Seminars in Dialysis

Correspondence

Dialysate Bicarbonate and the Risk of Death

To the Editor:

The recent article by Chen and Kalantar-Zadeh on serum bicarbonate and the risk of death (1) provides an excellent review and offers new information about a potential role of malnutrition-inflammation. In their critical comment about our 2013 DOPPS publication by Tentori et al. (2), however, the authors dismissed our main finding that higher *dialysate* bicarbonate concentration was associated with mortality, saying, "the presence of significant confounding by indication bias is a more likely explanation. It is likely that high-bicarbonate bath was prescribed to treat more severe metabolic acidosis" (p. 2).

The authors seem to have missed our key analysis, noted in the abstract and page 741, which specifically dealt with confounding by indication by only including dialysis facilities where a single dialysate bicarbonate level was used for virtually all (>90%) patients (confirmed when requiring 100%). In this analysis, there could be no confounding by indication since all patients received the same dialysate bicarbonate and the prescription is not individualized based on specific patient characteristics (e.g., more severe acidosis). The estimated effect of higher dialysate bicarbonate on mortality was nearly identical for patients in nonindividualized and individualized facilities. Because of concerns that the dialysate bicarbonate effect may be confounded with other practices that affect mortality, we not only adjusted for case mix and detailed comorbidities but also for two other dialysis facility practices —the percentage of patients using a catheter and the percentage with Kt/V <1.2.

We also found the inverse association between *serum* bicarbonate and mortality to be the same in facilities where dialysate bicarbonate was uniform as in facilities where it was individualized. That finding is consistent with the inverse association between predialysis serum bicarbonate and mortality, reported by Chen and Kalantar-Zadeh in their fully adjusted model.

In order to advance our understanding of dialysis practices using observational studies, we agree that possible bias due to confounding by indication must be carefully considered in the analysis and in the interpretation of results. Taking advantage of a natural experiment in which patients are "assigned" to facilities that do not individualize a treatment, as all patients at that facility are given a uniform dialysate bicarbonate, eliminates confounding by indication.

Additional studies are needed to address the impact of total base in the dialysate bicarbonate plus acetate, since neither of these two studies had information about the acetate component in the dialysate. Thus, we recommend randomized clinical trials with different total dialysate base levels.

Conflict of Interest

Francesca Tentori, Hal Morgenstern, Angelo Karaboyas, Bruce Robinson, and Friedrich Port: The DOPPS Program is supported by grants to Arbor Research by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGfN, Shire, WiNe Institute; for PDOPPS in Japan by the Japanese Society for Peritoneal Dialysis (JSPD). All support is provided without restrictions on publications. In addition, Hal Morgenstern is the consulting epidemiologist on dialysis acetate for an attorney representing plaintiffs in related litigation.

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References

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2. Tentori F, Karaboyas A, Robinson B, Morgenstern H, Zhang J, Sen A, Ikizler TA, Rayner H, Fissell R, Vanholder R, Tomo T, Port FK: Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study. *Am J Kidney Dis* 62(4):738–746, 2013

This letter was referred to the authors of the article in question who offer the following reply:

To the Editor:

Regarding the comments and referred article by Tentori et al., the group took great effort to reduce the confounding-by-indication bias by analyzing

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facility-level data and only included dialysis units with ≥90% patients prescribed with uniform dialysate bicarbonate prescriptions (1). The authors also adjusted for patients' serum bicarbonate levels, as well as case mix and other facility characteristics. However, the bias due to the diversity of practice patterns among international dialysis units cannot be completely eliminated. Dialysis units may have a majority of patients prescribed with a uniform dialysate, but the reason for choosing a specific dialysate protocol is unlikely random. Possible rationales for uniform prescription may be based on local patient case mix or the availability of dry acid concentrate. Additionally, the authors excluded data from Japan because most Japanese units used a lower bicarbonate bath (≤30 meq/l). Inclusion of the data from Japan may provide interesting insight into this difficult question.

Additionally, other issues such as the total base used in dialysate bicarbonate and acetate remain uncertain. The observed increased infection-related mortality rates are difficult to explain and should not be attributed to dialysate bicarbonate prescription.

While the Dialysis Outcomes and Practice Patterns Study may provide important findings in the practice of nephrology, an observation cohort study is unlikely able to explain all the differences of diagnostic standards and practice patterns (2). With the exception of randomization nothing can eliminate confounding- by- indication; thus, we agree that a randomized controlled trial will be needed to address the role of alkali in dialysis bath and mortality.

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References

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2. Meyer K: Dialysate bicarbonate: the case for foot-dragging. *Am J Kidney Dis* 62(4):650–652, 2013