CHAPTER 152

Composition of Hemodialysis Fluid

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OBJECTIVES

This chapter will:
1. Describe the main electrolyte components of modern dialysate.
2. Characterize clinical effects of changes in concentration of major dialysate constituents.
3. Outline the requirements for purity of dialysis water.

In a general sense, hemodialysis fluid can be considered a temporary "extension" of the patient's extracellular fluid.[1] As a result of a blood-dialysate contact via pores in extracorporeal semipermeable membranes, diffusion takes place along concentration gradients. Small uncharged solutes tend to reach similar concentrations on the two sides of a dialyzer membrane; uremic toxins from blood diffuse into toxin-free dialysate, and those solutes in higher concentration in the dialysate, such as buffers, are back-transported to the blood. Some other solutes also cross the membrane by convection, transferred by a net water movement. The countercurrent blood and dialysate flows within the dialyzer result in the generation of an internal hydrostatic pressure gradient between blood and dialysate, and back-transport from dialysate to the blood. Depending upon dialyzer design and flows, between 6 and 9 L of dialysate may be exchanged during a dialysis session in this form of internal diafiltration. Therefore the chemical, physical, and microbiologic characteristics of dialysate are crucial for safe and effective dialysis.

The complexity of modern dialysate composition has increased significantly since 1914, when 0.9% sodium chloride with some potassium was used by Abel, Rowntree, and Turner at Johns Hopkins University for dialysis in experimental animals (the history of dialysis is reviewed by Ronco et al.[2]). The problem of calcium precipitation in the presence of bicarbonate buffer was overcome in the Kolff-Brigham kidney in 1948 by bubbling carbon dioxide

through low-calcium dialysate, and intravenous calcium supplementation. In those coil-type devices, the dialyzer was immersed completely in a tank with a batch dialysate, which then was changed every 2 hours.

In the 1960s, the first central-delivery machines became available, which distributed ready-to-use fresh dialysate to dialysis stations. The typical cation composition of premade dialysate was as follows:

- Na 140 mmol/L
- K 1.5 mmol/L
- Ca 1.87 mmol/L
- Mg 0.5 mmol/L

Because the use of calcium bicarbonate as a dialysate buffer was linked to the risk of calcium precipitation and bacterial growth, bicarbonate was replaced by the more stable acetate around 1964. Because the earliest dialysis machines did not provide ultrafiltration, the original dialysates contained high concentrations of dextrose to generate an osmotic gradient designed to achieve ultrafiltration. Advances in dialysis machine technology allowed a progressive reduction in dialysate glucose concentrations and in some cases glucose-free dialysates.

After 1974, modern-type machines with bedside proportioning systems became available, which continuously improved reliability and precision of dialysate composition. Extemporaneous preparation of dialysate from treated water and concentrated solution or dry salts at the patient's bedside has made it possible to return to bicarbonate-buffered dialysis. Since that time, individualizing dialysate content for particular patient needs and maintaining water purity have been major fields of interest in dialysis practice.

With the modern dialysis machines, composition of dialysis fluid can be modified significantly to individualize the treatment. Dialysate can be made either for central delivery, or at the patient bedside, mixed by the dialysis machine. Depending upon the concentrations, dialysis grade water is proportioned with an A concentrate (containing electrolytes acetate, and acid) and a B concentrate (containing bicarbonate and sodium). After mixing, the dialysate is checked for pH meter and conductivity. Some dialysis machines are fitted with a positive feedback loop, to alter the proportioning of the solutions to achieve the desired final concentration, or simply fitted with alarms if conductivity or pH are not in range. As such, dialysis machines require calibration and servicing to ensure delivered dialysate quality.

The concentration of almost any dialysate component can be changed independently and maintained to the desired level during any given period. Meanwhile, certain "standard" dialysate prescriptions are offered in most centers and serve as the starting point for adjustments to meet patient needs.

Certainly, any change in dialysis fluid formulas will in turn change the patient's electrolyte homeostasis, with desired and undesired physiologic effects.

DIALYSATE COMPONENTS

Sodium

Sodium is the major determinant of volume and tonicity of extracellular fluids. As sodium can cross the dialyzer membrane readily, its concentration in dialysis fluid (Na_D) plays a role in cardiovascular stability during extracorporeal therapy. Acute changes in plasma sodium concentrations are known risks for brain cell damage. Long-term changes in sodium balance can affect patient morbidity via dialysis prescription noncompliance worsening of edema, and blood pressure control.

Because plasma is an aqueous solution of crystalloids and proteins, and plasma proteins (on average 70 g/L) occupy a certain volume, then the volume of plasma water is somewhat less than that of whole plasma. Therefore the concentration of sodium in plasma water, Na_{PW}, is always greater than that measured in total plasma and can be estimated using certain formulas.[3]

However, the concentration of sodium in the ultrafiltrate, Na_{UF}, is lower than that in plasma water because of the Donnan effect: some cations cannot cross the dialyzer membrane because they are retained in the blood by negatively charged proteins. When calculating the concentration of sodium available for diffusion, clinicians must correct Na_{PW} (calculated or measured) for the Donnan effect.[4,5]

Dialysate with both "high" and "low" Na_D values has been tried, with different clinical effects. Hyponatric dialysate (130 mmol/L) is reported to result in less thirst and interdialytic weight gain.[6] However, not all of the patients treated with hyponatric dialysate in one study showed an improvement in hypertension control, presumably because of high dietary sodium intake or possibly stimulated renin secretion.[7] In another study, dialytic dehydration in hyponatremic patients was obtained predominantly from the extracellular volume, with a high incidence of dialysis dysequilibrium, cramps, and hypotension.[8]

Raising Na_D from 130 to 136 mmol/L resulted in a decrease in reported muscle cramps,[9] and in another study, raising the Na_D from 132.5 through 135 mmol/L to 142 through 145 mmol/L led to lower rates of headache, nausea, and vomiting.[10,11] Moreover, some patients achieved better immediate hypertension control with higher dialysate sodium concentration, probably as a result of better achievement of "dry weight." On the other hand, when excretion of sodium is limited in anuric patients undergoing long-term dialysis, positive sodium balance at the end of dialysis sessions can contribute to thirst, greater interdialytic weight gain, and "volume-dependent" arterial hypertension over the long term.[12]

There are different approaches to "normalizing" Na_D concentration. One is to adjust it to Na_{PW}, to prevent a drop in plasma osmolarity secondary to diffusive losses.[10,13] Then, the only sodium removed is by convection. Another approach is to aim for normal sodium balance at the end of treatment. Because daily sodium and water intakes are about 100 mmol and 1 L, respectively, adequate Na_D should permit sodium and water removal in this proportion, resulting in an Na_D of approximately 145 mmol/L.[14]

With modern dialysis machines it is possible to change Na_D during the treatment continually, performing so-called sodium profiling. Usually, Na_D is hypertonic at the beginning of treatment, counteracting urea flux from cells to extracellular space while urea removal is at its peak.[15] Then Na_D is reduced progressively, approaching normal at the end of dialysis. Increased Na_D at the time of peak ultrafiltration rate can increase refilling of extracellular compartment with improved venous refill.[16,17] The limitations of using sodium profiling to limit intradialytic symptoms are the risk of positive sodium balance at the end of dialysis, difficulties in modeling complex interactions among Na_{PW}, serum protein concentration, total body water, and plasma refilling rate,[18,19] and variations in the temporal relationship between decreased circulating blood volume and hypotension.[20] The results of these studies depend upon the final dialysate sodium delivered being that which is desired, and manufacturers are allowed an error in the A and B dialysate concentrates. In the future, improved sodium kinetic

modeling may help create a software biofeedback loop based on online signals from the patient-machine complex.[21]

Potassium

In patients undergoing long-term dialysis and consuming a liberal diet, daily potassium intake varies between 60 and 80 mmol. With consideration of that fact, thrice-weekly dialysis with a potassium bath of 1.5 to 2.0 mmol/L seems to produce an acceptable potassium balance in most patients.[22] However, relative hypoinsulinemia and metabolic acidosis can shift potassium from the intracellular space to the extracellular space. Clinical scenarios of cytolysis (ischemia, hemolysis, trauma, internal bleeding), renal tubular acidosis type 4 or fasting in patients with diabetes, administration of various medicines (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs, trimethoprim, and nonselective beta blockers) also can contribute to hyperkalemia. Rapid correction of hyperkalemia in metabolic acidosis theoretically can hyperpolarize cells, with persistence of intracellular acidosis.[23] All of these factors, together with dietary variations, dictate personalization of dialysate potassium content. For life-threatening hyperkalemia, a zero-potassium bath is feasible. The contribution of dialysis with a low-potassium bath to the risks of dangerous ventricular ectopy and cardiac arrest is unclear.[24] Supraphysiologic dialysate bicarbonate concentrations in conjunction with higher acetate concentrations may exacerbate the propensity for cardiac arrhythmias by altering the QTc interval resulting from shifts of potassium between the extra- and intracellular space. For patients with poor potassium intake or increased losses through diarrhea, dialysis fluid containing 4 mmol/L of potassium can be advised.[22]

Calcium

The content of calcium in dialysate is an important component in the total management of calcium balance, and high and low serum calcium levels may in turn contribute to bone disease, cardiovascular morbidity, and mortality in patients undergoing hemodialysis.[25-27]

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) opinion, based on level III and IV evidence, recommends that in a patient with stage 5 kidney disease, the predialysis albumin-corrected serum calcium level should be kept within the normal laboratory reference range, preferably toward the lower end (2.1–2.4 mmol/L), provided that keeping serum calcium at this level does not worsen hyperparathyroidism.[28]

With the modern water treatment, the calcium content of final dialysate depends completely on composition of the liquid concentrate and therefore on dialysis prescription. To reach and maintain the goal serum calcium level, calcium concentration in dialysate may have to be individualized. The diffusible fraction of calcium, available for dialysis exchange, has been reported to be higher in uremic patients (57.6%—64.3% of total plasma calcium).[29] That amount corresponds to an average concentration of 1.6 mmol/L (6.5 mg/dL). Therefore dialysate with a calcium concentration of 1.25 to 1.75 mmol/L[30,31] likely will provide a net calcium balance close to zero, depending on the patient's calcium intake and calcium losses by convective means with ultrafiltrate. Increasing the dialysate calcium concentration to 1.75 to 2.0 mmol/L may help control hyperparathyroidism and metabolic bone disease but is linked to a risk of postdialysis hypercalcemia, arrhythmias, and hypertension[32,33] as well as decreased bone turnover.[28] On the other hand, for some patients taking calcium-containing phosphate binders and vitamin D analogues, a calcium bath containing 1.05 to 1.35 mmol/L can normalize serum ionized calcium and control osteodystrophy.[34] Generally, however, calcium dialysate levels below 1.5 mmol/L tend to promote hyperparathyroidism, even so concerns about vascular calcification and calciphylaxis have led to an increase in lower calcium dialysates of 1.0 to 1.25 mmol/L.[35,36]

For a subgroup of patients with cardiomyopathy who were undergoing hemodialysis, particularly those with left ventricular dysfunction, a dialysate calcium concentration less than 1.75 mmol/L was associated with a significant decrease in myocardial contractility[37] and intradialytic hypotension.[38,39]

Calcium-free dialysate can be used for the treatment of hypercalcemia (mean decrease in serum calcium 1.71 ± 0.54 mmol/L per session) but should be reserved for patients with hypercalcemic crisis or renal impairment because of the significant risk of adverse cardiovascular effects.[40]

Magnesium

Major guidelines do not comment on dialysate magnesium concentration, and trials of this topic with morbidity and/or mortality end points are lacking.

Magnesium is distributed predominantly intracellularly and in the bone tissue. Therefore serum magnesium levels (0.70–1.05 mmol/L) only partially reflect changes in total body magnesium content. The kidney is a major regulator of serum magnesium concentration, and renal insufficiency,[41] as well as consumption of magnesium-based drugs, can increase the serum magnesium concentration. However, the magnesium content of food and its absorption from food in patients undergoing dialysis also can be reduced, so high and low magnesium concentrations can occur.

Although only about 70% of serum magnesium is diffusible across dialysis membranes, the magnesium concentration in dialysate strongly affects total balance at the start of dialysis.[42,43] Intracellular (muscle and blood cell) magnesium content in dialysis populations seems to be normal and not to be influenced by magnesium in the dialysate, whereas extracellular fluid and bone magnesium levels change in parallel with the dialysate magnesium.[42] Although commercial dialysates contain a wide range of magnesium concentrations from 0.25 to 0.75 mmol/L, as magnesium is excreted by the kidney, patients with end-stage kidney disease are at risk of magnesium accumulation, so most dialysates contain the lower magnesium concentration of 0.5 mmol/L. In bicarbonate hemofiltration and hemodiafiltration, the replacement solution is generally magnesium free to prevent precipitation, unless bags with the option of mixing bicarbonate- and magnesium-containing components immediately before dialysis are available.

The relationship between serum magnesium levels, parathyroid hormone, and bone disease in dialysis populations is somewhat complex. Chronic hypermagnesemia seems to inhibit parathyroid hormone secretion, but to a lesser extent than was previously thought.[41,42,44] In several studies, however, decreasing dialysate magnesium concentrations for some, particularly hypermagnesemic patients from 0.5 to 0.25 mmol/L reduced the rate of osteomalacia without a change in bone resorption.[45,44] Chronic magnesium

depletion is well recognized to stimulate parathyroid hormone secretion. In one meta-analysis, 10 of 12 studies of patients undergoing hemodialysis showed a significant inverse relationship between levels of serum magnesium and serum intact parathyroid hormone,[46] even though the serum calcium concentration remained within the normal range. Four of the studies on magnesium concentration and dialysis also reported an inverse relationship between serum magnesium concentration and vascular calcification in patients undergoing hemodialysis.

Buffer

Correction of chronic metabolic acidosis is one of the tasks of renal replacement therapies. Hemodialysis cannot remove significant amounts of free hydrogen ions (H^+) because of their low concentration and rapid buffering in blood. Therefore acidosis is decreased mainly through providing alkaline equivalents (in the form of bicarbonate or acetate) that are diffusing from dialysate via concentration gradient to be consumed in blood for buffering H^+.

Acetate

Sodium salts of organic acids (NaOA) can bind H^+ according to the following formula:

$$NaOA + H_2CO_3 \rightarrow HOA + NaHCO_3$$

To deplete H^+, organic compounds should be metabolized to CO_2 and H_2O. Of all potential substrates, only acetate is used widely.

Sodium acetate has a molecular weight of 136 Da and is dissociated almost completely in body fluids because of low pK.[47] Acetate is metabolized mostly in peripheral tissues (and to a lesser extent in the liver), capturing one H^+ and forming acetyl–coenzyme A as an intermediate product. Acetyl–coenzyme A may enter via several metabolic pathways (Krebs cycle, ketone body formation, fatty acid synthesis, gluconeogenesis), and buffering is delayed until it is fully decarboxylated. Oxidation of 1 mol of acetate consumes 2 mol of O_2 and produces net 1 mol of CO_2 (1 mol of CO_2 is consumed with H^+ to form acetic acid from acetate).

About 54% of infused acetate is oxidized immediately, and the rest enters alternative pathways.[47] Consequently, if glucose-free acetate dialysate is used, this then increases ketone body and free fatty acid production[48] with decreased insulin levels. If ketone bodies persist in body fluids, they then typically dissociate, with a disappearance of their buffering effect.

The lower rate of oxidation can be explained by the fact that acetate is not commonly a major metabolic fuel. The maximal rate of acetate metabolism in normal subjects is estimated to be 5 mmol/min and seems to be lower in patients undergoing dialysis (3–4 mmol/min). When blood acetate levels exceed 7 mmol/L, blood concentrations of maleate and citrate increase,[49] with a higher risk of a continuing metabolic acidosis.

In the past, acetate replaced bicarbonate in the dialysate, with acetate concentrations ranging from 35 to 40 mmol/L. Taking into account the concurrent blood bicarbonate loss, the total amount of buffer gain at the end of a 4-hour session was 120 to 360 mmol.[2] This may not be enough to compensate for metabolic acid production during the interdialytic period, so low predialysis levels of blood bicarbonate (16–20 mmol/L) usually were observed. Moreover, the higher the dialyzer urea clearance, then the greater are expected bicarbonate losses in dialysate. Raising the acetate content of the dialysate is not a valid option to correct the lower predialysis bicarbonate concentrations, because of the risk of exceeding metabolic capacity, with resulting symptomatic metabolic acidosis and vasodilatation because of high plasma acetate levels during and after dialysis.[50,51] The major role of acetate in modern-day dialysis solutions is stabilization of ready-to-use bicarbonate and calcium-containing mixes preventing precipitation in the dialysate circuit and damage to pumps, with the great majority of the base load provided by bicarbonate.

Bicarbonate

Bicarbonate is a physiologic buffer in the body fluids. It is a part of a complex system that includes carbonic acid, carbonate, and carbon dioxide, which can be described as follows:

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3 \leftrightarrow 2H^+ + CO_3^-$$

When dissolved CO_2 leaves the system or acid is added, the reaction equilibrium shifts to the left. Carbonic anhydrase, which shifts the reaction to the right, is ubiquitous, so the carbonic acid concentration in body fluids is proportional to the dissolved CO_2 concentration. The second dissociation of carbonic acid,

$$HCO_3 \leftrightarrow H^+ + CO_3^-$$

has a pK of 9.8; usually it is not important for body fluids but can be seen in bone or in dialysis solution. In both settings, divalent cations of Mg and Ca are present, with the possibility of carbonate precipitation.

$$Ca(HCO_3)_2 \leftrightarrow CaCO_3\downarrow + H_2O + CO_2$$

Slow precipitation can start at pH higher than 7 and is inhibited by high CO_2 content. Historically the main problems with using high-bicarbonate dialysis solutions were instability and risk of bacterial contamination. The modern solution to those problems is the use of dry bicarbonate in a container (e.g., BiCart BiBag), in which saturated solution is prepared on the spot and automatically proportioned as needed.

The usual concentration of bicarbonate in dialysate, 30 to 35 mmol/L, is enough to provide a dialysate-blood gradient and repletion of buffer stores[52] in most patients.

Evidence from some small randomized trials suggests that increasing the dialysate bicarbonate concentration from 30 or 35 mmol/L to 40 mmol/L—which raised the serum bicarbonate concentration from a predialysis value less than 19 mmol/L to 23 to 24 mmol/L—may improve bone metabolism[52] and nutrition.[53] On the other hand, alkalosis may cause acute symptoms and chronic calcium deposition in vessels and other tissues. The bicarbonate profiling feature of new dialysis machines may help smooth the pH correction, but specific indications for this technique are yet to be determined.

Chloride

The chloride concentration in most dialysis fluids varies from 98 to 112 mmol/L. Because chloride and buffer are the only anions in the solution, the chloride concentration is determined by the differences between the sum of total prescribed concentrations of cations (Na, K, Ca, Mg) and

anions (acetate and bicarbonate) to maintain neutral ionic charge.

Glucose

The osmotic pressure of glucose, which was used for fluid removal during the early years of dialysis, is not important with the hydrostatic pressure-driven ultrafiltration of modern hemodialysis machines. Therefore contemporary dialysis fluids may contain from 0 to 200 mg/dL of glucose. Glucose losses of 30 ± 9 g per session have been reported with the use of dextrose-free dialysate, whereas a positive glucose balance of 15.8 ± 12 g per session was observed after the use of high-glucose dialysate (200 mg/dL). Meanwhile, the clinical significance of either positive or negative glucose parameter after dialysis is unclear, and hypertriglyceridemia and hypercholesterolemia seem to develop independently of dialysate glucose in this population.[54]

However, in critically ill patients, in children, and in some other patient groups, a physiologic concentration of glucose in dialysis fluid may help avoid hypoglycemia,[55] particularly with continuous techniques. As the number of hemodialysis patients with diabetes and treated with insulin increases, then most centers opt for a dialysate glucose of around 1 g/L to prevent hypoglycemia particularly in the postdialysis period, because insulin is not cleared by dialysis. In selected cases, the presence of glucose in the dialysate also can help counteract osmotic dysequilibrium.[56] However, glucose in a solution can be a substrate for bacteria if contamination occurs.[57]

Dialysate Quality

Treated water is the most abundant component consumed during dialysis sessions. Dialysis patients undergoing dialysis can be exposed to 300 to 600 L of water per week. Water purification to remove inorganic and organic compounds, the choice of "pure" concentrate, disinfection of dialysis machines, and control of the chemical and microbiologic purity of the final dialysate solution are paramount in achieving quality dialysis.

Different substances are removed by specific modalities applied sequentially. Combining different methods meets the standards of water purity.[58,59] First, particles (dust, sand, rust fragments) are removed by sediment or media filters. Then organic compounds (chloramine, endotoxin, various agricultural contaminants) are removed by absorbent carbon filters. Inorganic substances, such as trace elements, sodium, calcium, and fluoride, can be removed effectively by softeners, de-ionizers, and reverse osmosis equipment.

The most important substances with established toxicity for patients undergoing hemodialysis are aluminum, chlorine compounds (including trihalomethanes such as chloramine), copper, zinc, nitrates, and sulfates. Their effects include dementia, hemolytic anemia, osteomalacia, and acidosis.[58,60-66] Other monitored substances also may cause injury if present in excess amounts.[67,68]

Standards for water used in hemodialysis have been established in guidelines issued by the Association for the Advancement of Medical Instrumentation (AAMI) and European Best Practice; they are outlined in Table 152.1.

TABLE 152.1

Comparison of Maximum Water Contaminant Levels Recommended by the Association for the Advancement of Medical Instrumentation and European Pharmacopoeia

		MAXIMUM CONCENTRATION (mg/L)	
CONTAMINANT	CHEMICAL SYMBOL	AAMI	EUROPEAN PHARMACOPOEIA
Aluminum	Al	0.0100	0.0100
Antimony	Sb	0.0060	0.0060
Arsenic	As	0.0050	0.0050
Barium	Ba	0.1000	0.1000
Beryllium	Be	0.0004	0.0004
Cadmium	Cd	0.0010	0.0010
Calcium	Ca	2 (0.05 mmol/L)	2 (0.05 mmol/L)
Chloramines	NH_2Cl, $NHCl_2$, NCl_3	0.1000	0.1000
Chromium	Cr	0.0140	0.0140
Copper	Cu	0.1000	0.1000
Cyanide	CN	0.0200	0.0200
Fluoride	F	0.2000	0.2000
Free chlorine	Cl	0.5000	0.5000
Lead	Pb	0.0050	0.0050
Magnesium	Mg	4 (0.16 mmol/L)	2 (0.08 mmol/L)
Mercury	Hg	0.0002	0.0010
Nitrate	NO_3	2.0000	2.0000
Potassium	K	8 (0.2 mmol/L)	2 (0.08 mmol/L)
Selenium	Se	0.0900	0.0900
Silver	Ag	0.0050	0.0050
Sodium	Na	70 (3.0 mmol/L)	50 (2.2 mmol/L)
Sulfate	SO_4	100	100
Thallium	Tl	0.0020	0.0020
Zinc	Zn	0.1000	0.1000

Modified from European Best Practice Guidelines: Section IV: Dialysis fluid purity. *Nephrol Dial Transplant.* 2002;17(Suppl 7):45–62. Available at http://www.ndt-educational.org/images/Hemodialysis%201%20Section%20IV.pdf/
AAMI, Association for the Advancement of Medical Instrumentation.

TABLE 152.2

Comparison of Maximum Microbial Contaminant Levels in Water With Different Purity Grades, European Pharmacopoeia

MAXIMUM CONTAMINANT LEVEL	AAMI WATER	REGULAR WATER	ULTRAPURE WATER	STERILE WATER
Microbial contamination (CFU/mL)	200	100	0.1	0.000001
Bacterial endotoxins (IU/mL)	2	0.25	0.03	0.03

From European Best Practice Guidelines: Section IV: Dialysis fluid purity. *Nephrol Dial Transplant.* 2002;17(Suppl 7):45–62. Available at http://www.ndt-educational.org/images/Hemodialysis%201%20Section%20IV.pdf/
AAMI, Association for the Advancement of Medical Instrumentation.

The water cleaning system, as well as storage tanks and piping materials, can be the sources of contamination of dialysate. Most notable is bacterial contamination, with biofilm deposition, from water treatment system exhaustion, water stagnation, inaccurate disinfection of dialysis machines, and the use of infected concentrate.[69-72] As such it is preferable to have continuous water flow through dialysis ring mains, and cleaning with hot citric acid. If bleach (hypochlorite) solutions are used to clean the dialysate ring main, then careful rinsing is required to prevent patient exposure. Guidelines specify allowable levels of live bacteria (measured in colony-forming units [CFU]) and membrane components of dead gram-negative microorganisms (endotoxins of which are detected by the *Limulus* amebocyte lysate test) in dialysate water (Table 152.2). Large synthetic membranes can be placed in the dialysate line before the dialyzer to further reduce bacterial contamination and endotoxin content.[2] The resulting "ultrapure" dialysate, defined as containing less than 0.1 CFU/mL and less than 0.03 endotoxin unit per mL (EU/mL),[73,74] can improve chronic inflammation, anemia, and nutrition parameters (reviewed by Masakane[75]).[76] The European Best Practice Guidelines for Haemodialysis now recommend the use of ultrapure dialysis fluid as a goal for all patients and all modalities,[77] and ongoing debates by some other authorities about its use appear to have an economic rather than a clinical basis.[75]

CONCLUSION

Modern dialysis machines, which use pretreated water and precisely calculate dosage of dialysate concentrate components, can prepare dialysate of virtually any composition needed. To individualize dialysis prescription, it is essential to understand short-term and long-term physiologic effects of changes in dialysate composition. Given the frequency of dialysis treatments and their profound effects on patients' body fluid composition, dialysate can be viewed as one of the most important "medicines" prescribed for the uremic patient.

Key Points

1. Raising dialysate osmolarity by increasing the sodium concentration (Na_D up to 145 mmol/L) generally reduces morbidity during a dialysis session but poses the long-term risk of positive sodium balance.
2. Changes in dialysate calcium may have short-term effects on the cardiovascular system and long-term effects on hyperparathyroidism and total calcium balance.
3. The relationship between dialysate magnesium concentration and bone disorders in patients undergoing hemodialysis is complex and requires further study for clarification.
4. The main role of acetate in modern dialysate solutions is stabilization, not provision of buffer ions.
5. Bicarbonate load during dialysis provides patients with buffer stores for interdialytic periods. The long-term risks and benefits of postdialytic alkalosis versus interdialytic acidosis require further study.
6. Most problems of water contamination by chemicals are managed successfully by sequential purification in modern dialysis water treatment systems. Treated dialysate water is never sterile, but less contaminated, "ultrapure" water is increasingly being used.

Key References

4. Locatelli F, La Milia V, Violo L, et al. Optimizing haemodialysate composition. *Clin Kidney J.* 2015;8(5):580-589.
58. AAMI Standards and Recommended Practices. Dialysis, 2005 edition. Available at http://www.aami.org/standards/standards.dialysis.html/.
73. Ledebo I. Ultrapure dialysis fluid–how pure is it and do we need it? *Nephrol Dial Transplant.* 2007;22(1):20-23.

A complete reference list can be found online at ExpertConsult.com.

References

1. Smith HW. *From Fish to Philosopher*. Boston: Little Brown; 1966.
2. Ronco C, Fabris A, Feriani M. Hemodialysis fluid composition. In: Jacobs C, Kjellstrand CM, Koch KM, et al, eds. *Replacement of Renal Function by Dialysis*. 4th ed. Dor-drecht. The Netherlands: Kluwer; 1996:256.
3. Gotch FA, Lam MA, Prowitt M, et al. Preliminary clinical results with sodium-volume modeling of hemodialysis therapy. *Proc Clin Dial Transplant Forum*. 1980;10:12.
4. Locatelli F, Ponti R, Pedrini L, et al. Sodium and dialysis: A deeper insight. *Int J Artif Organs*. 1989;12:71.
5. Bosch J, Ponti R, Glabman S, et al. Sodium fluxes during hemodialysis. *Nephron*. 1987;45:860.
6. Boquin E, Parnell S, Grondin G, et al. Cross-over study of the effect of different dialysate sodium concentrations in large surface area short-term dialysis. *Proc Clin Dial Transplant Forum*. 1977;7:48.
7. Weidman P, Maxwell MH, Lupu AN, et al. Plasma rennin activity and blood pressure in terminal renal failure. *N Engl J Med*. 1971;285:757.
8. Levine J, Falk B, Henriquez M, et al. Effects of varying dialysate sodium using large surface area dialyzers. *Trans Am Soc Artif Intern Organs*. 1978;24:139.
9. Wilkinson R, Barber SG, Robson V. Cramps, thirst and hypertension in hemodialysis patient—the influence of dialysate sodium concentration. *Clin Nefrol*. 1977;7:101.
10. Redaelli B, Sforzini S, Bonoldi G, et al. Hemodialysis with "adequate" sodium concentration in dialysate. *Int J Artif Organs*. 1979;2:133.
11. Stewart WK, Fleming LV, Manuel MA. Benefits obtained by the use of high sodium dialysate during maintenance hemodialysis. *Proc Eur Dial Transplant Assoc*. 1972;9:111.
12. Charra B, Chazot C. Volume control, blood pressure and cardiovascular function: Lessons from hemodialysis treatment. *Nephron Physiol*. 2003;93:94.
13. Locatelli F, Perdini L, Ponti R, et al. Physiological and pharmacological dialysate odium concentrations. *Int J Artif Organs*. 1982;5:17.
14. Funck-Brentano JL, Man NK. Optimization of Na content in dialysis fluid. *Nephron*. 1984;36:197.
15. Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. *J Am Soc Nephrol*. 2001;12:151.
16. van Kuijk WH, Wirtz JJ, Grave W, et al. Vascular reactivity during combined ultrafiltration-haemodialysis: Influence of dialysate sodium. *Nephrol Dial Transplant*. 1996;11:323.
17. Ligtenberg G, Barnas MG, Koomans HA. Intradialytic hypotension: New insights into the mechanism of vasovagal syncope. *Nephrol Dial Transplant*. 1998;13:2745.
18. Coli L, Ursino M, De Pascalis A, et al. Evaluation of intradialytic solute and fluid kinetics: Setting up a predictive mathematical model. *Blood Purif*. 2000;18:37.
19. Iselin H, Tsinalis D, Brunner FP. Sodium balance-neutral sodium profiling does not improve dialysis tolerance. *Swiss Med Wkly*. 2001;131:635.
20. Cavalcanti S, Cavani S, Santoro A. Role of short-term regulatory mechanisms on pressure response to hemodialysis-induced hypovolemia. *Kidney Int*. 2002;61:228.
21. Locatelli F, Colzani S, Pozzoni P, et al. Sodium content and profiling. In: Ronco C, La Greca G, eds. *Hemodialysis Technology*. Contributions to Nephrology, Vol. 137. Basel: Karger; 2002:338.
22. Stewart SK. The composition of dialysis fluid. In: Maher JF, ed. *Replacement of Renal Function by Dialysis*. 3rd ed. Dordrecht, The Netherlands: Kluwer Academic; 1989:199.
23. Redaelli B, Sforzini S, Bonoldi L. Potassium removal as a factor limiting the correction of acidosis during hemodialysis. *Proc Eur Dial Transplant Assoc*. 1982;19:366.
24. Karnik AJ, Young SB, Lew NL, et al. Cardiac arrest and cardiac death in dialysis nit. *Kidney Int*. 2001;60:350.
25. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2004;44(suppl 3):S34.
26. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism. The Dialysis Outcomes Practice Patterns Study. *Kidney Int*. 2005;67:1179.
27. Lowrie EG, Lew NL. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis*. 1990;15:458.
28. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003; 42(suppl 3):S1.
29. Wing AJ. Optimum calcium concentration of dialysis fluid for maintenance haemodialysis. *BMJ*. 1968;4:145.
30. Carney SL, Gillies AHG. Effect of an optimum dialysis fluid calcium concentration on calcium mass transfer during maintenance hemodialysis. *Clin Nephrol*. 1985;24:28.
31. Goldsmith RS, Furszyfer J, Johnson WJ, et al. Calcium flux during hemodialysis. *Nephron*. 1978;20:132.
32. Zawada ET, Simmons J, Sica D. The importance of divalent ions to blood pressure regulation during hemodialysis. *Int J Artif Organs*. 1984;7:245.
33. Henrich WL, Hunt JM, Nixon JV. Increased ionized calcium and left ventricular contractility during hemodialysis. *N Engl J Med*. 1984;310:19.
34. Sawyer N, Noonan K, Altmann P, et al. High dose calcium carbonate with stepwise reduction in dialysate calcium concentration: Effective phosphate control and aluminum avoidance in hemodialysis patients. *Nephrol Dial Transplant*. 1989;4: 105.
35. Malberti F, Surian M, Montoli A, et al. Effect of dialysate calcium concentration changes on plasma calcium and PTH in dialysis patients treated with calcium carbonate and phosphate binder. In: Andreucci VE, Dal Canton A, eds. *Current Therapy in Nephrology*. Boston: Kluwer Academic; 1989:401.
36. Malberti F, Montoli A, Surian M. Long-term effect of low calcium dialysate on parathyroid activity in dialysis patients treated with calcium carbonate as a phosphate binder. *Nephrol Dial Transplant*. 1989;4:165.
37. Lang RM, Fellner SK, Neumann A, et al. Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med*. 1988;108:524.
38. Beige J, Sone J, Sharma AM, et al. Computational analysis of blood volume curves and risk of intradialytic morbid events in hemodialysis. *Kidney Int*. 2000;58:1805.
39. van der Sande FM, Cheriex EC, van Kuijk WH, et al. Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. *Am J Kidney Dis*. 1998;32:125.
40. Camus C, Charasse C, Jouannic-Montier I, et al. Calcium free hemodialysis: Experience in the treatment of 33 patients with severe hypercalcemia. *Intensive Care Med*. 1996;22:1432.
41. Schmidt P, Kotzaurek R, Zazgornic J, et al. Magnesium metabolism in patients on regular dialysis treatment. *Clin Sci*. 1971;41:131.
42. Gonella M. Plasma and tissue levels of magnesium in chronically hemodialyzed patients: Effect of dialysate magnesium levels. *Nephron*. 1983;34:141.
43. Mountokalakis TD. Magnesium metabolism in chronic renal failure. *Magnes Res*. 1990;3:121.
44. Gonella M, Calabrese G. Magnesium status in chronically haemodialyzed patients: The role of dialysate magnesium concentration. *Magnes Res*. 1989;4:259.
45. Massry SG. Magnesium homeostasis in patients with renal failure. *Contrib Nephrol*. 1984;38:175.
46. Wei M, Esbaei K, Barman J, et al. Relationship between serum magnesium, parathyroid hormone, and vascular calcification in patients on dialysis: A literature review. *Perit Dial Int*. 2006; 26:366.
47. Scutches CL, Singler MH, Teehan BP, et al. Contribution of dialysate acetate to energy metabolism: Metabolic implications. *Kidney Int*. 1983;23:57.
48. Wathen RL, Keshaviah P, Hommeyer P, et al. The metabolic effects of dialysis with and without glucose in the dialysate. *Am J Clin Nutr*. 1978;31:1870.
49. Yamakawa M, Yamamoto T, Kishimoto T, et al. Serum levels of acetate and TCA cycle intermediates during hemodialysis in relation to symptoms. *Nephron*. 1982;32:155.

50. Tolchin N, Roberts JL, Hayashi J, et al. Metabolic consequences of high mass transfer hemodialysis. *Kidney Int*. 1977;11:366.
51. Graefe U, Mlutinovich J, Follette WC, et al. Less dialysis-induced morbidity and vascular instability with bicarbonate dialysate. *Ann Intern Med*. 1978;88:332.
52. Lefebvre A, de Vernejoul MC, Gueris J, et al. Optimal correction of acidosis changes progression of dialysis osteodystrophy. *Kidney Int*. 1989;36:1112.
53. Williams AJ, Dittmer ID, McArley A, et al. High bicarbonate dialysate in haemodialysis patients: effects on acidosis and nutritional status. *Nephrol Dial Transplant*. 1997;12:2633-2637.
54. Ramirez G, Butcher DE, Morrison AD. Glucose concentration in the dialysate and lipid abnormalities in chronic hemodialysis patients. *Int J Artif Organs*. 1987;10:31.
55. Rodriguez VO, Arem R, Adrogue J. Hypoglycemia in dialysis patient. *Semin Dial*. 1995;8:95.
56. Ramirez G, Bercaw BL, Butcher DE, et al. The role of glucose in hemodialysis: The effects of glucose-free dialysate. *Am J Kidney Dis*. 1986;7:413.
57. Ward RA, Wathen R, Williams TE, et al. Hemodialysate composition and intradialytic metabolic, acid-base and potassium changes. *Kidney Int*. 1987;32:129.
58. AAMI Standards and Recommended Practices. Dialysis, 2005 edition. Available at http://www.aami.org/standards/standards.dialysis.html/.
59. The CARI Guidelines. Caring for Australians with Renal Impairment: Water Quality for Haemodialysis. July 2005. Available at http://www.cari.org.au/water_quality_for_hemodialysis_jul_2005.pdf/.
60. Association for the Advancement of Medical Instrumentation. Dialysate for Hemodialysis. Standard ANSI/AAMI RD 52:2004. Arlington, Virginia: Association for the Advancement of Medical Instrumentation, 2004.
61. Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome. *N Engl J Med*. 1976;294:184.
62. Carlson DJ, Shapiro FL. Methemoglobinemia from well water nitrates: A complication of home dialysis. *Ann Intern Med*. 1970;73:757.
63. Eaton JW, Koplin CF, Swafford HS, et al. Chlorinated urban water: A cause of dialysis-induced hemolytic anemia. *Science*. 1973;181:463.
64. Kaiser L, Schwartz KA. Aluminium-induced anemia. *Am J Kidney Dis*. 1985;6:348.
65. Petrie JJ, Row PG. Dialysis anemia caused by subacute zinc toxicity. *Lancet*. 1977;1:1178.
66. Manzler AD, Schreiner AW. Copper induced acute hemolytic anemia. *Ann Intern Med*. 1970;73:409.
67. McIvor M, Baltazar RF, Beltram J, et al. Hyperkaliemia and cardiac arrest from fluoride exposure during hemodialysis. *Am J Cardiol*. 1983;51:901.
68. Webster JD, Parker TF, Alfrey AC, et al. Acute nickel intoxication by dialysis. *Ann Intern Med*. 1980;92:631.
69. Cappelli G, Sereni L, Scialoja MG, et al. Effects of biofilm formation on haemodialysis monitor disinfection. *Nephrol Dial Transplant*. 2003;18:2105.
70. Lonnemann G. When good water goes bad: How it happens, clinical consequences and possible solutions. *Blood Purif*. 2004;22:124.
71. Ebben JP, Hirsh DN, Luehmann DA, et al. Microbiological contamination of liquid bicarbonate concentrate (LBC) for hemodialysis (HD). *Trans Am Soc Artif Intern Organs*. 1987; 33:269.
72. Man NK, Ciancioni C, Guyomard S, et al. Risks and hazards of contaminated dialysate associated with high flux membrane. *Prev Nephrol*. 1987;227.
73. Ledebo I. Ultrapure dialysis fluid—how pure is it and do we need it? *Nephrol Dial Transplant*. 2007;22:20.
74. Ledebo I, Nystrand R. Defining the microbiological quality of dialysis fluid. *Artif Organs*. 1999;23:37.
75. Masakane I. Review: Clinical usefulness of ultrapure dialysate—recent evidence and perspectives. *Ther Apher Dial*. 2006;10:348.
76. Ward RA. Ultrapure dialysate. *Semin Dial*. 2004;17:489.
77. European Best Practice Guidelines. Section IV: Dialysis fluid purity. *Nephrol Dial Transplant*. 2002;17(suppl 7):45.