58] Vascular calcification, caused by the deposition of calcium salt crystals (predominantly calcium phosphate, i.e., hydroxyapatite) in the arterial wall is extremely common among patients with CKD and shows a marked tendency to progress among patients undergoing HD, in whom survival is inversely related to the extent of vascular calcification. The degree of arterial calcification has been positively correlated with older age, male sex, white race, diabetes, daily doses of calcium-containing phosphate binders, duration of hypertension, and longer periods of dialysis, but these risk factors only partially explain the appearance and progression of vascular calcification.[59] Patients undergoing HD have periodic BIC loading during the procedure. The potential effect of this lifelong high-dose BIC supplementation on vascular calcification has barely been examined. Some authors have proposed intradialysis profiling of D_{BIC} with lower BICs at the beginning of the dialysis session and later with an increasing level to reduce intracellular alkali-induced shift of phosphate and at the same time correct acidosis.[60] Subsequent studies have shown no benefits from this approach.[54] It has long been known that sodium BIC and calcium mixed together in the same solution may form an insoluble precipitate, calcium carbonate, although the mechanism of precipitation is poorly understood. Calcium carbonate deposits are only 10% of bone tissue, but they play an essential role in the formation of hydroxyapatite by acting as a calcium core that precedes calcium phosphate precipitation. Calcium carbonate has been observed to precipitate in the fluid pathway of dialysate delivery systems, partially occluding the fluid pathway and leading to system malfunction.[61]

Immune system deficiency. Recently, Tentori *et al.*[28] showed a positive association between D_{BIC} and mortality. The latter was related mainly to the occurrence of infections (primarily sepsis and pneumonia). Extracellular acidosis has been reported to improve dendritic cell antigen-presenting capacity.[62] One could speculate that this mechanism may be impaired in the setting of metabolic alkalosis, hence providing a potential mechanism contributing to the association between D_{BIC} and infections. Furthermore, it is well known that neutrophil-endothelial cell adhesion and adhesion molecule expression are pH dependent.[63]

Practical recommendations for daily practice

Recently, Kraut and Nagami[2] summarized recommendations for the use and interpretation of serum BIC in the patient undergoing dialysis. Here we list some of them: (i) collect blood for measurement at the same time relative to the dialysis procedure (usually immediately before dialysis for the midweek treatment), (ii) obtain postdialysis values in patients with a high predialysis serum BIC who might be at risk for the development of alkalemia after dialysis, and (iii) measure value within a short time after sampling (<90 minutes when possible; if specimens are sent to a distant central laboratory, keep the tube containing the specimen tightly capped after collection), and (iv) know the variability in results for a given clinical laboratory.[2]

Metabolic alkalosis is as harmful as metabolic acidosis. In fact, both increase the mortality risk.[19] A key question to be answered before embarking on manipulating D_{BIC} is whether the level (e.g., 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.[6] 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.[19,21] A key finding in the latter studies was that the "ideal" level for predialysis serum BICs is somewhere between 18 and 23 mmol/l.[19,21] 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.[6] Improvement requires that attention be focused on patients with very low predialysis serum BICs (<18 mmol/l) and very high predialysis serum BICs (>27 mmol/l). For patients with low values, ensure 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, because excessive protein ingestion or fluid retention, or both, 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 mmol/l or higher on a consistent basis.[6] For patients with high values, it seems unlikely, based on data from Wu *et al.*,[19] that reducing D_{BIC} will provide any benefit. The only management strategy we have is to try to correct nutritional deficiencies and look for reversible comorbidities.[6]

CONCLUSIONS

Dialysate composition is 1 of the most fascinating topics in nephrology, in which the possibilities for improvements are

plentiful.[3] Learning about the art and science of fashioning hemodialysates (manipulation of dialysate sodium, K^+, Ca^{2+}, BIC, and magnesium) is 1 of the best ways to further the understanding of the pathophysiological processes underlying myriad acid-base, fluid, electrolyte, and blood pressure abnormalities.[64] Dialysate composition should be treated like other interventional drug or device and therefore studied in well-conducted trials to determine efficacy and safety. Acid-base equilibrium is a complex and vital system whose regulation is impaired in CKD. Unfortunately, no randomized studies exist regarding the effect of different D_{BICs} on hard outcomes, such as mortality. We await further studies to assess the extent to which it is a major determinant of overall survival. For the present, the clinician should understand that target values for predialysis serum bicarbonate concentration have been established primarily based on observational studies and expert opinion. Based on this information, we should keep the predialysis serum bicarbonate level at least at 22 mmol/l. Furthermore, a specific focus should be addressed by the attending nephrologist to the clinical and nutritional status of the major outliers on both the acid and alkaline sides of the curve.

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis*. 2005;45:978–983.
2. Kraut JA, Nagami GT. The use and interpretation of serum bicarbonate concentration in dialysis patients. *Semin Dial*. 2014;27:577–579.
3. Sam R, Vaseemuddin M, Leong WH, et al. Composition and clinical use of hemodialysates. *Hemodial Int*. 2006;10:15–28.
4. Bolasco P, Panichi V, Paletti S, et al. Will there be acetate in the dialysate of the future? *G Ital Nefrol*. 2011;28:359–368.
5. Mercadal L, Franck J–V, Metzger M, et al. Improved survival associated with acetate-free haemodialysis in elderly: a registry-based study. *Nephrol Dial Transplant*. 2015;30:1560–1568.
6. Gennari FJ. Very low and high predialysis serum bicarbonate levels are risk factors for mortality: what are the appropriate interventions? *Semin Dial*. 2010;23:253–257.
7. Basile C, Libutti P, Di Turo L, et al. Effect of dialysate calcium concentration on parathyroid hormone and calcium balance during a single dialysis session using bicarbonate hemodialysis: a crossover clinical trial. *Am J Kidney Dis*. 2012;59:92–101.
8. Gennari FJ. Acid-base balance in dialysis patients. *Semin Dial*. 2000;13:235–239.
9. Sargent JA, Gotch FA. Bicarbonate and carbon dioxide transport during hemodialysis. *ASAIO J*. 1979;2:61–72.
10. Morel H, Jaffrin MY, Lux C, et al. A comparison of bicarbonate kinetics and acid-base status in high flux hemodialysis and on-line post-dilution hemodiafiltration. *Int J Artif Organs*. 2012;35:288–300.
11. Morel H, Jaffrin MY, Paullier P, et al. *In vitro* tests and modelization of bicarbonate kinetics and mass transfers during online hemodiafiltration. *Int J Artif Organs*. 2009;32:482–491.
12. Sherwood L, ed. *Human Physiology: from Cells to Systems*. Boston, MA: Cengage Learning; 2015.
13. Fernandez PC, Cohen RM, Feldman GM. The concept of bicarbonate distribution space: the crucial role of body buffers. *Kidney Int*. 1989;36:747–752.
14. Garella S, Dana CL, Chazan JA. Severity of metabolic acidosis as a determinant of bicarbonate requirements. *N Engl J Med*. 1973;289:121–126.
15. Tzanatos H, Dalamangas A, Retsa K, et al. Relation of interdialytic water retention with apparent bicarbonate space, $HCO3^-$, and pH in hemodialyzed uremic patients. *Renal Fail*. 2005;27:235–238.
16. Agroyannis B, Fourtounas C, Tzanatos H, et al. Relationship between interdialytic weight gain and acid-base status in hemodialysis by bicarbonate. *Artif Organs*. 2002;26:385–387.
17. Annan K. Finite volume scheme for double convection-diffusion exchange of solutes in bicarbonate high-flux hollow-fiber dialyzer therapy. *Comput Math Methods Med*. 2012;973424.
18. Gennari FJ. Acid-base homeostasis in end-stage-renal disease. *Semin Dial*. 1996;9:404–411.
19. Wu DY, Shinaberger CS, Regidor DL, et al. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Clin J Am Soc Nephrol*. 2006;1:70–78.
20. Tovbin D, Sherman RA. Correcting acidosis during hemodialysis: current limitations and a potential solution. *Semin Dial*. 2016;29:35–38.
21. Bommer J, Locatelli F, Satayathum S, et al. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2004;44:661–671.
22. Vashistha T, Kalantar-Zadeh K, Molnar MZ, et al. Dialysis modality and correction of uremic metabolic acidosis: relationship with all-cause and cause-specific mortality. *Clin J Am Soc Nephrol*. 2013;8:254–264.
23. Graham KA, Reiach D, Channon SM, et al. Correction of acidosis in hemodialysis decreases whole–body protein degradation. *J Am Soc Nephrol*. 1997;8:632–637.
24. Graham KA, Hoenich NA, Tarbit M, et al. Correction of acidosis in hemodialysis increases the sensitivity of the parathyroid glands to calcium. *J Am Soc Nephrol*. 1997;8:627–631.
25. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis*. 2000;35(suppl 2):S1–S140.
26. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis*. 2003;42(suppl 3):S1–S202.
27. Locatelli F, Fouque D, Heimburger O, et al. Nutritional status in dialysis patients: a European consensus. *Nephrol Dial Transplant*. 2002;17:563–572.
28. Tentori F, Karaboyas A, Robinson B, et al. Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2013;62:738–746.
29. Fresenius Medical Care North America Medical Office. Dialysate bicarbonate. Available at: http://www.renalweb.com/writings/alkalosis/WithinFMC.htm. Accessed May 23, 2012.
30. FDA Safety Communication: Dialysate concentrates and alkali dosing errors with hemodialysis. US Food and Drug Administration. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm305477.htm. Accessed August 16, 2012.
31. Flythe JE, Li N-C, Lin S-F, et al. Associates of cardiopulmonary arrest in the perihemodialytic period. *Int J Nephrol*. 2014;2014:961–978.
32. Basile C, Lomonte C. Dialysis: a step towards optimal dialysate bicarbonate concentration. *Nat Rev Nephrol*. 2013;9:565–566.
33. Yamamoto T, Shoji S, Yamakawa T, et al. Predialysis and postdialysis pH and bicarbonate and risk of all-cause and cardiovascular mortality in long-term hemodialysis patients. *Am J Kidney Dis*. 2015;66:469–478.
34. Gennari FJ. Acid-base status and mortality risk in hemodialysis patients. *Am J Kidney Dis*. 2015;66:383–385.
35. Roderick P, Willis NS, Blakeley S, et al. Correction of chronic metabolic acidosis for chronic kidney disease patients. *Cochrane Database Syst Rev*. 2007;1:CD001890.
36. Sombolos KI, Bamichas GI, Christidou FN, et al. pO_2 and pCO_2 increment in post–dialyzer blood: the role of dialysate. *Artif Organs*. 2005;29:892–898.
37. Alfakir M, Moammar MQ, Ali MI, et al. Pulmonary gas exchange during hemodialysis: a comparison of subjects with and without COPD on bicarbonate hemodialysis. *Ann Clin Lab Sci*. 2011;41:315–320.
38. van Kuijk WH, Mulder AW, Peels CH, et al. Influence of changes in ionized calcium on cardiovascular reactivity during hemodialysis. *Clin Nephrol*. 1997;47:190–196.
39. Fissell R, Hakim RM. Improving outcomes by changing hemodialysis practice patterns. *Curr Opin Nephrol Hypertens*. 2013;22:675–680.
40. Weigand C, Davin T, Raij L, et al. Life-threatening hypokalemia during hemodialysis. *Trans Am Soc Artif Intern Organs*. 1975;25:416–418.

41. Ward RA, Wathen RL, Williams TE, et al. Hemodialysate composition and intradialytic metabolic, acid base and potassium changes. *Kidney Int*. 1987;32:129–135.
42. Heguilén RM, Sciurano C, Bellusci AD, et al. The faster potassium-lowering effect of high dialysate bicarbonate concentrations in chronic haemodialysis patients. *Nephrol Dial Transplant*. 2005;20:591–597.
43. Basile C, Libutti P, Lisi P, et al. Ranking of factors determining potassium mass balance in bicarbonate haemodialysis. *Nephrol Dial Transplant*. 2015;30:505–513.
44. Green D, Roberts PR, New DI, et al. Sudden cardiac death in hemodialysis patients: an in-depth review. *Am J Kidney Dis*. 2011;57:921–929.
45. US Renal Data System: USRDS 2012. Annual Data Report. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Available at: http://www.usrds.org/atlas12.aspx. Accessed 2012.
46. Jadoul M, Thumma J, Fuller DS, et al. Modifiable practices associated with sudden cardiac death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol*. 2012;7:765–774.
47. Pun PH, Lehrich RW, Honeycutt EF, et al. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int*. 2011;79:218–227.
48. Severi S, Grandi E, Pes C, et al. Calcium and potassium changes during haemodialysis alter ventricular repolarization duration: *in vivo* and *in silico* analysis. *Nephrol Dial Transplant*. 2008;23:1378–1386.
49. Di Iorio, Torraca S, Piscopo C, et al. Dialysate bath and QTc interval in patients on chronic maintenance hemodialysis: pilot study of single dialysis effects. *J Nephrol*. 2012;25:653–660.
50. Gabutti L, Ferrari N, Giudici G, et al. Unexpected haemodynamic instability associated with standard bicarbonate haemodialysis. *Nephrol Dial Transplant*. 2003;18:2369–2376.
51. Gabutti L, Bianchi G, Soldini D, et al. Haemodynamic consequences of changing bicarbonate and calcium concentrations in haemodialysis fluids. *Nephrol Dial Transplant*. 2009;24:973–981.
52. Gabutti L, Salvadè I, Lucchini B, et al. Haemodynamic consequences of changing potassium concentrations in haemodialysis fluids. *BMC Nephrol*. http://dx.doi.org/10.1186/1471-2369-12-14. Accessed 2011.
53. Silva BC, Freitas GRR, Silva VB, et al. Haemodynamic behavior during hemodialysis:effects of dialysate concentrations of bicarbonate and potassium. *Kidney Blood Press Res*. 2014;39:490–496.
54. Harris DC, Yuill E, Chesher DW. Correcting acidosis in hemodialysis: effect on phosphate clearance and calcification risk. *J Am Soc Nephrol*. 1995:1607–1612.
55. Graziani G, Casati P, Passerini M, et al. Pathophysiology and clinical consequences of metabolic alkalosis in hemodialyzed patients. *Arch Ital Urol Nefrol Androl*. 1987;59:105–111.
56. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32(suppl 3):S112–S119.
57. Speer MY, Giachelli CM. Regulation of cardiovascular calcification. *Cardiovasc Pathol*. 2004;13:63–70.
58. Raggi P, Boulay A, Chasan Taber S, et al. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*. 2002;39:695–701.
59. Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. *Am J Kidney Dis*. 2004;43:572–579.
60. Fischbach M, Hamel G, Simeoni U, et al. Phosphate dialytic removal: enhancement of phosphate cellular clearance by biofiltration (with acetate-free buffer dialysate). *Nephron*. 1992;62:155–160.
61. Klein E, Ward RA, Harding GB. Calcium carbonate precipitation in bicarbonate hemodialysis. *Artif Organs*. 1986;10:248–250.
62. Vermeulen M, Giordano M, Trevani AS, et al. Acidosis improves uptake of antigens and MHC class I-restricted presentation by dendritic cells. *J Immunol*. 2004;172:3196–3204.
63. Serrano CV Jr, Fraticelli A, Paniccia E, et al. pH dependence of neutrophil-endothelial cell adhesion and adhesion molecule expression. *Am. J Physiol*. 1996;27(3 Pt 1):C962–C970.
64. Basile C, Lomonte C. A neglected issue in dialysis practice: haemodialysate. *Clin Kidney J*. 2015;8:393–399.