Conclusion:
Recent analyses performed using FMCNA hemodialysis (HD) patient safety data confirms that alkalosis is a significant risk factor associated with cardiopulmonary (CP) arrest in the dialysis unit, independent of and additive to the risk of CP arrest associated with pre-dialysis hypokalemia. The major cause of metabolic alkalosis in dialysis patients is inappropriately high dialysate total buffer concentration. As recommended in previous communications, physicians should individualize dialysate bicarbonate and total buffer prescriptions. We further recommend that pre-dialysis serum bicarbonate level of >24 mEq/L should prompt immediate review of dialysate bicarbonate prescription.

Summary of findings:

- In September, 2011 the mean pre-dialysis bicarbonate level for FMCNA was 24.1±3.4 mEq/L, with over 25% of patients at ≥26.0 mEq/L, 15% with ≥28.0 mEq/L and 3% with ≥30.0 mEq/L.

- Over time, the progressive shift towards higher pre-dialysis serum bicarbonate levels not only implies that more patients have alkalosis prior to dialysis, but that an even higher percentage of patients have alkalosis post-dialysis.

- The current analysis determined that: "borderline elevated pre-dialysis bicarbonate levels and overt alkalosis are significantly associated with 6 to 8 fold greater risk of CP arrest and sudden cardiac death in the dialysis facility".

- In light of these troubling findings, we strongly recommend that physicians adjust dialysate bicarbonate prescriptions monthly for individual patients, with immediate attention to patients with serum pre-dialysis bicarbonate level of >24 mEq/L.

- The bicarbonate prescription entered into the dialysis machine underestimates the total buffer that the patient receives from the dialysate – by ~8 mEq/L in the case of dialysate prepared from Granuflo (powder) or by ~4 mEq/L in the case of dialysate
prepared from NaturaLyte (liquid) – since acetate is rapidly converted into bicarbonate by the liver. Please familiarize yourself with the formulation utilized in each of your facilities and consider lower bicarbonate prescriptions (e.g. 31-33 mEq/L so that total buffer is no greater than 39-41 mEq/L when using Granuflo), and adjust monthly depending on each patient’s pre-dialysis bicarbonate level.

Background:

Uremia leads to accumulation of protein breakdown products contributing to chronic metabolic acidosis.\(^1\) Acidemia contributes to muscle breakdown, protein degradation, decreased synthesis of albumin and vitamin D, and increased resistance to PTH and insulin.\(^2;3\) The HD procedure allows for a transfer of buffers from the dialysate to counteract acidosis and to safely bring acid-base status back into homeostasis.\(^4\) The KDOQI guidelines focused on correction of acidosis,\(^5\) so it was not surprising that pre-dialysis bicarbonate levels have increased over time, from 22.9±3.1 mEq/L in the 2004 FMCNA prevalent HD patient study, to 24.1±3.5 mEq/L for September, 2011 (median 24.0 mEq/L), with 25% of patients at ≥26.0 mEq/L, 15% with ≥28.0 mEq/L and ~3% with ≥30.0 mEq/L – shown in Figure 1, below.

Figure 1. Distribution of pre-dialysis serum bicarbonate for the month of September, 2011.
In a recent study from DOPPS, increased death risk was associated not only with acidosis (pre-dialysis bicarbonate <19 mEq/L), but also with high pre-dialysis bicarbonate (>27 mEq/L). There was also increased hospitalization risk observed at pre-dialysis bicarbonate <20 mEq/L and >24 mEq/L. The authors recommended that the lowest risk was likely around pre-dialysis bicarbonate of 20-22 mEq/L. We reviewed mortality data from 2008 (published electronically in the 2009 Medical Director Report) and confirmed similar associations to that observed by DOPPS. (The Spectra lab reference range of 22-29 mEq/L represents a very liberal target for the general population, not for ESRD patients. We are in the process of having Spectra report specific targets for ESRD.)

**FMCNA Analysis:**

A case-control study evaluated risk factors in HD patients who suffered from CP arrest in the facility (N=941 patients from 667 facilities) compared to other HD patients (N=80,516) within the same facilities between January 1 and December 31, 2010.

Logistic regression models indicated an unadjusted odds ratio (OR) for CP arrest of 6.3 and a case-mix (age, gender, race, and diabetes status) + lab (albumin, hemoglobin, phosphorus, calcium and WBC count) + vascular access adjusted OR for CP arrest of 4.7 (both p<0.0001) with pre-dialysis bicarbonate levels of ≥28 mEq/L, and a trend towards a doubling of risk both at low (<20 mEq/L) and slightly elevated (26-28 mEq/L) levels, shown in Figure 2, below.

**Relative Risk of CP Arrest: Bicarbonate**

![Graph showing relative risk associated with pre-dialysis serum bicarbonate categories.](EXHIBIT C)
The relative risks for CP arrest in HD patients associated with pre-dialysis potassium <4 mEq/L was OR=3.3 (unadjusted) and OR=2.8 (adjusted for case-mix + lab + vascular access), both p<0.0001. Since rapid increases in serum bicarbonate concentration has been associated with a faster decline in serum potassium during dialysis, we hypothesized that the risk would be greatest in the HD patient having a combination of pre-dialysis serum potassium <4 mEq/L and bicarbonate ≥28 mEq/L.

Figure 3. Relative risks associated with 4 combinations of bicarbonate and potassium categories.

Indeed, unadjusted OR=8.3 and case-mix + lab + vascular access adjusted OR=6.3, for CP arrest related to the combination (both p<0.0001). Nevertheless, it is important to recall that serum bicarbonate ≥28 mEq/L remained a significant predictor even with potassium ≥4 mEq/L, with unadjusted OR=4.4 and case-mix + lab + vascular access adjusted OR = 3.6 (both p<0.0001). These results are shown in Figure 3, above.

Recommendations:

Pre-dialysis alkalosis and hypokalemia are modifiable risk factors associated with CP arrest. Previous reports have identified hypokalemia as a risk factor for cardiac arrest and sudden cardiac death in the HD facility and this was related to the use of low potassium dialysate (0K, 1K). Thus, FMCNA policies and practices have required routine review of dialysate
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Potassium orders and have limited use of very low potassium dialysate. However, there has not been enough of a quality focus on alkalosis because the clinical guidelines have primarily emphasized avoidance of metabolic acidosis. Over time, there has been a shift towards higher dialysate bicarbonate prescriptions accompanied by increasing serum bicarbonate levels before dialysis and presumably much higher post dialysis. This issue needs to be addressed urgently.

High pre-dialysis serum bicarbonate level was independent of and may potentiate the death risk associated with low pre-dialysis serum potassium. It is an actionable risk factor, by individualization of dialysate bicarbonate prescriptions to keep patients’ pre-dialysis serum bicarbonate within a narrower range and to avoid alkalosis. We strongly recommend that physicians individualize dialysate prescriptions, review them monthly, with consideration of patient’s pre-dialysis bicarbonate and dialysate total buffer, with immediate attention to decreasing prescribed dialysate bicarbonate in patients with pre-dialysis bicarbonate level of >24 mEq/L.

Many facilities have converted to the Fresenius powdered “Granuflo” formulation that has total buffer equal to “prescribed bicarbonate plus 8” – due to 4 mEq/L of sodium acetate in addition to the 4 mEq/L of acetic acid (acetate). There are instances whereby the physicians’ bicarbonate prescriptions were kept the same when shifting to power concentrate (Granuflo) (failing to account for the additional 8 mEq/L of sodium acetate), thus exposing patients to a higher total buffer load than intended. While >80% of current dialysate prescriptions are for 37 mEq/L of bicarbonate, it may be prudent to initially target a prescription of 31-33 mEq/L of dialysate bicarbonate (with total buffer greater by up to ~8 mEq/L from acetate) and adjust according to patients’ monthly bicarbonate level. Please recall also that an additional source of bicarbonate may be the phosphate binders that are prescribed to patients.

Previously, several memos were sent to you from the Medical Office to explain the difference in total buffer between Naturalyte (liquid) and Granuflo (powder) dialysate formulations. The information was accompanied by a recommendation to address pre-dialysis alkalosis found in an increasing proportion of your patients, by decreasing the prescribed dialysate bicarbonate as needed. These previous memos, as well as a related article in the Medical Staff Newsletter, are accessible via Doctors Corner and also upon request. In addition, two presentations containing relevant information were recently presented at the Medical Directors’ Symposium, one by Brooks Rogers and the other by Dr. Jeff Sands and both are also available for download in Doctors Corner.

If you have questions or recommendations regarding the topic of this memorandum, please contact any member of the Medical Office.
Reference List


