The Fresenius Medical Care North America (FMCNA) Medical Office routinely corresponds with all medical directors to share current information. Over the past decade there have been scientific reports on the dangers of pre-dialysis serum bicarbonate levels < 20 mEq/L and >28 mEq/L. Both ends of the acid/base spectrum appeared to be associated with increased morbidity and mortality for patients leading to the recommendation that the prescribing physician be cognizant of the acid/base status in their patients. Understandably, these studies led nephrologists to consider prescribing practices that further controlled both acidosis and alkalosis.

During this same timeframe, the Medical Office has issued several memos to assist in prescribing the dialysate composition. Serum bicarbonate has been the subject of several of these memos, but the most recent one issued this past November discussing serum bicarbonate and in-center cardiopulmonary arrest has generated a substantial amount of discussion and controversy. To expand on this discussion, we wish to provide additional information regarding acid/base management and total buffer contribution in dialysis prescriptions.

To briefly review, the memo from 11-4-2011 looked retrospectively at a cohort of patients who had suffered cardiopulmonary arrest (CPA) during dialysis. This selected population of patients, when compared to a cohort of patients who did not have a cardiopulmonary arrest, was found to have a 4-6 times higher likelihood of having a pre-dialysis serum bicarbonate level ≥ 28 mEq/L at the last monthly blood draw and a 2-3 times higher likelihood of having a pre-dialysis serum bicarbonate level of ≤ 20 mEq/L. This finding was pronounced in the analysis when the CPA events were looked at with a combination of high bicarbonate and low serum potassium.

The Medical Office has been addressing additional information for analysis in the time since the most recent memo on bicarbonate and total buffer was issued, including trends in rates of the serious adverse event of cardiopulmonary arrest, characteristics surrounding inter-dialytic and intra-dialytic serum bicarbonate levels, other sources of buffering capacity in ESRD patients, current distributions of pre-dialysis serum bicarbonate status in ESRD patients and careful interpretation of the Odds Ratio and statistical analysis.

As part of our review, data from the FMCNA clinical database are presented. It is important to note, however, that when observational data are reported care must be taken not to assume the conclusions are definitive as they do not represent randomized, controlled and blinded analysis. They are, however, important in elucidation of associations, inferences and observations from actual patient care and can help frame questions for further inquiry.

**Trends in CPA, Mortality and Clinical Correlates**

CPA during dialysis is a serious adverse event that is fortunately very rare and in the context of an analysis of CPA events it is prudent to recognize the low frequency of occurrence. Data in Figure 1 shows the rate of CPA at FMCNA has remained stable between 0.4 and 0.6 events per 10,000 treatments over the past decade. Prior published reports from the late 1990's show similar results and rates as high as 0.7 CPA events per 10,000 treatments. The analysis reported in the memo of 11-4-2011 included 941 of the patients who suffered a CPA event.
During the calendar year 2010. During 2010 FMCNA facilities performed 20,850,242 treatments and had an overall CPA event rate of 0.00549%.

**FIGURE 1 - Rate of CPA during Hemodialysis - FMCNA**

![Graph showing rate of CPA per 10,000 treatments from 2001 to 2011.]

CPA events are distinct from analyses of overall mortality. While the rate of CPA events has been stable over the last decade, the mortality rate of the overall population of hemodialysis patients has been gradually declining as shown in Figure 2.

**FIGURE 2 - Hemodialysis Mortality + Withdrawal Trends - FMCNA**

![Bar chart showing FMCNA HD Mortality Trends from 2007 to 2011.]

**Variability in Serum Bicarbonate Levels in ESRD Patients**

The original analysis of the 2010 CPA events characterized in the memo from 11-4-2011 utilized serum bicarbonate levels from the monthly ESRD laboratory tests. Within the context of the discussion which followed the publication of the memo, we subsequently evaluated the
variability between the timing of the lab test and the CPA event, as well as the variability of the patients’ bicarbonate during the preceding six months. Figures 3, 3a and 4 show the results of this analysis.

Figure 3 depicts along the x-axis the number of days between the pre dialysis serum bicarbonate measurement and the CPA event in 911 of the 941 patients reported in the previous discussion. The mean and median serum bicarbonate values are depicted on the y-axis. These levels show a standard deviation of up to 3.4 mEq/L with a mean and median serum bicarbonate level of 24 mEq/L. Figure 3a shows the distribution of pre dialysis serum bicarbonate levels in the 99 patients who suffered a CPA event on the day serum bicarbonate testing was performed. These patients had a similar distribution of bicarbonate levels in the high and low ranges, as well as, a mean and median serum bicarbonate level of 24 mEq/L.

**FIGURE 3: Timing of Serum Bicarbonate Prior to CPA**

**Overview of Cardiopulmonary Arrests**

CPA Patient's Serum Bicarbonate by Blood Draw Interval Prior to Event 2010

**Figure 3a: Serum Bicarbonate Distribution in 99 Patients with a CPA Event and a Serum Bicarbonate on the Same Day**
Figure 4 examines the variability in pre-dialysis serum bicarbonate for individual patients. At least 6 serum bicarbonate values were available during the 6 months prior to CPA for 549 of the 941 patients. A degree of variability is displayed in both patients who did and did not have cardiopulmonary arrest with standard deviations of 2.16 to 2.53 mEq/L. These data imply that the serum bicarbonate level should be evaluated in the context of the clinical conditions experienced by an individual patient and that within this expected variability serum bicarbonate, as opposed to an arterial blood gas measured pH, is the best available assessment of acid/base status for your patients despite these limitations.

**FIGURE 4: Six Month Pre CPA Serum Bicarbonate Trends**

*Overview of Cardiopulmonary Arrest Study*

*Patient’s Serum Bicarbonate on before Event Date*

**2010 Matched Study Samples**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Pre CPA Causation</th>
<th>Patient</th>
<th>Mean of 6 Pre CPA Serum Bicarbonate levels</th>
<th>SD of 6 Pre CPA Serum Bicarbonate levels</th>
<th>Median of 6 Pre CPA Serum Bicarbonate levels</th>
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<td></td>
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<td>n</td>
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<td>2-10 Matched Control (Died)</td>
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<td>511</td>
<td>2.35</td>
<td>1.07</td>
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</table>

Figures 5a & b and 6 are from a recent analysis of Pre and Post hemodialysis serum bicarbonate levels obtained from a cohort of 22,101 patients in a general hemodialysis population from 2007. Figure 5a displays patients with pre-dialysis serum bicarbonate values ≤24 mEq/L and 5b displays patients with values ≥25 mEq/L. Figures 5a & 5b demonstrate that during a dialysis session the greatest change in bicarbonate level occurs when the pre dialysis serum bicarbonate is low. The degree of change declines as the patient’s pre-dialysis serum bicarbonate level rises. When high serum bicarbonate exists before dialysis the degree of change is minimal across the whole spectrum of dialysate buffer concentrations. This is consistent with previously published data on bicarbonate based dialysis.
FIGURES 5a & 5b: Change in Serum Bicarbonate during Hemodialysis

Overview of Bicarbonate Study

Pre & Post HD Serum Bicarbonate vs. Dialysate Total Buffer
2007 October Blood Draw Data (Proton ONLY)
(N = 22,101)

Delta Bicarbonate Distribution by Bicarbonate Dialysate Total

Pre Dialysis Bicarbonate
- 18 or less
- 19-20
- 21-22
- 23-24
- 25-26
- 27-28
- 29-30
- >30

Bicarbonate Dialysate Total

<table>
<thead>
<tr>
<th>Range</th>
<th>18 or less</th>
<th>19-20</th>
<th>21-22</th>
<th>23-24</th>
<th>25-26</th>
<th>27-28</th>
<th>29-30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 or less</td>
<td>(5.4%)</td>
<td>(23.4%)</td>
<td>(39.2%)</td>
<td>(10.7%)</td>
<td>(9.1%)</td>
<td>(11.0%)</td>
<td>(8.6%)</td>
<td>(1.9%)</td>
</tr>
</tbody>
</table>

% of Pts

Overview of Bicarbonate Study

Pre & Post HD Serum Bicarbonate vs. Dialysate Total Buffer
2007 October Blood Draw Data (Proton ONLY)
(N = 22,101)

Delta Bicarbonate Distribution by Bicarbonate Dialysate Total

Pre Dialysis Bicarbonate
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Bicarbonate Dialysate Total

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<td>(8.6%)</td>
<td>(1.9%)</td>
</tr>
</tbody>
</table>

% of Pts
In figure 6, the distribution of aggregated post-dialysis bicarbonate levels is displayed in relationship to total buffer exposure during the treatment. In conjunction with figures 5a & 5b this suggests not only that the obvious reduced buffer gradient mitigates bicarbonate excursions, but internal acid/base regulation may also contribute to the observed mitigation of larger acid/base excursion.

**FIGURE 6: Post Bicarbonate Levels by Total Buffer Concentration**

![Graph showing distribution of post-dialysis bicarbonate levels by total buffer concentration.](image)

**Other Potential Buffering Sources in ESRD Patients**

Alkalosis in patients with ESRD is complex and may involve numerous conditions and external sources of base beyond dialysate composition. These include the various acute and chronic conditions that lead to volume contraction, loss of acid or respiratory system pathophysiology. There are also sources of buffer in the patient’s diet and medications.9,10 One such area examined was the association of phosphate binders to elevated pre-dialysis serum bicarbonate levels. In a single time analysis in January 2012 of 125,539 patients, the percentage of patients with a 3 month average serum bicarbonate level > 28 mEq/L suggests a slight increase in patients using carbonate based phosphate binders, as follows:

<table>
<thead>
<tr>
<th>Phosphate Binder</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Sevelamer Hydrochloride</td>
<td>9.2%</td>
</tr>
<tr>
<td>Calcium Acetate</td>
<td>9.4%</td>
</tr>
<tr>
<td>Lanthanum Carbonate &amp; Other</td>
<td>10.1%</td>
</tr>
<tr>
<td>Sevelamer Carbonate</td>
<td>10.5%</td>
</tr>
</tbody>
</table>
As with the analysis of bicarbonate based dialysate, this information suggests that an association exists, but does not elucidate pathophysiology or impute causation for any specific outcome. These agents represent potential contributors to the state of acid/base balance for a given patient. Further study and analysis of contributors to both acidosis and alkalosis is warranted when these states are persistent in patients with bicarbonate levels <20 mEq/L or >28 mEq/L.

**Insights into the Interpretation of the “Odds Ratio” Analysis**

It is important to avoid misinterpretation from the statistical methods used in the risk analyses that we perform. When a case control study is performed, as was the case last November, the Odds Ratio Analysis conclusions should be limited to those supported by the analysis. Specifically, the finding was that in a cohort of patients who were known to suffer a CPA event there was a 4-6 times greater chance of having had a pre-dialysis serum bicarbonate level > 28 mEq/L. These statistics show the association of bicarbonate to the known event, but do not necessarily imply the converse statement, that a patient with serum bicarbonate of > 28 mEq/L has a 4-6 times higher risk of a CPA event. This inference should be considered within the context of the rarity of occurrence of such events and with regard to other factors that may coexist with a high bicarbonate level that could predispose a patient to a CPA event.

Recent statements demonstrate some confusion in the interpretation of the higher relative risk of having an elevated last available pre-dialysis serum bicarbonate level in patients with cardio-pulmonary arrest in the facility (“cases”) vs. patients who did not experience the event (“controls”). The higher relative risk highlights overrepresentation of certain characteristics of the cases that differed from the controls. However, it does not represent an absolute risk estimate or prediction of control patients to have the event.

This concept is supported by the periodic analysis that FMCNA performs to look at the relative risk of death. These analyses show that the relative mortality risk across the entire population associated with both low (<20 mEq/L) and high serum bicarbonate (>28 mEq/L) is approximately 1.3 times when compared to specific reference levels. This supports a long held position by the Medical Office that those prescribing dialysis should take the acid/base status of their patients into consideration when prescribing dialysis and that the concept of total buffer should be considered in conjunction with these prescriptions. Figure 7 shows these analyses for bicarbonate from 2004, 2007, 2008 and 2011. It is important to focus on the case mix, laboratory and nutrition analyses (the white bars). This analysis shows the importance of malnutrition in confounding the bicarbonate data.
FIGURE 7: Mortality Analyses for FMS related to Bicarbonate

Analysis of 2004 FMS Data

Follow-up Analysis of 2007 FMS Data
Analysis of the Current Acid/Base Status of Patients on Hemodialysis

To give a picture of the acid/base status of FMCNA dialysis patients the following graphs provide a view of recent acidosis and alkalosis distributions. Figure 8 shows the overall distribution of serum bicarbonate levels in June 2012. These data show 11.2% of patients have pre dialysis serum bicarbonate levels below 20 mEq/L and 6.2% of patients have pre dialysis serum bicarbonate levels above 28 mEq/L. As previously mentioned both of these conditions should generate physician consideration of a therapeutic approach to bring these patients to the middle of the bicarbonate distribution whenever possible.
Impact of Dry versus Liquid Acid Concentrate

Figure 9 displays the pre-dialysis serum bicarbonate distribution for 13,931 patients who were treated with either liquid or dry acid concentrate mixtures. The mean pre-dialysis serum bicarbonate among these two cohorts differs by 0.7 mEq/L.

**Figure 9: Distribution of Serum Bicarbonate by Concentrate Type-2012**
Conclusions

In summary, the acid/base status of ESRD patients is important. Both extremes of acidosis and alkalosis are associated with undesirable outcomes and should be factored into the decision making process when prescribing therapy for dialysis patients. Those prescribing dialysis should avoid, to the extent the patient’s primary and secondary medical conditions will allow, such extremes. The additional analyses regarding buffer presented here provide further guidance to prescribing physicians who are making decisions for treatment as follows:

1. If acidosis is present then the adjustment of dialysis parameters including dialysis time and/or dialysate composition may provide a way to mitigate persistent acidosis.

2. If alkalosis is present, then the adjustment of dialysate total buffer content is an appropriate and reasonable clinical approach. Reducing external sources of buffer, such as buffer containing phosphate binders, other carbonate based oral medications and dietary adjustments may be considered as adjunctive options.

3. All bicarbonate based dialysis products deliver additional buffering capacity through mixing and metabolism of acetate, acetic acid or citric acid when mixed for dialysate. The following chart shows the degree that each contributes additional buffer. Prescribing providers should be aware of the buffering capacity of the products outlined below.

4. A pre dialysis serum bicarbonate level is a reasonable, but not perfect measure of a patient’s state of acid/base balance. The test has a degree of variability that requires the clinician to look at the values with knowledge of the patient’s conditions that may affect acid/base balance. It remains useful in assessing the overall metabolic state of patients undergoing hemodialysis.

5. Many questions have not been answered with respect to the nature of events that lead to cardiopulmonary arrest in ESRD patients and further study of these rare events should be carried out to determine if any opportunities exist to avoid this serious adverse event by understanding clinical conditions, treatments and laboratory assessments.

### Available Acid Concentrates

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Acid concentrate</th>
<th>Acetic acid (mEq/L)</th>
<th>Acetate (mEq/L)</th>
<th>Citric acid (mEq/L)</th>
<th>Sum of acetic acid, acetate and citric acid (mEq/L)</th>
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<tr>
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<td>Dryesol®</td>
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</table>

*Note: contribution of the acid concentrate to the final dialysate depends on the prescribed post reaction bicarbonate setting and the chosen acid concentrate. All acid concentrates have either acetic acid, acetate, citric acid or a combination of these.

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5. Many questions have not been answered with respect to the nature of events that lead to cardiopulmonary arrest in ESRD patients and further study of these rare events should be carried out to determine if any opportunities exist to avoid this serious adverse event by understanding clinical conditions, treatments and laboratory assessments.
The Medical Office provides this information for the consideration by our Medical Staff in an effort to help advance our understanding of what prudent practices may help patients that we serve. We look forward to further study and innovation that will help to create the highest quality, safe and efficient use of resources in the delivery of renal replacement therapy for our patients. We welcome your thoughts and recommendations as we continue our ongoing dialogue with you about the care of patients with ESRD.
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