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Replenishing Alkali During Hemodialysis: Physiology-Based Approaches

F. John Gennari, Marco Marano, and Stefano Marano

Complete author and article information provided before references.

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The acid-base goal of intermittent hemodialysis is to replenish buffers consumed by endogenous acid production and expansion acidosis in the period between treatments. The amount of bicarbonate needed to achieve this goal has traditionally been determined empirically with a goal of obtaining a reasonable subsequent predialysis blood bicarbonate concentration ($[HCO_3^-]$). This approach has led to very disparate hemodialysis prescriptions around the world. The bath $[HCO_3^-]$ usually chosen in the United States and Europe causes a rapid increase in blood $[HCO_3^-]$ in the first 1-2 hours of treatment, with little change thereafter. New studies show that this abrupt increase in blood $[HCO_3^-]$ elicits a buffer response that removes more bicarbonate from the extracellular compartment than is added in the second half of treatment, a futile and unnecessary event. We propose that changes in dialysis prescription be studied in an attempt to moderate the initial rate of increase in blood $[HCO_3^-]$ and the magnitude of the body buffer response. These new approaches include either a much lower bath $[HCO_3^-]$ coupled with an increase in the bath acetate concentration or a stepwise increase in the bath $[HCO_3^-]$ during treatment. In a subset of patients with low endogenous acid production, we propose reducing the bath $[HCO_3^-]$ as the sole intervention.

The acid-base goal of kidney replacement therapy is to replete body alkali stores to prevent metabolic acidosis, a debilitating and eventually fatal complication of kidney failure. With intermittent hemodialysis, one can never replicate the pattern of blood bicarbonate concentration ($[HCO_3^-]$) seen in patients with normal kidney function, which varies little from day to day (Fig 1, dashed line).[1] Instead, the blood $[HCO_3^-]$ is increased rapidly by alkali influx from the bath with each treatment, followed by a gradual decrease in the interval before the next treatment, causing a sawtooth pattern (Fig 1, solid line).[1]

In practice, a value for the bath $[HCO_3^-]$ is usually chosen empirically to achieve the goal of maintaining the blood $[HCO_3^-]$ at the nadir of the sawtooth (ie, predialysis) in a reasonable range. Studies over the last 2 decades have shown increased morbidity and mortality risks both when the predialysis blood $[HCO_3^-]$ is too low (<19 mmol/L) and too high (>26 mmol/L).[2-4] The National Kidney Foundation guidelines for the recommended predialysis blood $[HCO_3^-]$ are from more than 20 years ago and do not take these more recent studies into account.[5] Thus, this empiric approach has an uncertain goal and, as a result, the bath $[HCO_3^-]$ varies widely in countries around the world, ranging from as low as 25 mmol/L in Japan to as high as 35-40 mmol/L in the United States.[2,6,7] In Europe, the most common values are between the 2 extremes (32-35 mmol/L).[2]

In this article, we provide a brief history of the quest for the "right" bath $[HCO_3^-]$ needed to produce a reasonable posttreatment blood $[HCO_3^-]$. Following this history, we discuss recent studies describing the patient response to an abrupt increase in blood $[HCO_3^-]$ and pH during hemodialysis. These new studies provide evidence that intradialytic events may be important to consider in finding the optimal dialysis prescription.

HISTORY

When hemodialysis was initially developed for the treatment of acute kidney injury, the bath $[HCO_3^-]$ was empirically set at a normal blood level, 24 mmol/L. After the procedure was adapted for long-term treatment of kidney failure in 1960, it became apparent that this bath concentration was too low to correct the patient's acidosis, and the level was gradually increased to 28 mmol/L.[8] Acetate replaced bicarbonate as the sole alkali source in the late 1960s to solve the problem of alkaline calcium and magnesium precipitation. This technique was eventually abandoned because it left the patient acidotic at the end of treatment, caused hypoventilation, and resulted in symptomatic acetate toxicity due to the need to deliver acetate at a rate that exceeded its rate of metabolism.[8] With a return to bicarbonate as the primary alkali source in the 1980s, a small amount of acetic acid was added to the bath to generate carbon dioxide and, thereby, lower bath pH, preventing alkaline precipitation. The resulting chemical reaction adds acetate, a bicarbonate precursor, to the final bath in a low concentration (2-4 mmol/L). At these concentrations, acetate is well tolerated because it is rapidly and completely metabolized as soon as it enters the circulation, leaving a small standing, bath-to-blood concentration gradient that provides a stable rate of bicarbonate generation throughout the dialysis procedure.[9-11]

The reintroduction of bicarbonate into the bath solution markedly improved patient tolerance of dialysis, but the same empiric trial-and-error approach was reinstituted for

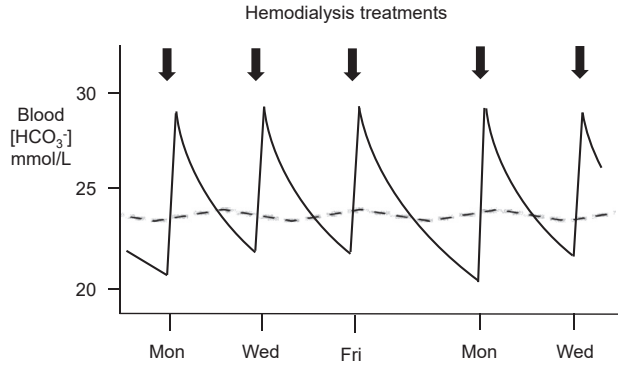

Figure 1. Contrast between the daily variation in blood bicarbonate concentration ([HCO_3^-]) over the course of 1 week in individuals with normal kidney function and in those on hemodialysis. In those with normal kidney function, the blood [HCO_3^-] varies little from day to day (dashed line), whereas in those receiving hemodialysis, the blood [HCO_3^-] increases abruptly by 6-8 mmol/L during treatment and then gradually decreases in the interval between treatments, creating a "sawtooth" pattern (solid line). The nadir value in the sawtooth occurs after the longest interval between treatments. Adapted from Gennari.[1]

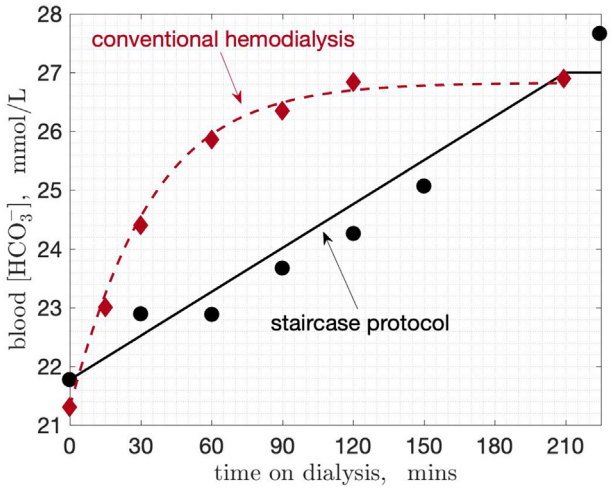

Figure 2. Contrast between the pattern of the blood bicarbonate concentration ([HCO_3^-]) during conventional hemodialysis with the bath [HCO_3^-] maintained at 32 mmol/L throughout treatment[8] and the pattern seen during treatment using a staircase protocol with the initial bath [HCO_3^-] set at 25 mmol/L and ending at 32 mmol/L (see Subsequent Studies Using the Sargent Analytical Model).[19] The triangles in the upper curve are the average measured values in 14 patients and the circles in the lower curve are the average measured values in 20 patients. The curved lines are generated by the best fit using our analytical model. At 90 and 120 minutes, the confidence intervals (not shown) do not overlap. Adapted from Marano et al.[20]

determining the bath [HCO_3^-]. The goal remained unchanged: to allow for sufficient bicarbonate addition during each treatment to obtain a predialysis nadir concentration at a reasonable level. Even without adjusting the bath [HCO_3^-] upward, current dialysis prescriptions expose many patients to a bath [HCO_3^-] 10-15 mmol/L higher than the blood [HCO_3^-] at the onset of treatment.[12,13] This gradient results in a rapid initial bicarbonate influx, causing an abrupt increase in the blood [HCO_3^-] and pH, followed by a leveling off for the remainder of the treatment (Fig 2, upper curve).[9,12,14-16] Because fluid removal occurs during most treatments, reducing the extracellular fluid (ECF) volume, this pattern means that the ECF bicarbonate content actually decreases from its peak value during the latter half of treatment (Fig 3, upper curve).[9] In patients dialyzed with a bath [HCO_3^-] > 30 mmol/L, in fact, more bicarbonate is removed from the ECF than is added in the latter half of treatment. In addition to this futile increase and decrease in the ECF bicarbonate content, recent studies have shown that a higher bath [HCO_3^-] is associated with an increased morbidity and mortality risk.[6]

NEW INSIGHTS

To elucidate the impact of this empiric approach on patient alkali stores during treatment, John Sargent created a novel analytic model in the last decade of his life that could track the bicarbonate influx and the amount remaining in the ECF on a continuous basis during treatment (Fig 4).[9] Central to Sargent's analytical model is his estimate of the rate of bicarbonate entry from the bath to the patient. This rate is dependent on the dialysance of bicarbonate and the transmembrane bicarbonate concentration gradient.

BICARBONATE DIALYSANCE

Although the transmembrane bicarbonate concentration gradient is straightforward to assess, the dialysance of this volatile anion is complicated by the carbon dioxide influx from the bath. Recall that the partial pressure of carbon dioxide in the dialysis bath solution is raised to 80-120 mmHg by the addition of acetic acid to prevent calcium precipitation in the bath. The resultant bath-to-blood CO_2 pressure gradient causes a rapid influx of CO_2 into the blood traversing the dialysis membrane. Once there, it enters the red cells and combines with cell water to produce carbonic acid, a reaction facilitated by carbonic anhydrase. The free hydrogen ions produced by this reaction bind to hemoglobin in the red cell, creating new bicarbonate ions that are instantaneously released into the ECF via a chloride/bicarbonate cell membrane ion exchanger.

Thus, even a simplified view of bicarbonate dialysance has 2 components. One is the influx of bicarbonate ions from the bath to the patient, which is determined by the membrane permeability and surface area and by the concentration gradient at any given blood and dialysate flow rate. The second is due to carbon dioxide influx during

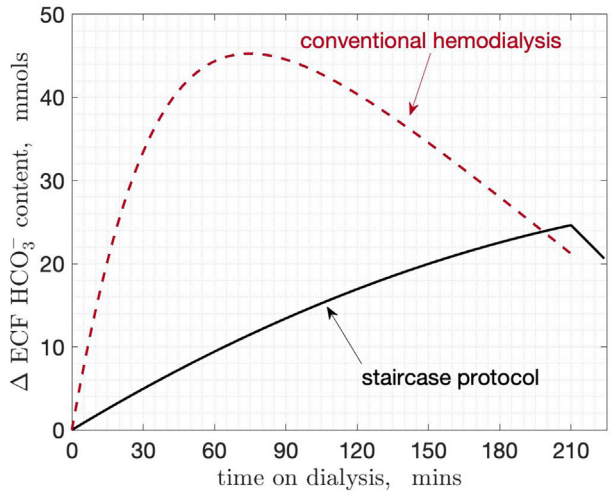

Figure 3. Contrast between the change in the extracellular fluid (ECF) bicarbonate content over the course of a hemodialysis treatment with the bath [HCO_3^-] maintained at 32 mmol/L throughout the treatment[9] and the pattern seen when using a staircase protocol.[20] Both curves were generated from the data obtained from study subjects using the Sargent analytical model. The dashed line represents the change in ECF bicarbonate content plotted against time on dialysis with conventional hemodialysis. The solid line represents the change in ECF bicarbonate content plotted against time on dialysis using the staircase protocol (see Subsequent Studies Using the Sargent Analytical Model). Adapted from Marano et al.[20]

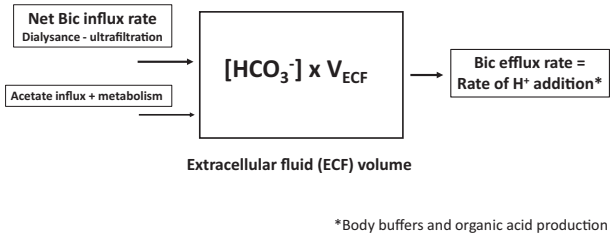

Figure 4. Schematic representation of the Sargent analytic model for alkali addition during hemodialysis.[9] Bicarbonate (Bic) is considered to be confined to extracellular fluid (ECF) water. Three sources of bicarbonate addition from the hemodialysis bath to the ECF are included (left side of figure). The first is the influx of the bicarbonate ion itself, driven by the bath-to-blood water concentration gradient. The second is influx of CO_2, driven by its pressure gradient across the dialysis membrane, and its interaction with blood hemoglobin. The third is the influx of acetate and its metabolism. Any bicarbonate lost into the bath by ultrafiltration is subtracted from the total influx. In addition to the bicarbonate lost by ultrafiltration, bicarbonate exits the ECF because of H^+ released from body buffers and from organic acid production. The net addition of H^+ is considered to be directly related to the increase in blood [HCO_3^-] (right side of figure). The key variables of the model are iteratively evaluated during treatment, and the rate of H^+ addition is determined by a least squares analysis of the measured blood water [HCO_3^-] values minus the model-generated values.

treatment and its interaction with hemoglobin in the blood traversing the dialysis membrane.

Pietribiasi and Leypoldt[17] have developed an analytic tool that allows for quantitation of each of these 2 sources of bicarbonate entry. Not surprisingly, the dialysance of CO_2 is much higher than that of ionic bicarbonate, and the 2 dialysances together actually exceed the blood flow rate. An unexpected finding in their analysis is that the dialysance of bicarbonate anions decreases and the dialysance of CO_2 increases as the blood [HCO_3^-] increases with the time on dialysis. The authors provide no explanation for these countervailing changes, and the impact they have on total bicarbonate influx is unclear. Morel et al[18] report an even more dramatic decrease in ionic bicarbonate dialysance with more time on dialysis, but they cannot exclude an H^+ addition to the ECF—that is, the body buffer response—as the cause of the drop in dialysance. Thus, the issue of whether specific components of bicarbonate dialysance change significantly during treatment remains unclear and the effect they have on the net bicarbonate influx is unresolved.

Sargent's analysis avoids this entire controversy because it is based on an empirically measured value for bicarbonate dialysance that includes all the components of bicarbonate entry.[19] Using his model to analyze the acid-base events during hemodialysis in 3 patient studies, we found that Sargent's dialysance predicts the pattern of change in the blood [HCO_3^-] very well.[7,9,20] To the extent that the Sargent model overestimates the bicarbonate influx because it fails to consider a drop in dialysance, the calculated H^+ addition (buffer response) to the ECF would be overestimated. Based on the available data, we believe any such error is minimal and that the continuous addition of H^+ to the ECF from body buffers and organic acid production throughout treatment is the principal cause of the decrease in ECF bicarbonate stores.

Two additional studies have analyzed the acid-base events during hemodialysis,[16,21] and have reported a much lower rate of bicarbonate influx because they isolated the bicarbonate generated from carbon dioxide influx and the reaction with hemoglobin and "corrected" for it. Their correction assumes that the bicarbonate generated from this reaction remains in the red cell and is stoichiometrically back-titrated as the blood returning from the dialyzer equilibrates with the systemic carbon dioxide pessure. This assumption is incorrect because, as noted earlier, the bicarbonate generated by the CO_2 reaction with hemoglobin leaves the cell instantaneously and enters the ECF. This bicarbonate exodus is reflected in the measurement of ECF [HCO_3^-] in the efferent blood. This source of bicarbonate is thus combined with the pool of all the bicarbonate added to the ECF and contributes to inciting the physiological response. As a result, we believe the authors of these articles have significantly underestimated the net addition of bicarbonate to the patient during hemodialysis.

Box 1. Suggested Strategies to be Explored to Moderate the Rate of Bicarbonate Influx During Hemodialysis

- Reducing the bath [HCO_3] in patients whose diet results in low endogenous acid production.
- Shifting bicarbonate addition from bicarbonate influx to acetate influx and metabolism.
- Using a stepwise increase in the bath [HCO3-] during treatment when the predialysis blood [HCO3-] is much lower than the bath [HCO3-].

IMPLICATIONS OF THE SARGENT MODEL ANALYSIS

As noted above, our analysis indicates that a brisk buffer response is quickly initiated in response to the acute alkalinization engendered by the rapid addition of bicarbonate and continues for the duration of the treatment.[9] Because the blood pH changes little, if at all, during the latter half of treatment, we presumed that cellular organic acid production rather than buffer titration was primarily responsible for the continued H^+ addition to the ECF. One of us (F.J.G.) had proposed many years ago that increased lactic acid production was responsible for the leveling off of blood [HCO_3^-] after 2 hours of treatment.[15] Although this hypothesis is compatible with the results of the Sargent model analysis, a recent study indicates that it is likely incorrect. In that study, organic acid production accounts for only a small fraction of the H^+ addition and, more to the point, organic acid production is not notably affected by reducing the bath [HCO_3^-].[16] A review of older studies, as well as our most recent patient study, also shows that while organic acid production may be a contributing factor, it is unlikely to be the primary cause of the excessive buffer response.[19,20,22]

An alternate explanation is suggested by a study of acute alkali loading in dogs that shows the same phenomenon: that is, continued removal of bicarbonate from the ECF more than 60 minutes after rapid intravenous bicarbonate administration.[23] The authors postulated that the most likely cause of this phenomenon was the delayed activation of bone buffering. Release of H^+ from bone epithelial cells appears to be a slowly activated response to acute alkali loading, gradually increasing over time, and this response has a huge capacity.[23,24] The time frame of activation of bone buffering is consistent with the continued removal of added bicarbonate during the latter half of hemodialysis, but at present there is no direct evidence with which to verify or to refute this hypothesis. Thus, the cause of the continued release of H^+ in the latter half of treatment remains unknown.

At the end of the hemodialysis treatment, the patient's buffer response removes over 80% of the added bicarbonate, a much larger amount than predicted by the "apparent space" of distribution of bicarbonate. As noted earlier, the buffer response removes more bicarbonate than is added during the second half of the treatment, reducing the ECF bicarbonate content dramatically from its peak value at 2 hours (Fig 3). Thus, in patients receiving standard outpatient hemodialysis, alkali addition is a futile cycle that begins with an abrupt increase in body alkali stores, followed by a subsequent loss of most of what is gained after 2 hours of treatment. We have described this response as maladaptive, but whether it contributes to patient morbidity and mortality is unknown.

SUBSEQUENT STUDIES USING THE SARGENT ANALYTICAL MODEL

The Sargent analytical model was also used to evaluate the patient responses to alkali addition in 17 patients receiving hemodialysis in Japan with a very different bath composition.[7] These patients were unique in that they had an average predialysis blood [HCO_3^-] of 25 mmol/L and were dialyzed against a bath with a bicarbonate concentration of only 25.5 mmol/L. The final bath also contained acetate in a higher concentration than in the US, 8 mmol/L (a mixture of 6 mmol/L of sodium acetate and 2 mmol/l of acetic acid), than that in the United States. In these patients, all the net bicarbonate added during treatment came from acetate influx and metabolism. The small resultant increase in blood [HCO_3^-] achieved at the end of treatment was due to the fact that bicarbonate generation from acetate influx and metabolism exceeded bicarbonate loss into the bath. This bath composition dramatically minimized the total-body buffer response.[7] Strikingly, both the decrease in blood [HCO_3^-] between treatments and the increase during treatment were fully accounted for by the buffer response to changes in the ECF volume. The only way to account for the stable high predialysis blood [HCO_3^-] in these patients, therefore, was that their diet did not generate any endogenous acid production, a conclusion supported by diet analysis. This study reemphasized the importance of diet in determining the need for the addition of alkali during treatment and also illustrated that the acetate influx and metabolism provided a uniformly stable rate of bicarbonate generation during hemodialysis. By contrast, when the bath [HCO_3^-] is higher, the rate of bicarbonate influx from the bath varies as a function of the transmembrane concentration gradient by initially high and then progressively lower as the gradient collapses.

Two of us (S.M. and M.M.) proposed that the futile and potentially harmful cycle of an abrupt increase in ECF bicarbonate content followed by a rapid decrease in the latter half of the treatment could be avoided if the rate of bicarbonate addition during dialysis was moderated during treatment.[11] Some investigators have proposed lowering the bath [HCO_3^-] in the latter half of treatment to reduce the continued bicarbonate addition.[25] Although their proposal was never tested, a recent study indicated that simply lowering the bath [HCO_3^-] was not useful in patients with significant endogenous acid production, because the blood [HCO_3^-] fell during treatment.[16]

As an alternative to lowering the bath [HCO_3^-], 2 of us developed a protocol that involved a low initial bath value followed by a stepwise increase.[26] By analytically solving John Sargent's differential equations, a protocol was designed to force a linear increase in blood [HCO_3^-] over the duration of hemodialysis, rather than the exponential initial increase seen with conventional hemodialysis. Initially, the bath [HCO_3^-] was set approximately 3 mmol/L higher than the blood [HCO_3^-], and then it was increased at 30-minute intervals, in a "staircase" fashion.

We tested this protocol in 20 patients, using our mathematical approach for determining the initial value for the bath [HCO_3^-] and for making the stepwise increases during treatment.[20] The staircase progression was deliberately ended with a bath [HCO_3^-] that would achieve our goal of an end-treatment blood [HCO_3^-] of approximately 27 mmol/L. This blood value is what we currently obtain with a standard dialysis protocol using a bath [HCO_3^-] of 32 mmol/L throughout treatment.[9] As shown in Figs 2 and 3, we achieved our goal, producing more gradual linear increases both in blood [HCO_3^-] and in ECF bicarbonate stores during treatment. The rate of increase in blood [HCO_3^-] we achieved validated the predictive ability of the Sargent model. The staircase protocol tested in our patients reduced the magnitude of their buffer responses dramatically, as would be expected by our model design. In addition, lactic acid production was reduced during treatment as compared to that of historical controls. Notably, this protocol also shifted the majority of the bicarbonate addition from bicarbonate influx to acetate influx and metabolism, without any adjustment in the bath acetate concentration.

CONCLUSIONS AND RECOMMENDATIONS

These recent studies, while all short term and with low numbers of patients, have opened the possibility to study and implement new approaches to bicarbonate replenishment in hemodialysis therapy that can minimize the patient's buffer response (Box 1). Option 1 is to simply lower the bath [HCO_3^-] in patients with little or no dietary endogenous acid production. These patients can be identified by a dietary assessment and usually have a predialysis blood [HCO_3^-] > 24 mmol/L. There is no reason to expose such patients to a bath [HCO_3^-] > 30 mmol/L, which can increase the risk of severe alkalinity during treatment. Option 2 is to consider reducing the bath [HCO_3^-] in all patients and to couple it with an increase in the bath acetate concentration. Bath acetate levels as high as 10 mmol/L have been used in Japan, together with lower bath [HCO_3^-] values, and are well tolerated.[7] As noted earlier, such a combination allows for a uniformly slow rate of bicarbonate addition throughout treatment, as opposed to the traditionally high bath [HCO_3^-] that causes a rapid initial entry rate followed by a slower rate due to the collapse of the transmembrane bicarbonate concentration gradient. The most flexible approach, however, is the staircase protocol (option 3), which both moderates the initial rate of bicarbonate addition and shifts the source from bicarbonate influx to acetate influx and metabolism without any change in the bath acetate concentration. Our staircase protocol study involved some elaborate mathematical derivations to predict the approximate values for the initial bath [HCO_3^-] and the bath [HCO_3^-] at each step along the way,[20] but we believe a much simpler protocol could be used for adjusting the bath [HCO_3^-] during treatment to approximate a linear increase in the blood [HCO_3^-]. Current dialysis machines can be prescheduled to make the changes, so that treatment need not involve additional time or personnel.

It is unclear at present, of course, what the best approach should be. While option 1 is only recommended for a subset of patients with very low endogenous acid production, options 2 and 3 could be used for most patients. The key question is whether any of these changes will affect patient morbidity and mortality over the long term. We recommend that these new approaches be studied, as they make physiological sense. Our suggestions may complicate hemodialysis therapy, but we believe it is time to consider moving beyond a one-size-fits-all approach for alkali addition in patients receiving incenter intermittent hemodialysis for treatment of kidney failure.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: F. John Gennari, MD, Marco Marano, MD, and Stefano Marano, PhD.

Authors' Affiliations: Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont (FJG); Unit of Nephrology and Dialysis, Maria Rosaria Clinic, Pompeii, Italy (MM); and Department of Information and Electrical Engineering and Applied Mathematics (DIEM), University of Salerno, Fisciano, Italy (SM).

Address for Correspondence: F. John Gennari, MD, 66 Malletts Head Rd, Colchester, VT 05446. Email: fgennari@uvm.edu

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REFERENCES

1. Gennari FJ. Acid-base considerations in end-stage renal disease. In: Henrich WL, ed. *Principles and Practice of Dialysis*. Williams & Wilkins; 2003:393-407.
2. 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(4):661-671.
3. Wu DY, Shinaberger CS, Regidor DL, McAllister CJ, Kopple JD, Kalantar-Zadeh K. Association between serum

bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Clin J Am Soc Nephrol*. 2006;1(1):70-78.
4. 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(3):469-478.
5. National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis*. 2000;35(Suppl):S1-S140.
6. Tentori F, Karaboyas A, Robinson BM, et al. Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2013;62(4):738-746.
7. Sargent JA, Yamamoto T, Yamakawa T, De Waal D, Gennari FJ. Hemodialysis using a low bicarbonate dialysis bath: implications for acid-base homeostasis. *Semin Dial*. 2020;33(5):402-409.
8. Gennari FJ, Feriani M. Acid-base complications in hemodialysis and peritoneal dialysis. In: Lameire NH, Mehta RL, eds. *Complications of Dialysis*. Marcel Dekker; 2001:169-189.
9. Sargent JA, Marano M, Marano S, Gennari FJ. Acid-base homeostasis during hemodialysis: new insights into the mystery of bicarbonate disappearance during treatment. *Semin Dial*. 2018;31(5):468-478.
10. Sargent JA, Marano M, Marano S, Gennari FJ. Changing dialysate composition to optimize acid-base therapy. *Semin Dial*. 2019;32(3):248-254.
11. Marano S, Marano M. Frontiers in hemodialysis: solutions and implications of mathematical models for bicarbonate restoring. *Biomed Signal Process Control*. 2019;52:321-329.
12. Oettinger CW, Oliver JC. Normalization of uremic acidosis in hemodialysis patients with a high bicarbonate dialysate. *J Am Soc Nephrol*. 1993;3(11):1804-1807.
13. Gennari FJ. Acid-base balance in dialysis patients. *Semin Dial*. 2000;13(4):235-239.
14. Symreng T, Flanigan MJ, Lim VS. Ventilatory and metabolic changes during high efficiency hemodialysis. *Kidney Int*. 1992;41(4):1064-1069.
15. Gennari FJ. Acid-base homeostasis in end-stage renal disease. *Semin Dial*. 1996;9(5):404-411.
16. Park S, Paredes W, Custodio M, et al. Intradialytic acid-base changes and organic anion production during high versus low bicarbonate hemodialysis. *Am J Physiol Ren Physiol*. 2020;318(6):F1418-F1429.
17. Pietribiasi M, Leypoldt JK. Modeling acid-base transport in hemodialyzers. *Biocybern Biomed Eng*. 2021;41(3):1150-1161.
18. 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(4):288-300.
19. Gotch FA, Sargent JA, Keen ML. Hydrogen ion balance in dialysis therapy. *Artif Organs*. 1982;6(4):388-395.
20. Marano S, Marano M, Gennari FJ. A new approach to bicarbonate addition during hemodialysis: testing model predictions in a patient cohort. *IEEE Access*. 2022;10:17473-17483.
21. Uribarri J, Zia M, Mahmood J, Marcus RA, Oh MS. Acid production in chronic hemodialysis patients. *J Am Soc Nephrol*. 1998;9(1):114-120.
22. Ward RA, Wathen RL, Williams TE, Harding GB. Hemodialysate composition and intradialytic metabolic, acid-base and potassium changes. *Kidney Int*. 1987;32(1):129-135.
23. Adrogué HJ, Brensilver J, Cohen JJ, Madias NE. Influence of steady-state alterations in acid-base equilibrium on the fate of administered bicarbonate in the dog. *J Clin Invest*. 1983;71(4):867-883.
24. Burnell JM. In vivo response of muscle to changes in CO2 tension or extracellular bicarbonate. *Am J Physiol*. 1968;215(6):1376-1383.
25. Tovbin D, Sherman RA. Correcting acidosis during hemodialysis: current limitations and a potential solution. *Semin Dial*. 2016;29(1):35-38.
26. Marano S, Marano M, Pecchia L. Frontiers in hemodialysis part 2: toward personalized and optimized therapy. *Biomed Signal Process Control*. 2020;61:1-9.
27. Moura-Neto JA, Daugirdas JT. Mathematical modeling of hemodialysis: a tribute to John A. Sargent, PhD (1939-2020). *Kidney Int*. 2022;101(3):430-431.