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Sorbent Dialysis Systems: An Expert Commentary by Stephen R. Ash, MD, FACP

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Editor's Note:

Sorbent dialysis is an innovative technology that has been used for over 35 years and is safe and proven. Through the years, sorbent dialysis therapy has evolved greatly, and recently a technologically advanced, simple-to-use sorbent system for home hemodialysis has been developed. The Allient *Sorbent Hemodialysis System combines sorbent dialysis technology and a new blood pump with a unique, pressure-limited, 2-chamber design. Anne G. Le, PharmD, RPh, Editorial Director of Medscape Nephrology, spoke with Stephen R. Ash, MD, FACP, Clinical Assistant Professor at Indiana University School of Medicine in Indianapolis, Indiana, and Director of Research at HemoCleanse, Inc. and Ash Access Systems, Inc., in Lafayette, Indiana, about this new system and the significance of sorbent compounds in dialysis.*

Dr. Ash: Sorbent compounds are chemicals that absorb other chemicals. In dialysis, the sorbent column has allowed regeneration of dialysate, removing uremic toxins from dialysate, while replenishing other beneficial chemicals. The sorbent column was first implemented in the REDY system over 30 years ago, but in that application it was designed for acute dialysis of patients with very high BUN (blood urea nitrogen) levels in general. However, it also was used for support of patients on home dialysis for over 1 year. More recently, the *Allient* Sorbent Hemodialysis System (Renal Solutions Inc; Warrendale, Pennsylvania) has been developed, with an improved sorbent column. The sorbent column advantages for the *Allient* system are similar to the previous REDY system but have been improved. The *Allient* system includes the following innovations (Table 1).

The sorbent cartridge components are actually relatively simple. They include an activated carbon and purification layer, a urease layer, a zirconium phosphate layer, and a zirconium oxide and zirconium carbonate layer. The overall scheme is shown in Figure 1.

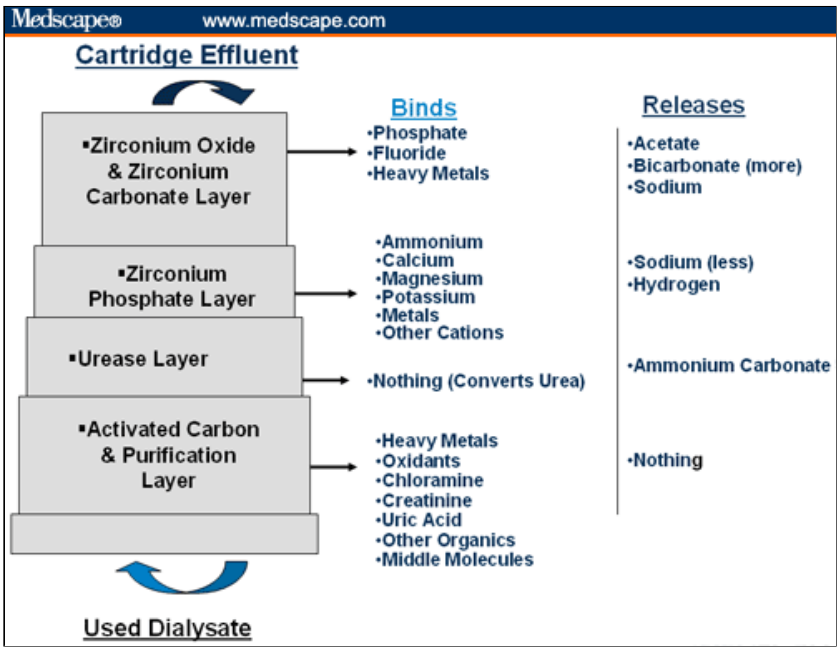

Figure 1.

The sorbent cartridge.

As you can see, the pure function of the activated carbon and purification layer is to remove organic compounds, middle molecules, uric acids, creatinine, chloramine oxidants, and heavy metals. Numerous studies have indicated that essentially all organic uremic toxins are removed by the activated carbon, with one notable exception: urea. Carbon is avid for compounds of greater than 100 molecular weight, especially ones of modest charge; so all of the other organic uremic toxins fit this category. The next layer is the urease layer, which actually binds nothing but converts urea to ammonium and carbonate. In the next layer, zirconium phosphate is loaded with hydrogen and sodium, and these are released in exchange for binding of ammonium, calcium, magnesium, potassium, metals, and other cations. The hydrogen then binds with the carbonate, essentially making CO_2. In this way, hydrogen is a "free" counter ion, disappearing after release from the column. The final layer of zirconium oxide and zirconium carbonate binds phosphate, fluoride, and heavy metals and releases acetate and bicarbonate. In the newer sorbent cartridges developed by Renal Solutions for the *Allient* system, the output is principally bicarbonate rather than acetate.

In distinction from hemodialysis, there are some compounds that are not very well removed by carbon. An example is branched-chain amino acids. The carbon is exceedingly avid for aromatic amino acids but has limited capacity for branched-chain amino acids. When used in "liver dialysis" therapy developed by HemoCleanse, we used this property to our advantage and found that we could actually add branched-chain amino acids to the dialysate saturated with carbon, allowing a return of these vital substances to patients with acute or chronic liver failure. In terms of organic compounds, Figure 2 indicates that of all the organic compounds tested, especially in comparison to drugs, creatinine is actually the one least well bound by carbon.

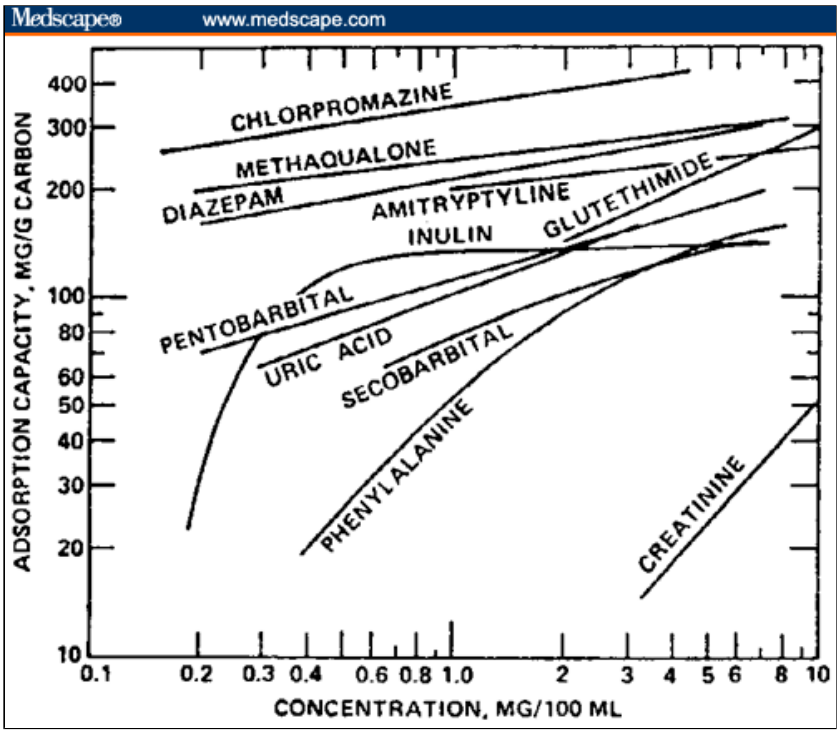

Figure 2.

Organic compounds and absorption by carbon.

In the lower right of this graph, you can see the relationship between concentration and absorption and that creatinine is actually bound only in relatively high concentrations and at relatively modest amounts. Therefore, any carbon column which binds creatinine effectively in the state of urea will certainly bind all of these other drugs or uremic substances, such as uric acid. It will also have an excess capacity for compounds, such as phenylalanine.

Whereas there used to be merely 2 sorbent cartridges, there currently are 4 choices offered by Renal Solutions for the *Allient* machine. The SORB+ and HISORB+ are designed for relatively short treatments of 3-6 hours, and the HISORB is designed for higher ranges of urea loading, from 23 g to 35 g; whereas the sorbent column is designed for total urea nitrogen load of < 23.5 g. The SORB HD and HISORB HD are designed for long therapies, such as overnight use. You therefore have the capacity to treat patients with relatively low BUNs for 6-8 hours. The SORB HD binds < 25 g of urea nitrogen, and the HISORB HD binds 15-30 g.

One limitation of sorbent devices is that there is an interplay between the chemical state of the patients and the chemical changes that occur during dialysis. We have analyzed what the major determinants of sorbent chemical function are, such as column capacity, the release of sodium, and the release of bicarbonate. In a recent paper by Ben Rosenbaum[1] that was published in *ASAIO* [journal of the American Society for Artificial Internal Organs], we looked at the determinants of column capacity for urea nitrogen, and found that the BUN level in the

patient and the volume, or the size of the patient, were the 2 most important predictors. An example of the outcome of a multivariate analysis of in-vitro work is in Figure 3.

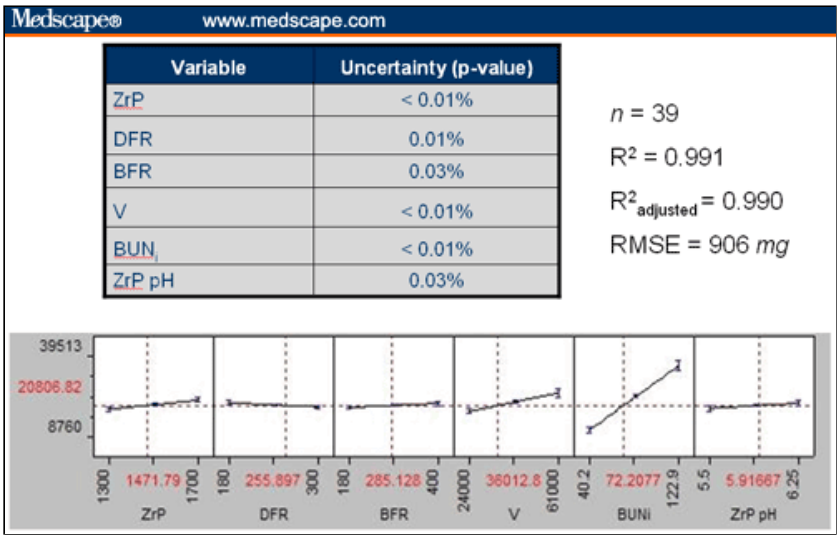

Figure 3.

Urea nitrogen capacity.

In predicting sodium release, various models have been developed. Some include patient chemistries and some do not. Model 2, which is depicted in Figure 4, indicates that the higher the volume of the patient, the greater the sodium release.

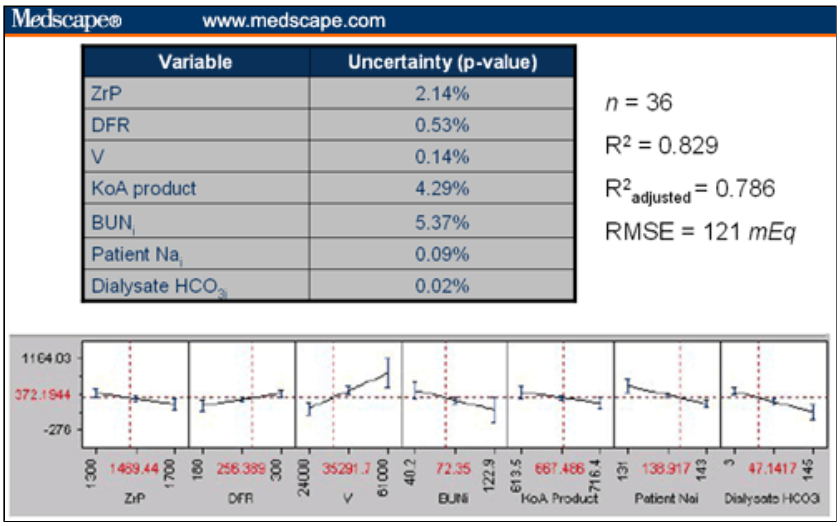

Figure 4.

Sodium release model #2.

Ironically and interestingly, the higher the BUN levels of the patient, the less sodium release. These 2 determinants may seem illogical, but they really aren't. When the BUN is higher, then there is more carbonate produced by the urease layer. The carbonate sucks hydrogen off the column, leaving a space for sodium to move onto the column. In regard to patient volume, a strong determinant of how much sodium comes off the column is sodium concentration change in the patient. Larger patients can absorb more sodium released by the column without having a significant increase in their serum concentration.

A number of improvements have been made in sorbent columns, specifically for function and the *Allient* machine. Some of these improvements are shown in Table 2 .

In the zirconium phosphate layer, the new columns have a decreased pH and, therefore, more hydrogen, less sodium, and less sodium release. The charcoal was moved to the first layer to improve water purification. Zirconium oxide was replaced principally by zirconium carbonate, which means more bicarbonate release and less pH decrease. This offset the decreased pH level in the zirconium phosphate. In all of the layers there was an increased amount of sorbent, allowing a higher dialysate flow rate. The current columns allow the *Allient* machine to run at 400 mL per minute, as opposed to 250 mL per minute for the old REDY machine; even higher dialysate flow rates may be possible. The result of all of these changes is that the sodium profile of dialysate, the pH profile, and the bicarbonate concentration are all much more stable using the current series of sorbent columns as opposed to the prior columns, plus dialysate flow rate is higher. Additionally, it is important to realize that the changes in sodium that occur in dialysate in the sorbent system represent a relatively small amount of sodium delivered to the dialysate and, therefore a relatively small amount of sodium delivered to the patient. A normal patient's water volume may be around 40 L, and in the standard hemodialysis, the dialysate volume is 3 times the patient volume; but in sorbent dialysis, the sorbent side dialysate volume is generally 6 L or less. Therefore, changes in sodium in dialysate may appear to result in transfer of sodium from dialysate to patient or vice versa, but in fact they represent little mass transfer and little effect on the patient. In numerous clinical experiments, we have demonstrated that sodium changes in patients are held within 5 milliequivalents per liter (mEq/L) of the goal during sorbent therapy.

Turning to column saturation, I have always been amazed that the sorbent column works so well in absorbing ammonium up to the point of breakthrough. Figure 5 is a photograph of a column cut open after ammonium breakthrough occurred during a clinical treatment. The zirconium phosphate layer has been stained with nihydrin.

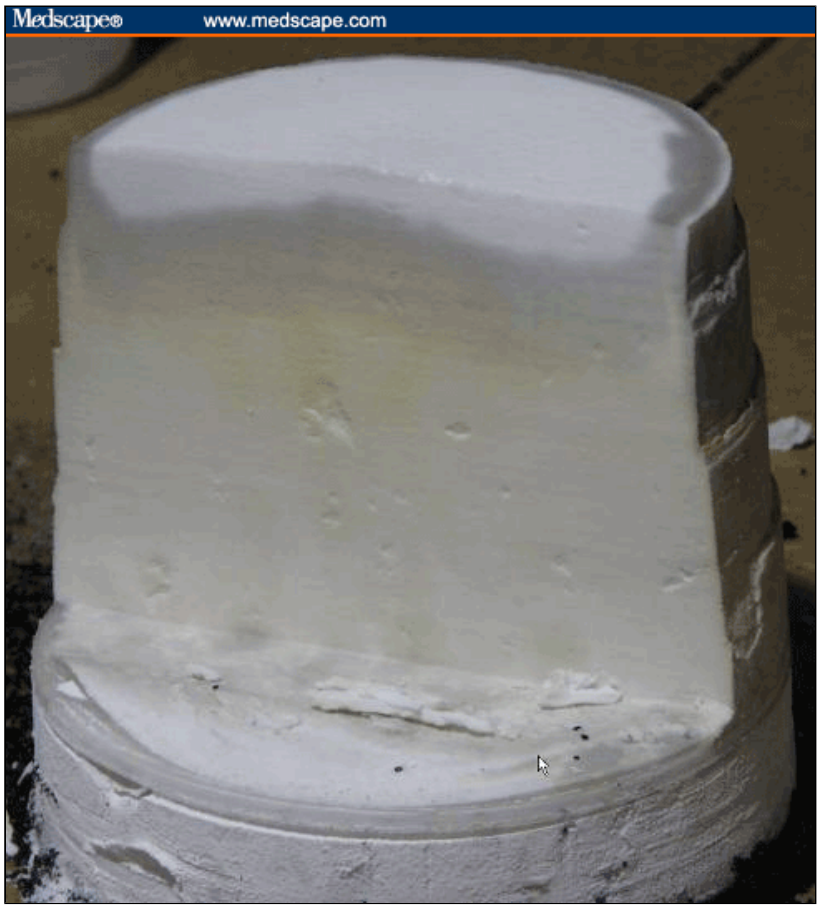

Figure 5.

Column saturation with ammonium.

As you can see, the dark band near the top of the zirconium phosphate layer, which is spent zirconium, is a very flat surface approaching the end of this layer of the column. There is only a little breakthrough at the edges. Years of experience and care in creating uniform very tiny particles of zirconium phosphate result in such uniform flow through the column. Though an ammonium sensor stops the machine when breakthrough occurs, it is annoying and disappointing to have column breakthrough with ammonia before the planned end of a patient treatment. Therefore, we have developed what's called a "prescription guide" for use of the sorbent column in the first treatment of a patient with kidney failure. This program allows us to create a bath which is approximately the right concentration of sodium bicarbonate and sodium chloride to result in the desired changes of sodium and bicarbonate in the patient during treatment, and also allows us to predict either the time of dialysis or the dialysate flow rate, which will produce about 95% column saturation. Data input in this program includes demographics, age, weight, gender, diabetes; monthly labs such as sodium bicarbonate and BUN; disposables such as the dialyzer and cartridge choice; the dialysate potassium, calcium, magnesium, blood flow rate, and desired time of dialysis or the dialysate flow rate. The

output is time in dialysis or dialysate flow rate to produce 95% column saturation and the number of packets needed for producing the starting premix dialysate. The column saturation calculation for the sorbent column is based on rather simple kinetics. As shown in Figure 6, there is a roughly linear relationship between the urea nitrogen capacity of a SORB + column, and the average post-dialyzer BUN.

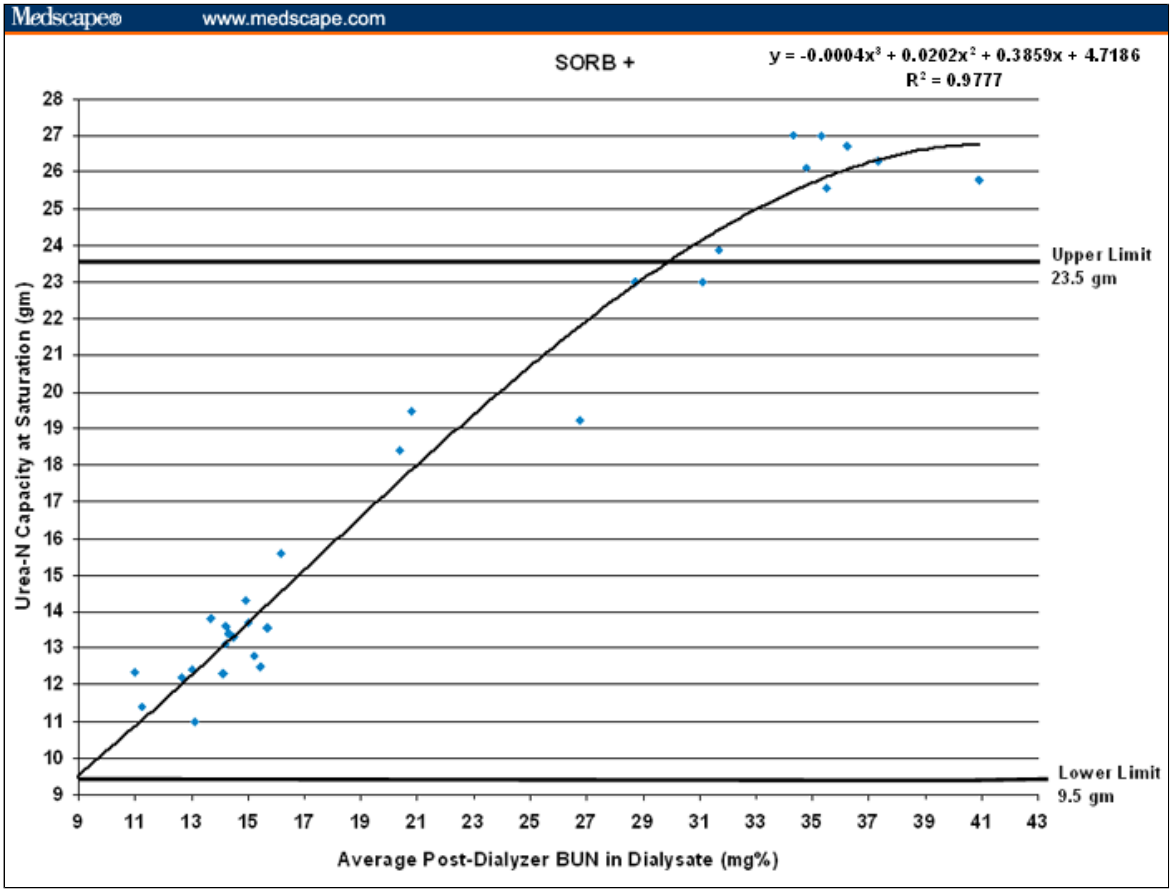

Figure 6.

Column saturation.

The program calculates the expected clearance of the dialyzer, and from that, the Daugirdas formulas predict BUN in the patient. These factors allow us to calculate the BUN level in the dialysate and therefore predict the actual column capacity. Although this is a somewhat crude model, it actually works quite well clinically and it is simple and easily verifiable from laboratory tests. Using the prescription guide, it is possible to calculate the sodium change that will occur in the patient during a single treatment period. Figure 7 is a graphic correlation between the predicted sodium change of patients using a prescription guide and the actual sodium change during clinical treatments.

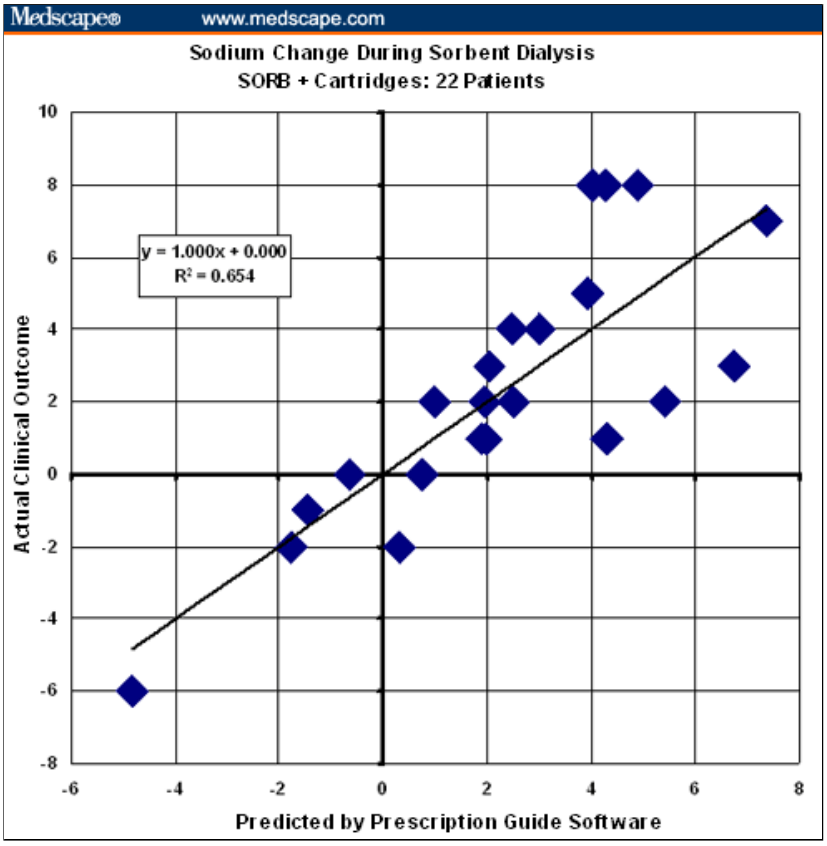

Figure 7.

Sodium change during sorbent dialysis.

As you can see, the prediction is reasonably accurate, and we can predict the sodium change in the patient within a few meq/L. Similar analysis for bicarbonate has shown that we can predict the change in sodium bicarbonate in the patient within 5 mEq/L in all treatments. Regarding overall efficiency of dialysis, the equilibrated Kt/V can be predicted almost exactly from knowledge of the clearance of the dialyzer at a particular blood flow rate and dialysate flow rate. An example of this calculation is shown in Figure 8. What this means clinically is that at the same dialysate and blood flow rate and with the same dialyzer, the *Allient* system will produce exactly the same chemical effects as any standard single-pass hemodialysis system.

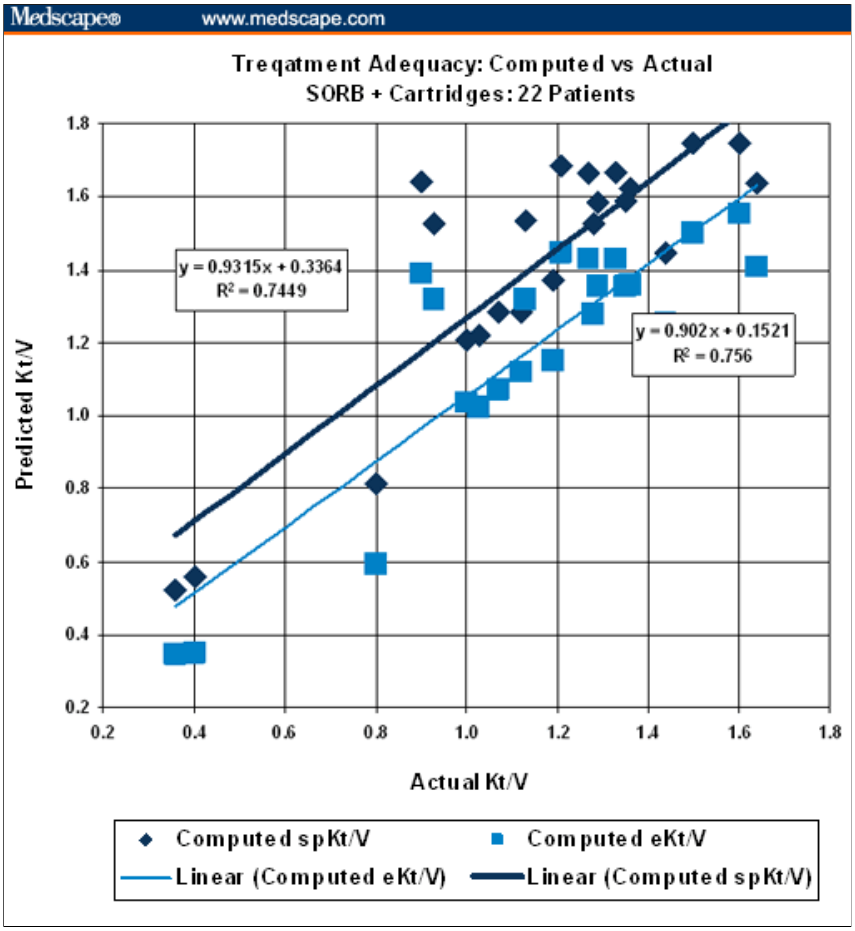

Figure 8.

Treatment adequacy.

Another advantage to sorbent dialysis systems is that they actually produce much higher purity in the dialysate than the standard single-pass system used in home or in center dialysis. Dr. Derrick L. Latos of West Virginia has done considerable work to demonstrate that with use of the current sorbent columns and starting with tap water, the *Allient* system with disposable dialysate set components produces water which is very near the ultra pure standard and easily meets the AAMI [Association for the Advancement of Medical Instrumentation] standards and European quality standards.[2] Even under huge loads of endotoxin or bacteria, the water very quickly approaches ultrapure levels after 1 hour of dialysis. Almost all bacteria and endotoxin are removed by the single-pass purification alone, which is used at the start of dialysis.

We all know the importance of ultrapure dialysate. Numerous studies have shown that ultrapure dialysate results in approved nutritional parameters.[3,4] It decreases the C-reactive protein in inflammatory cytokine production, decreases beta 2-microglobulin and advanced glycosylation endproduct, improves response to erythropoietin, and improves immune response, and preserves kidney function. When using therapies which result in greater dialysate exposure of patients, such as short daily or overnight dialysis, we must assure that water quality is as high as possible. Chronic endotoxin exposure and chronic inflammation increase production of beta 2-microglobulin and need to be minimized, especially in patients who will be on home dialysis for a long time.

Implementation of dialysis in a nonstandard location is considerably easier using a sorbent system. Whether the patient is at home or in an ICU or a ward isolation room, there are many components of single-pass dialysis that are just not needed for when the sorbent column regenerates dialysate. It's true that you need a sorbent cartridge in sorbent dialysis, which you don't need in single-pass systems, but you don't need: a water treatment system, a water softener, a reverse osmosis system, deionization tanks, water treatment installation, daily, weekly, monthly, quarterly, annual maintenance, and labor associated with all of the above. There is an improved level of safety of sorbent devices, not only by the achievement of higher dialysate purity, but also by the stability of chemistries within the sorbent system. Once the proper premix has been loaded through the column and dialysis begins, there is virtually nothing that can happen to a sorbent-based system to radically the sodium bicarbonate, potassium, calcium, or other components of a dialysate.

Over the years, the greatest challenge for sorbent regenerative dialysis systems has been to capture urea. Urea is the main chemical responsible for obtaining nitrogen balance, excreting all of the nitrogen taken in in our diet safely through the urine. Table 3 reviews a few of the basic approaches that have been tried in the past for urea removal.

Of all of these, the only practical device that has evolved for clinical use has been the sorbent column. However, this field will soon have other workable approaches to urea and ammonia removal; especially promising is work being done with zirconium silicate. As shown in Figure 9, in physiologic solution, zirconium phosphate has very low capacity for a bound ammonium in micromoles per gram. The brown line in the right lower quadrant was an improved zirconium phosphate, which bound very little ammonia when exposed also to calcium, magnesium, potassium, sodium, and bicarbonate, typical of extracellular fluid.

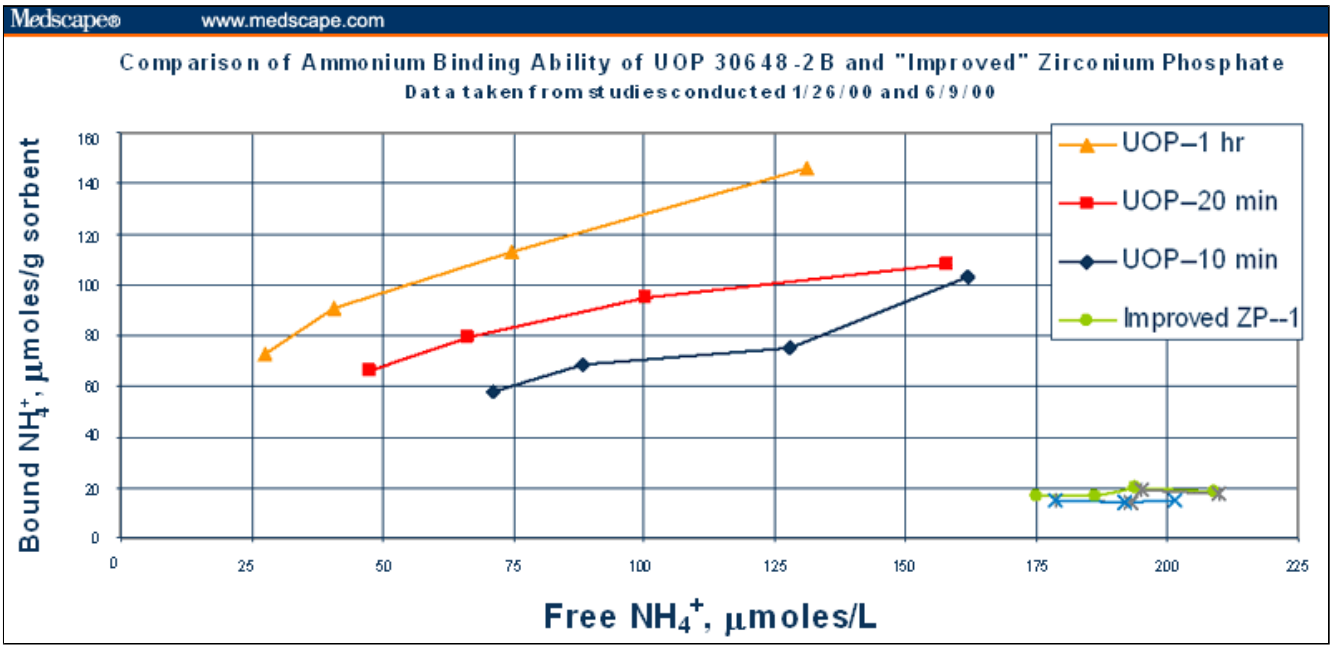

Figure 9.

Zirconium phosphate in physiologic salt concentrations.

By contrast, the UOP-manufactured compounds, which are zirconium silicates, have much greater capacity for ammonium in a physiologic solution. The reason for this is that zirconium silicates are actually ion sieves. Being crystals, they have pores at the surface and internally; and these pores are small enough that the larger hydrated radius of calcium and magnesium does not allow these divalent cations to get in, and therefore all of the internal sites are open for absorption of monovalent cations such as ammonium or potassium. Zirconium silicates have at least 10 times the functional capacity of any of the nonselective cation exchangers in a physiologic solution. Animal tests have proven that zirconium silicates can be workable as oral sorbents not only for ammonia derived from urea, but also potassium. In a study reported at the ASAIO conference in 2007, we demonstrated that by feeding zirconium silicate at 10% of food weight to rats, we could decrease the urine concentration of urea nitrogen by 33%. This meant that the clearance that we got from urea was approximately 50% of the normal kidney clearance. We also showed that the urinary potassium excretion decreased by 93% in the first few days after zirconium silicate was added to foodstuff. The potassium excretion barely recovered after foods returned to normal.

There is a promising future for oral absorbents for patients with CKD. If we had a sorbent taken orally, which would bind 3050% of the nitrogen taken in by the patient and inordinate amounts of potassium at the same time, then our patients reaching chronic kidney disease would not need severe dietary restrictions. In fact, we could ask them to eat all of the protein, potassium, and even phosphate foods that they wished. Thus, we would not have people coming to dialysis in a malnourished state, but rather with normal nutrition.

Besides improvements in sorbents for ammonium and potassium and other cations, there have also been significant improvements in charcoal that have been completed in the past 10 years. We now have the capability for mesoporous carbons to be tailor-made with pores that fit particular middle-sized molecules, such as cytokines. This carbide-derived technology developed by Drs. Yushin and Gogotsi,[8] among others, allows pore size to be matched exactly to the larger progenesis compounds, which are to be removed.

Carbon block technology, which is well known now for under-the-sink water filters, allows for high carbon density and exceedingly small particle size. In fact, the powdered carbon included in some carbon blocks is similar to the powdered carbon used in suspension in "liver dialysis." By hooking these particles together, a carbon block can be made that can be perfused at very high flow rates with no release of charcoal fines, and with very high capacity for all organic compounds, even in when in competition with each other. Nanofiber technology has come a long way, and this allows inclusion and restraint of all types of carbon particles, as well as other sorbents. Finally, fractile sphere technology, as developed by Dr. Nikolaev has shown great promise for binding toxins directly from albumin and from whole plasma.[9] In this technology, the spheres, which appear smooth on the outside, actually have tiny fractures through which plasma can flow and contact directly uncoated large active surface area with the spheres Improvements in carbon technology means that we can design smaller systems with much greater capacity for all of the organic compounds and uremic toxins we wish to remove. Further, we can begin to go after removal of strongly protein-bound toxins, either by direct hemoperfusion or by purposely placing albumin in our dialysis circuits, similar to what has been done in the MARS (molecular adsorbent recirculating system) device.

In conclusion, sorbent-based dialysis is just as effectively as single-pass systems, and in many ways is safer than single-pass dialysis. Implementation in the home and alternate locations is simplified, and the sorbent columns are well suited to wearable applications. Some chemical complexity is unavoidable with current sorbents for urea, but new sorbent systems are in evolution to increase capacity, minimize size, and simplify chemistry. Matching the economy and efficiency of the urease/cation exchange of the sorbent column is a challenge, but it is also a matter of scale and production.

Table 1. Characteristics of the *Allient* System

Completely disposable dialysate tubing set and dialysate bag replaces the tank
Automatic monitor for ammonium breakthrough
Controlled filtration based on changes in scale weight, with any dialyzer allowed
Increased column capacity for up to 8 hours of dialysis
Water purified by the column in a single-pass mode yielding highly pure dialysate from the start of dialysis
Dialysate changes in sodium, bicarbonate, and pH, which have been minimized
Automated fluid bolus and final rinse with accurate fluid measurement
Bubble detectors on inflow/outflow and saline lines to minimize air entry to the blood side
Ventricular blood pump instead of roller pump, which creates predefined blood side pressures automatically and yields optimal flow from any access
Simplified blood tubing set (no drip chambers)
Blood flow measurement on inflow and outflow lines
Single or dual access by push-button choice
Operation of a machine through a graphical user interface depicting installation, response to alarms, and assisting in training

Table 2. Changes in Sorbent Components of New Sorbent Columns

Component	Change	Result
Zirconium phosphate	Decreased pH, decreased sodium	Less sodium release
Charcoal	Moved to first layer	Improved water purification
Zirconium oxide	Added zirconium carbonate	More bicarbonate, less pH decrease
All of the above	Increased amount	Higher flow rates and clearances for longer duration

Table 3. Various Approaches to Urea Removal

Urease-cation exchanger • Sorbent system: conventional divalent-selective cation exchanger (Renal Solutions; Fresenius; Bad Homburg, Germany) • Zeolite (aluminosilicates), a monovalent-selective cation exchanger from John Sherman, Joe White, and Union Carbide • Zirconium silicate, a crystalline monovalent-selective cation exchanger (UOP from John Sherman and other collaborators) • Resin-based system proposed by Baxter • Mixed anion/cation exchangers with hydrogen hydroxide loading to avoid counterion load release, under investigation by Relypsa and Amgen (Santa Clara, California)
Direct absorption on strong acid cation exchanger, proposed by Fresenius
Urease and liquid membrane acid-filled microcapsules, proposed and developed by Bill Asher of Exxon
Direct adsorption on cold charcoal, proposed by Giordano[5]
Adsorption on gum resins, proposed by Yatzidis[6,7]

Other charged membrane and reverse osmosis membrane approaches which are in progress (Fresenius, Relypsa).

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Disclsoure: Stephen R. Ash, MD, FACP, has disclosed that he has served as chairman and consultant to HemoCleanse, Inc. Dr. Ash has also disclosed that he has served on the Medical Advisory Board of Renal Solutions, Inc.