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1. Introduction

The original dialysate sodium prescription was 126.5 mEq/L (Kolff, 1947). Before volumetric controlled ultrafiltration, sodium was removed primarily, slowly and most predictably by diffusion. With the development of high flux dialysis membranes, dialysate osmolality asserted a faster and more dramatic effect on serum osmolality. Hypotonic dialysate rapidly drops serum osmolality that leads to net fluid shift out of the vascular space, causing significant intradialytic symptoms (Stewart et al., 1972). Further, the duration of dialysis sessions was shortened as clearance of urea was improved, requiring an accelerated rate of ultrafiltration.

To counter symptoms of hypo-osmolarity and rapid ultrafiltration, dialysate sodium concentration was increased. In the early 1970s, Stewart demonstrated less cramping with sodium of 145 mEq/L than with 132 mEq/L (Stewart et al., 1972). In the early 1980s, Locatelli showed improved cardiovascular stability when sodium concentration was raised to 148 mEq/L from 142 mEq/L (Locatelli et al., 1982). As the sodium prescription increased, concerns about sodium overloading arose. In 1985, Cybulsky demonstrated worsening of hypertension in already hypertensive patients (Cybulsky et al., 1985); and Daugirdas showed increasing thirst and interdialytic weight gain (IDWG), in both level and modelled high sodium techniques (Daugirdas et al., 1985). Nevertheless, intradialytic hemodynamic stability remained a valid concern and the data were not always clear. For example, Barré showed no worsening of hypertension and pulmonary edema at [Na+] 145, 150 and 155 mEq/L (Barré, 1988). The technique of sodium modelling offered a theoretical means to attenuate the risk of sodium loading. By the early 1990s, Acchiardo advocated, “[s]odium modelling [149mEq/L dropping to 140 mEq/L] should always be used in patients being maintained on high flux dialysis” (Acchiardo & Hayden, 1991). This approach was widely practiced throughout the 1990s. After more than a decade of high sodium and sodium profiling dialysis, trends toward exacerbation of hypertension and interdialytic weight gain were becoming evident (Song, 2002).

Despite a growing body of literature on the effects of dialysis sodium, the sodium prescription is frequently overlooked or ineffectually utilized. Further, despite the increasing sophistication of dialysis delivery systems, the sodium prescription is often not adjusted to suit individual patient needs. First, we will erect a conceptual framework for understanding the dialysate sodium prescription. Second, we will review the primary literature regarding dialysate sodium and outcomes. Third, we will formulate recommendations on prescribing dialysate sodium. Finally, we will explore the technical and systems challenges to adjusting the actual sodium delivered to an individual patient.
2. Theoretical framework for consideration of dialysate sodium

2.1 The relationship of sodium to volume

Traditionally, sodium content of the body and extracellular volume are equivalent concepts. Sodium concentration is a function of osmotic regulation while total sodium content is a function volume regulation. In renal, hepatic, or cardiac impairment, excess sodium cannot be adequately offloaded, leading to extracellular fluid accumulation in the form of peripheral and pulmonary edema, and ascites. Dialysis offers a means of volume regulation in the form of ultrafiltration. Hydrostatic gradients generated across the dialysis membrane are used to remove (relatively) isotonic fluid from the vascular space. Intradialytic weight gain (IDWG) is a function of the salt and water intake between dialysis sessions. Increased IDWG is attributed to dietary non-compliance; conversely, decreased IDWG reflects excellent dietary compliance or can be a harbinger of poor nutritional status as low salt intake can parallel inadequate protein-calorie intake (Sarkar et al., 2006). These mutually confounding factors must always be recognized when designing or evaluating outcomes research evaluating IDWG. An occult source of sodium can offset even the most compliant diet: hypertonic dialysate. While the programmed hydrostatic gradient moves sodium (volume) out of the patient in the form of ultrafiltrate, osmotic gradients can move sodium in or out of the patient by diffusion.

2.2 Defining the sodium space

When dialyzing against hypertonic sodium, patient’s sodium rises – but not so much that causes adverse osmotic sequelae. Problems arise by utilizing the osmotic utility of elevated interdialytic serum sodium without weighing the volume implications. When using profiling techniques, serum sodium concentration only increased from a predialysis average of 138.6 +/- 0.2 to 141.0 +/- 0.1 when dialyzing against an average dialysate sodium of 147mEq/L (Song et al., 2002). This change is an increase in of 2.4mEq/L; multiplying by the volume of distribution of sodium in a 70 kg male patient results in 33meq of sodium transferred by diffusion. Once the set-point serum osmolality is restored by oral fluid intake, this represents just a little more than 200cc of normal saline (NS). As an osmotic agent, however, sodium’s effects are distributed beyond the extracellular fluid. A change in serum sodium reflects a change in total body osmolality, or “total body cation” (Charrast & Chazot, 2003; Gotch et al., 1980). When the extracellular sodium concentration rises, intracellular water will diffuse into the extracellular space reaching a new equilibrium: the predominant intracellular cation, potassium, would rise similarly to the extracellular sodium. Using the data presented by Song et al. (2002), an increase in serum sodium of 2.4mEq/L could be multiplied across the total body water; in a 70 kg person this would result in a net diffusion of 100meq of sodium, equivalent to 650cc of NS. Based on these calculations, the increase in IDWG should be between 0.20kg (ΔNa+ ≈ Δextracellular volume) and 0.65kg (Δsodium ≈ Δtotal body cation). The measured increase in IDWG, however, was greater than either calculated value. IDWG increased by 1.20kg. It is clear that the “osmolar space” is greater than the total body water. The body must be able to store sodium/osmoles outside the osmolar pool.

2.3 Non-Osmotic sodium

Increasing serum osmolality causes increased thirst leading to rapid re-accumulation of volume. As demonstrated above, this cannot account for all the sodium/volume transfer of hypertonic dialysate. Hypertonic dialysate causes sodium to accumulate in the extracellular
matrix in a concentration dependent, non-osmotic fashion. In a now classic experiment, Saul Farber, Maxwell Schubert, and Nancy Schuster demonstrated how sodium behaves in connective tissue (Farber et al., 1957). Completely ionized chondroitin sulfate can complex with “counterions” at a ratio of 1:100. Every mol of chondroitin can associate with 100 mols of sodium- thereby reducing soluble (osmotically active) sodium. The proportion of sodium complexed with chondroitin is positively correlated to the concentration of sodium in the surrounding solution. In addition to chondroitin sulfate, hyaluronic acid and other mucopolysaccharides can interact with multiple sodium ions (Dunstone, 1959; Schubert, 1964). Given relative equal binding capacity of chondroitin sulfate for most cations (Na+, K+, Mg2+, Ca2+, Sr2+, Ba2+), the relative concentration will determine the quantity of ion bound to the polyanion (Woodbury, 1956). Therefore, when the serum sodium concentration is increased (such as when dialyzing against a high sodium dialysate), it follows that the sodium content of the mucopolysaccharides will also increase. As each ion of sodium complexes with a polyanion, it leaves the osmotic pool, leaving a lower serum sodium concentration - restoring the dialysate:serum sodium gradient. Sodium will continue to diffuse into the patient until the polyanions are saturated while the patient osmolality will not rise appreciably. Thus, the net transfer of sodium into the patient will be much more than simply the difference between the predialysis and postdialysis serum sodium as demonstrated by the calculations in paragraph 2.2. When dialysis is complete, water intake will eventually restore serum sodium to the set-point determined by the hypothalamic osmostat. The mucopolysaccharide sodium reservoir will release sodium into the osmotic pool, stimulating thirst and driving extracellular volume expansion.

Polyanions are ubiquitously distributed: bone (Woodbury, 1956), cartilage (Dunstone, 1959), blood vessels (Tobain et al., 1961), liver, intestine, brain, kidney (Law, 1984), lung and skin (Titze et al., 2003). Given this distribution, it should not be surprising that extracellular, soluble sodium makes up approximately 75% of total body sodium (Bergstrom, 1955). Therefore, 25% of total body sodium is sequestered out of the extracellular osmotic pool. The amplitude of the effect of non-osmotic sodium reservoirs should be significant. The typical acid/base cycle in hemodialysis patients amplify pathologic sodium binding & release of polyanions, especially those of bone. Approximately 25% of total body sodium is sequestered in the bone and cartilage (Harrison, 1936). Thirty to forty percent of skeletal sodium is exchangeable with circulating sodium every 24hrs (Kaltreider, 1941; Forbes & Perley, 1951; Forbes & Lewis, 1956). During acidosis, sodium is freed from the bone, the hydrogen ion displacing the sodium ion (Levitt, 1955; Bergstrom, 1955). This model approximates the interdialytic period. The inverse process occurs during dialysis; as pH rapidly corrects, H+ ions disassociate from bone easily leaving room for sodium – a process amplified by high dialysate sodium. After dialysis, pH begins to fall; hydrogen ions reaccumulate, displacing bound sodium back into the osmotically active sodium pool, driving volume expansion.

Polyanions are not a static quantity. A high sodium environment leads to increased glycosaminoglycans synthesis: the expression mRNA of various enzymes for the synthesis of glycosaminoglycans increases 120% to 210% during high sodium intake (Heer, 2009). Increased polyanion synthesis leads to an expansion of the non-osmotic sodium pool. Further, there is increasing evidence that hypertonic stress and sodium overload stimulate mononuclear phagocyte system cells to release vascular endothelial growth factor C (VEGF-C) promoting lymphangiogenesis (Titze & Machnik, 2010). Thus, hypertonic dialysate may stimulate the creation of reservoirs for further sodium storage.
3. Review of the primary literature: dialysate sodium and outcomes

At least fourteen studies can be identified that examine the relationship between variation in the dialysate sodium prescription and various clinical measures. Four retrospective, case-control studies and ten prospective, cohort studies were identified. Three additional studies examine variation of dialysate conductivity in a similar manner.

3.1 Retrospective studies

As seen in Table 1, we identified four retrospective studies evaluating the relationship between dialysate sodium and interdialytic weight gain and blood pressure control. In these chart-review approaches, patients were compared in a case-control manner. In two studies, 58 patients dialyzed against the same sodium bath of 143mEq/L (Keen & Gotch, 2007; Levin et al., 2001). Patient’s pre-dialysis serum sodium ‘set point’ was compared to the dialysate sodium resulting in a positive or negative “sodium gradient.” Patients with a negative gradient had a serum sodium concentration greater than the dialysate sodium concentration; these patients had better interdialytic weight gain and improved blood pressure control than those with a positive gradient, without any change in intradialytic hypotension. Therefore, the lower the dialysate (compared to the patient’s sodium) the better the IDWG and BP control.

In the two audits, patients dialyzing against a relatively lower sodium concentration had less IDWG (Davenport 2006, 2008). In the initial study, lower dialysate sodium was correlated with an improvement in BP control (defined as decrease in pre-dialysis blood pressure or number of antihypertensives prescribed). However, in the larger follow-up study, this relationship did not hold. It must be remembered that this retrospective design cannot account for the prescribing physicians reasons for the choice of dialysate sodium. It is likely that hypotension prone patients would be prescribed a higher sodium bath and less antihypertensives.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Dialysate [Na+] (mEq/L)</th>
<th>Effect of Lower Dialysate [Na+] on IDWG</th>
<th>BP Control</th>
<th>Intradialytic hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keen, Gotch (2007)</td>
<td>58</td>
<td>143 c/w patient’s set point&lt;sup&gt;a&lt;/sup&gt;</td>
<td>improved</td>
<td>improved</td>
<td>no change</td>
</tr>
<tr>
<td>Levin, Keen (2001)</td>
<td>58</td>
<td>143 c/w patient’s set point&lt;sup&gt;a&lt;/sup&gt;</td>
<td>improved</td>
<td>improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Davenport (2006)</td>
<td>469</td>
<td>136-139, 140, &gt;140</td>
<td>improved</td>
<td>improved</td>
<td>no change</td>
</tr>
<tr>
<td>Davenport (2008)</td>
<td>2187</td>
<td>136-139, 140, &gt;140</td>
<td>improved</td>
<td>no change</td>
<td>improved</td>
</tr>
</tbody>
</table>

Table 1. Four retrospective studies examining the relationship of dialysate sodium prescription on interdialytic weight gain (IDWG), Blood Pressure (BP) Control, and Intradialytic hypotension. BP control is defined as improved pre-dialysis blood pressure measures and/or reduction in number of antihypertensives prescribed. n = number of patients in the study. c/w = ’compared with’. N/A = data not available. <sup>a</sup>“Set Point” was defined as mean monthly predialysis plasma sodium concentration.
3.2 Prospective studies
As seen in Table 2, we identified ten (10) prospective involving 165 patients evaluating the relationship between the dialysate sodium prescription and IDWG, BP control, intradialytic hypotension and thirst.

3.2.1 IDWG
Of the nine (9) prospective studies reporting data on IDWG, eight (8) showed statistically significant improvement in IDWG during dialysis on the lower sodium dialysate. The one study that did not show any change in IDWG compared the narrowest sodium difference (141mEq/L vs. 138 mEq/L), making it the most susceptible to beta error (Thein et al., 2007). This 8 month study did show a blunting of the expected seasonal increase in IDWG and BP (Argiles, 2004), perhaps due to the lower sodium dialysate used during the four months of winter typically associated with higher IDWG.

3.2.2 Blood pressure control
Six prospective studies demonstrate improvement in blood pressure control after switching patients to lower dialysate sodium. Blood pressure control is defined as reduction in predialysis blood pressure measures or reduction in number of prescribed antihypertensives. Three studies showed no change in blood pressure control. No study, however, showed worsening blood pressure on lower dialysate sodium. It seems certain that a modest reduction in dialysate sodium can have beneficial influence on blood pressure management.

3.2.3 Interdialytic hypotension
Of the five studies reporting interdialytic hypotensive events, two demonstrated more frequent hypotension on the lower sodium dialysate. The first found, 9% fewer dialysis sessions complicated by hypotension using higher dialysate sodium (Cybulsky et al., 1985). Of note, the dialysate sodium used in the “low sodium” cohort was 133mEq/L, the second lowest in all of the studies reviewed. However, given the yearlong duration of this study, the results cannot be dismissed lightly. The other study showing worsening BP stability during dialysis had an increased incident rate of approximately 10% as well (Song, 2002). These studies highlight the limitations of reducing sodium indefinitely. There is a lower limit on decreasing serum osmolality before fluid shifts into the interstitium enough to cause hypotension. Two studies showed no change in interdialytic hypotension. One had the narrowest range of dialysate sodium (Thein et al., 2007) while the other had nearly the largest (see table 2 and Daugirdas et al., 1985). One study actually demonstrated better hemodynamic stability on lower sodium dialysate highlighting the sometimes paradoxical effects of high sodium (de Paula et al., 2004): As hypertonic dialysate drives higher IDWG, ultrafiltration must increase in order to maintain steady dry weight. If IDWG becomes great enough, removing this excess fluid will put the patient at risk for intradialytic hypotension.

3.2.4 Thirst
Effect of dialysate sodium on thirst was quite variable. Thirst is probably most dependent on subjective patient factors than any other factor.
### Table 2. Ten prospective studies examining the relationship of dialysate sodium prescription on interdialytic weight gain (IDWG), Blood Pressure (BP) Control, Intradialytic Hypotension, and Thirst. BP control is defined as improved pre-dialysis blood pressure measures and/or reduction in number of antihypertensives prescribed. Estimated dry weight was not changed during these studies. n = number of patients in study. N/A = data not available.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>t (weeks)</th>
<th>Dialysate [Na+] (mEq/L)</th>
<th>Effect of Lower Dialysate [Na+] on IDWG</th>
<th>BP Control</th>
<th>Intradialytic Hypotension</th>
<th>Thirst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cybulsky (1985)</td>
<td>16</td>
<td>52</td>
<td>133, 144</td>
<td>improved&lt;sup&gt;d&lt;/sup&gt;</td>
<td>improved&lt;sup&gt;e&lt;/sup&gt;</td>
<td>worsened</td>
<td>no change</td>
</tr>
<tr>
<td>Daugirdas (1985)</td>
<td>7</td>
<td>12</td>
<td>135, 143, 160/133 model</td>
<td>improved</td>
<td>no change</td>
<td>no change</td>
<td>improved</td>
</tr>
<tr>
<td>Barré (1988)</td>
<td>5</td>
<td>24</td>
<td>145, 150, 155</td>
<td>improved</td>
<td>no change</td>
<td>N/A</td>
<td>variable</td>
</tr>
<tr>
<td>Krautzig (1998)</td>
<td>8</td>
<td>24-30</td>
<td>135, 140</td>
<td>improved&lt;sup&gt;d&lt;/sup&gt;</td>
<td>improved</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kooman (2000)</td>
<td>6</td>
<td>6</td>
<td>136, 140</td>
<td>N/A</td>
<td>no change</td>
<td>N/A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N/A</td>
</tr>
<tr>
<td>Song (2002)</td>
<td>11</td>
<td>24</td>
<td>138, 140, 147&lt;sup&gt;c&lt;/sup&gt;</td>
<td>improved</td>
<td>improved&lt;sup&gt;d&lt;/sup&gt;</td>
<td>worsened</td>
<td>N/A</td>
</tr>
<tr>
<td>de Paula (2004)</td>
<td>27</td>
<td>6</td>
<td>138, serum [Na+] x 0.95</td>
<td>improved</td>
<td>improved&lt;sup&gt;d&lt;/sup&gt;</td>
<td>improved&lt;sup&gt;d&lt;/sup&gt;</td>
<td>improved</td>
</tr>
<tr>
<td>Oliver (2004)</td>
<td>15</td>
<td>8</td>
<td>132, 137</td>
<td>improved&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>worsened</td>
</tr>
<tr>
<td>Thein (2007)</td>
<td>52</td>
<td>32</td>
<td>138, 141</td>
<td>no change</td>
<td>improved</td>
<td>no change</td>
<td>N/A</td>
</tr>
<tr>
<td>Sayarlioglu (2007)</td>
<td>18</td>
<td>8</td>
<td>‘higher’ to 137 or 135&lt;sup&gt;b&lt;/sup&gt;</td>
<td>improved</td>
<td>improved</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients on Sodium Profiling with [Na+] expressed as Time Averaged Concentration (TAC).<br>
<sup>b</sup>Patients placed on 135 if serum was below 137, and on 137 if serum was above 137 (not explained what they did if it WAS 137). No record of baseline Na+ Rx prior to the change.<br>
<sup>c</sup>Improvement was seen in the normotensive subset.<br>
<sup>d</sup>Half of the participants had an unquantified improvement.<br>
<sup>e</sup>Improvement seen in patients with baseline IDWG greater than 1kg/day.<br>
<sup>f</sup>Improvement was seen in the ‘previously hypertensive’ subset.<br>
<sup>g</sup>138 & 140 groups were improved when compared to 147 group.<br>
<sup>h</sup>There was a ‘tendency’ toward worsened intradialytic hypotension, data not reported.

### 3.3 Conductivity studies

Electrical conductivity of solutions reflects the concentration of solute in solution. Substituting conductivity measurements for concentration measurements allows real-time estimations of solute concentrations. Modeling solute clearance, sodium mass transfer, and access recirculation by differences in pre/post dialyzer conductivity represent powerful applications of this technology (Polaschegg, 1993; Locatelli et al., 1995; Petitclerc, 1999). In its most straightforward application, dialysate conductivity can be used as a surrogate for dialysate sodium concentration with one mS/cm conductivity equivalent to 10meq/L sodium. Three short, prospective studies involving 36 patients were identified which
examined the effect of lowering dialysate conductivity on blood pressure. One study showed improved control in blood pressure as conductivity was decreased (Farmer et al. 2000). Another study found improvement in blood pressure control and IDWG but worsening intradialytic hypotension with decreasing dialysate conductivity (Lambie et al., 2005). The study with the narrowest range of comparison did not show changes in any parameters (Selby et al., 2007).

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>n</th>
<th>t (weeks)</th>
<th>Approximate [Na+] (mEq/L)(^b)</th>
<th>Effect of Lower Dialysate Conductivity on IDWG</th>
<th>BP Control</th>
<th>Intradialytic Hypotension</th>
<th>Thirst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer (2000)</td>
<td>10</td>
<td>4</td>
<td>132.7, 137.7</td>
<td>no change</td>
<td>improved</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lambie (2005)</td>
<td>16</td>
<td>8(^a)</td>
<td>130, 132, 134, 136</td>
<td>improved</td>
<td>improved</td>
<td>worsened</td>
<td>N/A</td>
</tr>
<tr>
<td>Selby (2007)</td>
<td>10</td>
<td>6</td>
<td>132, 134, 136</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
</tr>
</tbody>
</table>

Table 3. Three prospective studies showing the effect of lowering dialysate conductivity on interdialytic weight gain (IDWG), Blood Pressure (BP) Control, Intradialytic Hypotension, and Thirst. Estimated dry weight was not changed during these studies. n = number of patients in study. N/A = data not available. \(^a\)Exact duration not reported, but estimated from number of stepwise changes in conductivity and duration of dialysis for each step. \(^b\)Calculated from dialysate conductivity.

4. Recommendations for the dialysate sodium prescription

4.1 Facility-wide approach

As demonstrated above, higher dialysate sodium provides questionable and inconsistent benefit for intradialytic hemodynamic stability at the cost of proven exacerbation of hypertension and interdialytic weight gain. “Lower” dialysate sodium should therefore be preferred, however, the exact definition of “lower” concentration is variable between studies. In the prospective studies, “lower” was defined from below 132 mEq/L to 145mEq/L while “higher” was defined from 137 to 155 or higher. Of the 165 patients in these studies, we could identify 131 patients where the exact high and low settings could be identified. The weighted average for the lower sodium was 137mEq/L and 143mEq/L for the higher sodium settings.

Given the number of potential barriers to crafting an individualized approach the sodium prescription for each patient, implementing a facility-wide change to 137mEq/L may be safely recommended. Typically, each dialysis unit sets a ‘usual’ dialysate sodium concentration based on the decision of the medical director. The ‘standard’ sodium can serve as the default with each provider making individualized changes based on individual patient’s needs. Therefore, the initial step is encouraging dialysis directors to choose a default dialysate sodium concentration at, or close to, 137mEq/L.

4.2 Individualized approach

Several questions must be answered when formulating an individualized dialysate sodium. Will changing dialysate sodium cause long-term changes in serum osmolality? Are serum
and dialysate sodium estimations equivalent concepts? As will be demonstrated below, predialysis serum sodium tends to be relatively constant over time, eliminating the need to measure the sodium every treatment. Further, conventions in laboratory reporting and the Gibbs-Donnan effect influence the direction of diffusive mass transfer between serum and dialysate.

4.2.1 Sodium setpoint
Pre-dialysis serum sodium remains rather constant over time. The sodium setpoint in dialysis patients is the mean monthly pre-dialysis sodium concentration. In 58 patients over 9 to 16 months, dialyzing against constant dialysate sodium of 143mEq/L, within-subject variability of serum sodium was only 0.62 +/- 0.42 mEq/L (Mean +/- 2 Standard Deviations). Further, the average serum sodium among the 58 patients was 137.3 +/- 2.5 mEq/L (mean +/- SD). Therefore, 98% of this population was dialyzing against relatively hypertonic dialysate even at the rather 'physiological' sodium of 143meq/L (Keen & Gotch, 2007).

Over the short term, the sodium set point remains constant even when dialysate sodium is manipulated. During a brief evaluation, 27 patients maintained constant pre-dialysis serum sodium despite reduction of dialysate sodium to 95% of serum sodium. The average serum sodium was 134.0 +/- 1.4 during the first 3 weeks dialyzing against 138 mEq/L and remained 134.0 +/- 1.5 (mean +/- SD) after the decrease (de Paula et al., 2004).

During longer studies it appears that the sodium set point can be influenced slightly by changes of dialysate sodium. Over an 18-week period, 11 patients had a small but statistically significant increase in pre-dialysis sodium when the time-averaged concentration (TAC) of Na+ was raised from 140 to 147 mEq/L (138.1+/-0.1 to 138.6+/-0.2) (Song et al., 2002). Similar findings were seen in subgroup analysis of 52 patients over 8 months. Patients in the upper tertile of pre-dialysis serum sodium at study entry had a small but statically significant decrease in pre-dialysis serum sodium from 141 to 140 mEq/L (p=0.003) after the dialysate sodium was dropped from 141 to 138 mEq/L (Thein et al, 2007). Several other studies show that the sodium set point may be somewhat more mutable; however, each significant change seems to be related to sub- or super-physiologic dialysate sodium concentrations (Wilkinson et al., 1977; Fischbach et al., 1988; Acchiardo & Hayden, 1991). When dialyzing across a physiologic range of dialysate sodium, however, the concept of a set point remains valid, as variation of predialysis serum sodium is less than 1% (Song et al., 2002; de Paula et al., 2004; Keen & Gotch, 2007; Thein et al, 2007).

4.2.2 Sodium measurements and Gibbs-Donnan considerations
By convention, ionometric serum sodium measurements are corrected to reflect sodium concentration in the total serum volume thereby giving results to historical results equivalent to historical flame photometry (Burnett et al., 2000). Given that sodium is distributed only in the water phase, laboratory measures will underestimate the sodium available for dialytic exchange. Actual values should be raised by 7% given usual levels of proteins and lipids. The Gibbs-Donnan effect demonstrates, however, that not all this sodium is available for dialytic exchange. Negatively charged plasma proteins interact with a portion of ionized sodium essentially removing it from the ionic pool. This effect lowers the "plasma diffusible sodium by 4-5%" (Santos, 2008), essentially cancelling out the overestimation of the lab value (Lindley, 2009). More correctly, the accounting for plasma proteins is unnecessary as lab convention and Gibbs-Donnan cancel each other out; however, lipids are uncharged and
therefore do not participate in Gibbs-Donnan. Thus diffusible serum sodium is higher than expected in proportion to the lipid content of serum. In patients with relatively normal lipids, however, this difference is small enough to be ignored. In summary, dialysate sodium set to serum sodium can be considered functionally isonatric.

4.2.3 Final individualized guidelines
The default sodium prescription should be equal the serum sodium. Dialysate with identical sodium concentration to serum keeps sodium diffusion neutral; this approach relies exclusively on ultrafiltration for mass transfer of sodium/volume. If attempting to minimize variables, an isotonic dialysate is preferred; in this way ultrafiltration is responsible for the net sodium transfer while not being silently counteracted by dialysate sodium diffusing into the patient.
Dialysate with higher sodium concentration than the patient’s serum sodium will provide a net sodium transfer into the patient. Hypertonic dialysate is only indicated chronically for non-hypertensive patients with significant, recurrent intradialytic hypotension or acutely for prevention of disequilibrium syndrome.
Dialysate with lower sodium concentration than the patient’s serum sodium will accept a net sodium transfer out of the patient. If attempting to maximize methods for BP control and IDWG management, the utilization of hypotonic dialysate is preferred, insofar as is tolerated by interdialytic symptoms.

5. Technical & systems requirements for adjustment of dialysate sodium
As with any prescription, benefits are never greater than the level of compliance. In the case of dialysate sodium, several technical and systems issues must be understood in order to modify a dialysate sodium level. Given the many daily problems that dialysis unit staff must face, awareness of the prescribed sodium can easily be overlooked. Further, both doctors and staff may not be aware of the mechanisms required to change dialysate sodium.
Depending on each unit’s equipment and dialysate formulation, changing dialysate sodium may cause changes in the other electrolytes; this can cause consternation or confusion.
Staff awareness of the importance and compliance and Medical director interventions: In our experience, despite excellent and capable dialysis staff, modifications to the sodium prescription can easily be overlooked. In our unit, dialysate is delivered from a central system. The sodium concentration “out of the wall” is determined by the concentrate formula ordered by the unit – or even determined by a corporate purchasing office. There are several points of intervention. First, medical directors, need to be aware of the level of sodium in their concentrates. There are several manufactures of dialysate concentrate each with its unique formulation. Further, some manufacturers offer a variety of sodium levels within their own product lines. One intervention could be for the medical director to select the formulation that delivers the desired default sodium – based on our recommendation this would be 137mEq/L (see Paragraph 4.1). Changing the base solution is not the only method to vary the sodium in a unit and may not be economical or practical. Even if the central supply of dialysate does not match the “Facility-Wide” prescription, the staff can change to sodium concentration at each individual dialysis machine. Dialysis unit staff should be educated regarding the importance and technique of making changes to match the prescription. This education should be done even if the central supply of dialysate has
the ‘ideal’ sodium level as eventually an “Individualized” approach should be introduced. Staff awareness, training and ‘buy in’ are the only way to deliver individualized sodium.

5.1 Review of dialysate generation
Modern dialysate contains bicarbonate; it also contains variable amounts of calcium and magnesium. If such a solution were stored for any length of time, calcium and magnesium would combine with bicarbonate and precipitate out of solution. Dialysate must also be at physiologic pH which is, unfortunately, ideal for bacterial growth. In order to avoid these untoward consequences, bicarbonate is kept separate from calcium and magnesium in separate solutions or powders. The nomenclatures for these concentrates are “Acid” and “Bicarbonate”. The Acid typically consists of sodium, chloride, potassium, magnesium, calcium, dextrose, acetate, and sometimes citrate. The Bicarbonate concentrate consists of sodium bicarbonate with some brands containing some additional sodium chloride.

Creation of dialysate is requires mixing the Acid and Bicarbonate solutions in exact proportions. This is performed in ‘real time’ in the dialysis machine based on the pre-mixed concentrates of Acid and Bicarbonate and the software programmed for each concentrate.

5.2 Concentrate formulations
All the liquid and dry concentrates in the Fresenius NaturaLyte® - 4000 Series of Acid and Bicarbonate will result in a final sodium concentration of 137 mEq/L once mixed. Fresenius Citrasate® Series results in a base sodium of 137.3 mEq/L once mixed with the NaturaLyte® Bicarbonate (Fresenius, 2010). Rockwell Medical produces three series of formulations available in dry and liquid. The Rockwell Medical R-Series results in final sodium concentrations of 138, 139, 140, 143 mEq/L. The C-Series results in 137 mEq/L. The F-Series results in 135 or 138 mEq/L (Rockwell Medical, 2009). Minntech’s Centrisol® results in a final sodium concentration of 137 mEq/L and their Renasol® results in 139,140,142, or 143 mEq/L (Minntech, 2010).

<table>
<thead>
<tr>
<th>Company/Product</th>
<th>Final Na+ (mEq/L)</th>
<th>Na+ from Acid (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresenius</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaturaLyte®</td>
<td>137</td>
<td>100</td>
</tr>
<tr>
<td>Citrasate®</td>
<td>137.3</td>
<td>100.3</td>
</tr>
<tr>
<td>Minntech</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrisol®</td>
<td>137</td>
<td>unlisted</td>
</tr>
<tr>
<td>Renasol®</td>
<td>139, 140, 142, 143</td>
<td>unlisted</td>
</tr>
<tr>
<td>Rockwell Medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-Series*</td>
<td>138, 139, 140, 143</td>
<td>79, 80, 81, 84</td>
</tr>
<tr>
<td>C-Series*</td>
<td>137</td>
<td>100</td>
</tr>
<tr>
<td>F-Series*</td>
<td>135, 138</td>
<td>100, 103</td>
</tr>
</tbody>
</table>

Table 4. The default sodium concentration of several available dialysate concentrates and the sodium contribution from the acid portion (Fresenius, 2010; Minntech, 2010; Rockwell Medical 2009). *RenalPure® Liquid Acid with SteriLyte® Liquid Bicarbonate or Dri-Sate® Dry Acid with RenalPure® Powder Bicarbonate.
5.3 Dialysate proportioning systems
Given that both the Acid and Bicarbonate concentrates contain significant sodium (sodium chloride in Acid and sodium bicarbonate in the Bicarbonate). The sodium can therefore vary by adjusting the dilution of the Acid, Bicarbonate or both. The mechanism of this variation is determined by the design and software of the dialysis machine. Each manufacturer may have slightly different approach. All models of the Fresenius 2008® series (2008H, 2008K, 2008K2, 2008T) have an explicit mechanism behind sodium variation: the amount of Acid concentrate is varied to change the sodium concentration to the target value. The other electrolytes in the Acid component will vary in proportion to the sodium change, while the electrolytes in the Bicarbonate solution will remain unchanged (Fresenius Medical Care, 2001, 2009a, 2009b, 2010). Other manufactures advertise the ability to vary sodium across a wide range. The Gambro Artis® System can vary sodium concentration from 130-160mEq/L - much wider than the Bicarbonate variability (24-38mEq/L). Therefore the majority, if not all, of the variation in sodium is produced from variation in the Acid concentrate (Gambro, 2008). Similar ranges apply to the Gambro AK96 Advance® and Bio® models: Sodium varies 130-160mEq/L and Bicarbonate 20-40mEq/L (Gambro, 2009). B.Braun’s Dialog+® has a conductivity range from 12-17mS/cm, indicating a wide range of sodium variation, however, the relative contribution of Acid and Bicarbonate portions are not readily accessible (B.Braun Medical Inc., 2009). The capability and mechanism of sodium variation for the Baxter TINA® and ARENA® systems are not easily obtainable in an “open access” format. However, given the wide use if sodium modeling over the past two decades, any modern dialysis machine probably has the capability to generate individualized sodium concentrations.

Systems like the Fresenius 2008® Series, which hold the Bicarbonate constant and vary the Acid in order to alter the sodium, will show the greatest variation in the other electrolytes in the acid component. As will be demonstrated below, however, these changes are minute and clinically irrelevant. If any of the other systems utilize a combination of Acid and Bicarbonate variations to alter sodium concentration, the changes in Acid electrolytes will be even less effected (the bicarbonate concentration would vary somewhat, however, the change would also be minimal).

5.4 Electrolyte variability during sodium individualization
The question arises, will there be a change in other electrolyte components during the sodium variation? Clinically these variations are insignificant and should not hinder the use of tailored sodium. Dialysis staff needs to be reassured of this, as many of the newer generation dialysis machines will display the changes to all electrolytes when one is changed. Some staff may see a small change in the potassium and undo the change because the potassium level does not match the prescription. Dialysis unit policy and dialysis orders should be written to accept small variation in other electrolytes during adjustment of sodium. Of note, during sodium profiling, all the acid electrolytes in the same way, resulting in wider, yet still clinically insignificant, fluctuations in the other components.

Here is an example of the nature of electrolyte variation with individualized sodium. A clinician determines that a particular patient’s individualized dialysate sodium should be 133mEq/L. Some adjustment of the dialysis machine is required as none of the available base solutions result in this a sodium of 133mEq/L. A Fresenius 2008T®, for example, manipulates the final dialysate sodium by varying concentration of the Acid component.
(Fresenius Medical Care, 2010a). If the available dialysate has a base sodium of 137mEq/L and the Acid concentrate contributes 100mEq/L (such as Fresenius NaturaLyte®, Citrasate® or Rockwell Medical C-Series), it is possible to predict the changes on the other electrolytes. Reducing the final sodium from 137 to 133 mEq/L requires reducing the Acid component from 100meq/L to 96meq/L (a change of 4%). Reducing each Acid component by 4% will give the final concentration of that component. Using a standard Acid solution, such as Fresenius NaturaLyte® Product Number 08-2201-5, contributes 100mEq/L of sodium.

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Product Number / Acid Concentration</th>
<th>New Concentration After 5meq/L Sodium Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>100</td>
<td>95 (5% reduction)</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Ca²⁺ (mEq/L)</td>
<td>2.00</td>
<td>1.90</td>
</tr>
<tr>
<td>Mg²⁺ (mEq/L)</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>105.0</td>
<td>99.8</td>
</tr>
<tr>
<td>Acetate (mEq/L)</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Dextrose (mg/dL)</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Product Number / Acid Concentration</th>
<th>New Concentration After 5meq/L Sodium Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>79</td>
<td>74 (6.33% reduction)</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Ca²⁺ (mEq/L)</td>
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<td>3.2</td>
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<tr>
<td>Mg²⁺ (mEq/L)</td>
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<td>1.4</td>
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<tr>
<td>Cl⁻ (mEq/L)</td>
<td>86</td>
<td>80.6</td>
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<tr>
<td>Acetate (mEq/L)</td>
<td>4</td>
<td>3.7</td>
</tr>
<tr>
<td>Dextrose (mg/dL)</td>
<td>200</td>
<td>187</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Product Number / Acid Concentration</th>
<th>New Concentration After 5meq/L Sodium Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>103</td>
<td>98 (4.85% reduction)</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>Ca²⁺ (mEq/L)</td>
<td>2.5</td>
<td>2.37</td>
</tr>
<tr>
<td>Mg²⁺ (mEq/L)</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>107.5</td>
<td>102.3</td>
</tr>
<tr>
<td>Acetate (mEq/L)</td>
<td>3</td>
<td>2.85</td>
</tr>
<tr>
<td>Dextrose (mg/dL)</td>
<td>200</td>
<td>190</td>
</tr>
</tbody>
</table>

Table 5. Change in electrolyte concentrations resulting from an individualized sodium prescription. This example shows what happens to the other electrolytes after a 5mEq/L reduction in dialysate sodium. The breakdown of the Acid portion of several common concentrates is shown in the center column (Rockwell Medical, 2009; Fresenius Medical Care, 2010b). Based on the percent change of Acid sodium, the resulting values for potassium, calcium, magnesium, chloride, acetate and dextrose are listed in the left column.
2.00mEq/L of potassium and 100mg/dL of dextrose (Fresenius Medical Care, 2010b). Diluting this Acid by 4% results in Na⁺ 96mEq/L, K⁺ 1.92mEq/L, and dextrose 96mg/dL. None of these changes carry a significant clinical effect. The smaller the sodium contribution of the Acid, the other electrolytes will show a larger variation. Table 5 shows the final electrolyte changes of several standard dialysate solutions when using the proportioning system to decrease the base sodium by 5mEq/L.

6. Conclusions
Dialysate sodium concentration must be prescribed for each dialysis session. Dialysate sodium standards vary from 126.5mEq/L to greater than 155mEq/L throughout the history of dialysis. While higher concentrations can be used to promote greater hemodynamic stability during dialysis, their cost is worsening hypertension and greater interdialytic weight gain. Glycosaminoglycans and other polyanions sequester sodium out of the osmotic pool and amplify the sodium gain during hypertonic dialysis causing greater effects than the traditional ‘sodium space’ model would predict. We reviewed 17 prospective and retrospective studies that quantify the effects of dialysate sodium on hypertension, interdialytic weight gain and intradialytic hypotension. In order to minimize undesired effects of high or low sodium for the most patients, “facility-wide” dialysate sodium setting of 137mEq/L should be implemented. An individualized sodium prescription can be calculated by setting dialysate sodium equal the patient’s serum sodium. This calculation can be done without adjustments since laboratory conventions and the Gibbs-Donnan effect essentially negate each other. In order to deliver a facility-wide or individualized sodium prescription, changing dialysate concentrates could be undertaken but not necessary: modern proportioning systems can adjust the dilution of dialysate Acid or Bicarbonate components. Usually the dilution of the Acid is adjusted while Bicarbonate remains constant. The other Acid electrolytes will vary by the same percentage as the sodium variation: a clinically inconsequential change.

7. Acknowledgments
MG thanks Camelia, Natalie & Kaitlyn. You are the light of my world.

8. References


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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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