

Dialysis Water as a Determinant of the Adequacy of Dialysis

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Hemodialysis patients are exposed to large volumes of water in the form of dialysate. Contaminants from the dialysate may cross the dialyzer membrane into the blood and have the potential to compromise the adequacy of dialysis. Several chemicals found commonly in drinking water have long been known to be toxic to hemodialysis patients. More recently, it has become apparent that even low levels of bacterial products in dialysate may adversely impact dialysis adequacy through their ability to stimulate an inflammatory response. Minimum levels of water and dialysate quality have been recommended to protect patients from chemical and microbiologic contaminants. Complying with these recommendations requires an appropriately designed water purification and distribution system, combined with a surveillance program designed to maintain dialysate quality.

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Webster's Dictionary defines adequate as "enough or good enough for what is required or needed." The application of this definition to dialysis presupposes that we know what is required or needed. Although National Kidney Foundation Disease Outcome Quality Initiative guidelines have established minimum targets for some aspects of dialysis, such as urea removal, anemia correction, and nutrition; targets for other aspects of the therapy are only vaguely understood. Given this gap in knowledge, defining the role of water and dialysate in determining adequate dialysis is a daunting task. There is no debate that water and dialysate should not cause overt patient injury. However, whether or not water or dialysate has a more subtle impact on dialysis adequacy and patient outcomes remains controversial. This article summarizes our current understanding of the role of water and dialysate quality in dialysis adequacy and what that means in terms of the routine delivery of dialysis. The emphasis of this article is on the impact of water and dialysate quality on patient outcomes. The effect of varying the concentration of standard dialysate components, such as calcium and bicarbonate, or of the dialysate flow rate on solute removal, are not discussed.

Exposure to Water

Water is an absolute requirement for all current renal replacement therapies except transplantation. Water is the principal component of dialysate, which establishes the concentration gradient for diffusive solute removal in hemodialysis and peritoneal dialysis, and of the replacement solution used to maintain fluid balance in hemofiltration. Water also is required for processing dialyzers for reuse. Hemodialysis patients, in particular, are exposed to large volumes of water. A typical dialysis schedule of 4 hours, 3 times per week, with a dialysate flow of 800 mL/min exposes a patient to 576 L of dialysate per week. This amount contrasts with an estimated 14 L/wk of water intake for an individual with normal renal function. In other words, a hemodialysis patient is exposed to more water in less than 2 years than an average person is in their lifetime. In hemodialysis, an inert dialyzer membrane is the only barrier between a patient and substances in the dialysate, in marked contrast to the complex barrier provided by the gastrointestinal tract after oral ingestion of water. Furthermore, the disposition of a solute once it enters the blood from the dialysate may serve to maintain a maximal concentration gradient for continued transfer. For example, the presence in plasma of carrier proteins for a metal ion, such as copper, allows continued transfer of that ion even though the whole-blood concentration is greater than that in the dialysate.¹ Finally, exposure of hemodialysis patients to substances in dialysate occurs in the absence of any capacity for renal excretion of those substances.

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Table 1 Chemical Contaminants of Water and Dialysate With Particular Toxicity in Hemodialysis Patients

Contaminant	Source*	Principal Toxicities	References
Aluminum	Raw water and municipal water	Anemia, bone disease, encephalopathy syndrome	18,29-31,71-74
Chloramine	Municipal water	Anemia	8-12
Copper	Dialysis facility	Anemia	14-16
Fluoride	Municipal water	Cardiovascular	50-52
Nitrate	Raw water	Anemia	21,22
Sulfate	Raw water	Nausea, vomiting, acidosis	54
Zinc	Dialysis facility	Anemia	17

*Raw water refers to the water used as a source of drinking water before its treatment by a municipality.

Water Quality Standards

At the beginning of chronic hemodialysis therapy, dialysate was prepared using tap water. It is well recognized that impurities in water can have an adverse impact on health. For this reason, the quality of drinking water is regulated. In the United States, the Safe Drinking Water Act (SDWA)² set maximum allowable levels for a wide range of inorganic, organic, and microbiologic contaminants based on evidence of their ability to cause harm to the general population. However, the large exposure, the limited protection afforded by the dialyzer membrane, and the lack of renal excretion means that hemodialysis patients are at far greater risk for injury from contaminants in water than are healthy persons ingesting a glass of tap water. Indeed, once the more immediate problems of hemodialysis, such as blood access, were solved, it became apparent that contaminants in tap water that were harmless to healthy persons could cause significant injury to hemodialysis patients. Paradoxically, some of these injuries were caused by substances added to drinking water to safeguard public health. Between 1960 and 1970, 7 chemical contaminants were identified as injurious to hemodialysis patients when present in tap water at concentrations harmless to healthy individuals (Table 1).

The finding that chemicals commonly found in tap water are toxic to dialysis patients led to the development of quality standards for water used to prepare dialysate. In the United States, these standards were written by the Association for the Advancement of Medical Instrumentation (AAMI),³ in consultation with the American Society for Artificial Internal Organs, and with considerable input from the Food and Drug Administration via a report prepared for the Food and Drug Administration by Keshaviah et al.⁴ The resulting standard, first published in 1982, included the following: (1) the 7 chemicals known to be toxic to hemodialysis patients; (2) chemicals normally included in dialysate; and (3) other chemicals regulated by the SDWA (Table 2). There are no clinical data to support including the latter group of chemicals in the quality standard; however, it was considered prudent to include them based on their toxicity in the general population and the increased exposure associated with hemodialysis. The maximum allowable level for each contaminant was based on clinical outcomes data for the chemicals listed in Table 1, a concentration that would not significantly alter the final dialysate concentration for substances normally included in dialysate, or one tenth of the level allowed in the

SDWA for the remaining contaminants. The quality standard also included a maximum level for bacteria. The quality standard has been revised over the years. Additional trace elements were added in 2001 and the scope of the standard was expanded to include all applications for which water is used in hemodialysis.⁵ Also, an upper limit was added for the concentration of endotoxin in the water (Table 3).

Hemodialysis patients are not treated with water, but with dialysate prepared from water and concentrates that contain the chemicals found in the final dialysate. The importance of dialysate to patient outcomes was recognized in 1982 with the inclusion, in an appendix, of a maximum bacterial count of 2,000 CFU/mL under specific culturing conditions. By the late 1990s, it was recognized that more stringent microbiologic quality control was needed for dialysate. Several organizations, including the European Renal Association⁶ and AAMI,⁷ then put

Table 2 Maximum Recommended Concentrations for Chemical Contaminants in Water Used for Hemodialysis Applications

Chemicals with known toxicity for hemodialysis patients	
Aluminum	0.01 mg/L
Chloramine	0.10 mg/L
Copper	0.10 mg/L
Fluoride	0.20 mg/L
Nitrate (as N)	2.00 mg/L
Sulfate	100 mg/L
Zinc	0.10 mg/L
Chemicals normally included in dialysate	
Calcium	2 mg/L
Magnesium	4 mg/L
Potassium	8 mg/L
Sodium	70 mg/L
Chemicals regulated by the SDWA	
Antimony	0.006 mg/L
Arsenic	0.005 mg/L
Barium	0.10 mg/L
Beryllium	0.0004 mg/L
Cadmium	0.001 mg/L
Chromium	0.014 mg/L
Lead	0.005 mg/L
Mercury	0.0002 mg/L
Selenium	0.09 mg/L
Silver	0.005 mg/L
Thallium	0.002 mg/L

Adapted from the Association for the Advancement of Medical Instrumentation.⁵

Table 3 Recommendations for the Maximum Levels of Microbiologic Contaminants in Water, Standard Dialysate, and Ultrapure Dialysate

	Water		Dialysate	
	Bacteria (CFU/mL)	Endotoxin (EU/mL)	Bacteria (CFU/mL)	Endotoxin (EU/mL)
AAMI, RD62:2001 ⁵	200	2	NS	NS
AAMI, RD52:2004 ⁷	NS	NS	200	2
ERA-EDTA ⁶	100	0.25	100*	0.25*
Ultrapure ⁶	0.1	0.03	0.1	0.03

Abbreviation: NS, not specified; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association.

*Implied.

forward recommendations that encompassed both standard dialysate and dialysate of very high microbiologic purity, referred to as *ultrapure dialysate* (Table 3). Ultrapure dialysate is prepared from standard dialysate with an additional step of ultrafiltration at the point of use.

Dialysate Quality and Clinical Outcomes

The concept of adequate dialysis implies that the dialysis procedure should not have an adverse impact on patient outcomes, either acutely or chronically. After 40 years of chronic hemodialysis, however, it is clear that contaminants derived from dialysate can have an adverse impact on a wide range of clinical outcomes, many of which already are compromised by the loss of renal function (Table 4). This section summarizes these outcomes and the water contaminants known to affect them.

Table 4 Clinical Outcomes Affected by Dialysate Contaminants

Outcome	Contaminant	References
Anemia	Aluminum	18
	Bacterial products	24,27,28
	Chloramine	8-12
	Copper	14-16
	Nitrate	21,22
	Zinc	17
Bone disease	Aluminum	29-31
	Bacterial products	44,45
	Fluoride (?)	35-37
	Strontium (?)	39,40,42
Cardiovascular complications	Bacterial products (?)	49
	Fluoride	50-52
Intradialytic complications*	Bacterial products	57,58,61,67-70
	Calcium and magnesium	53
	Copper	14-16
	Fluoride	50-52
	Nitrate	21
	Zinc	17
Neurologic complications	Aluminum	19,71-76
Nutrition	Bacterial products	79,80

*Includes symptoms such as nausea, vomiting, diarrhea, weakness, and hypotension.

Anemia

Chronic renal failure is characterized by a normochromic, normocytic anemia that arises largely from underproduction of erythropoietin secondary to the loss of functional renal mass. Before the advent of recombinant human erythropoietin, most dialysis patients had hemoglobin concentrations in the range of 6 to 8 g/dL and transfusion of red blood cells was common. In this circumstance, any insult that decreased red blood cell production or survival had a significant impact on the adequacy of therapy. Recombinant human erythropoietin has resulted in more normal hemoglobin concentrations and largely eliminated the need for transfusions. However, anything that decreases the effectiveness of erythropoietin compromises the adequacy of dialysis.

The water contaminant that has contributed to anemia in hemodialysis patients most frequently is chloramine, which is added to municipal water as an alternative disinfectant to chlorine. Chloramine oxidatively denatures hemoglobin to methemoglobin and inhibits the hexose monophosphate shunt, which normally protects red blood cells from oxidative damage.⁸ Heinz bodies, formed by precipitated denatured hemoglobin, may be seen in red blood cells.⁸ In severe cases, acute hemolysis may be evident as dark blood in the venous blood line.⁹ A chloramine concentration of 3 mg/L, which is not uncommon in tap water, can decrease red cell half-life by a factor of 3.⁹ Although the toxicity of chloramine to hemodialysis patients has been known since the 1970s, reports of chloramine-induced hemolysis continue to appear,¹⁰⁻¹³ most often because of unrecognized changes in municipal water treatment practices.

Three metals—copper, zinc, and aluminum—may cause anemia in hemodialysis patients.¹⁴⁻¹⁸ The mechanisms by which these metals cause anemia are understood incompletely. Copper may induce anemia by inhibiting key enzymes of erythrocyte metabolism, whereas zinc and aluminum may interfere with heme synthesis. High levels of copper (>5 mg/L) in dialysate are associated with nausea, vomiting, diarrhea, abdominal pain, and chilling during dialysis, followed 8 to 24 hours later by acute hemolysis.^{14,15} Methemoglobinemia may be present.^{14,16} In severe cases, the hemolysis can be fatal.¹⁴⁻¹⁶ High concentrations of copper have resulted from acidic water leaching copper from a brass coupling or a copper heating coil in the dialysis machine. Paradoxically, in 2 cases the acidic water came from a deionizer used to purify water for the preparation of dialysate.^{14,15}

Water containing high concentrations of zinc—the result of storing the water in a galvanized tank—also has been associated with anemia.¹⁷ Finally, high dialysate levels of aluminum can cause multiple toxicities in hemodialysis patients, including a microcytic hypochromic anemia.¹⁸ High dialysate aluminum levels have resulted from the leaching of aluminum from dialysis fluid circuits,¹⁹ although the most common source of aluminum is alum added to municipal water as a flocculating agent.²⁰

Nitrate, probably derived from fertilizers, has been associated with methemoglobinemia, Heinz body formation, and anemia in rural areas where the water used for dialysis was obtained from local wells.^{21,22}

In addition to chemical contaminants, it now appears that the microbiologic purity of the dialysate may affect anemia correction. Microbiologic contaminants in the dialysate are associated with inflammation in hemodialysis patients^{23,24} and the effectiveness of erythropoietin therapy is diminished by inflammation.^{25,26} A link between dialysate purity, inflammation, and responsiveness to erythropoietin is suggested by the results of a study in which point-of-use ultrafilters were used to provide dialysate of high microbiologic quality.²⁴ Patients treated with ultrafiltered dialysate required less erythropoietin to obtain a target hemoglobin concentration of 10 to 10.5 g/dL than did patients treated with standard dialysate.²⁴ In a multiple regression analysis, the plasma interleukin-6 concentration was found to be the strongest predictor of erythropoietin dose.²⁴ Other investigators have reported similar results after installing dialysate ultrafilters on individual dialysis machines.^{27,28} Spittle²⁷ reported an average decrease of 25% in erythropoietin dose over 1 year in 11 dialysis facilities, whereas Matsuhashi and Yoshioka²⁸ found a decrease in the median erythropoietin dose from 90 to 57 U/kg/wk, and an increase in median hematocrit level from 30.3% to 32.2%, in 27 patients over 5 months. In the 2 studies in which it was measured, there was a significant decrease in the serum C-reactive protein (CRP) concentration concomitant with the decrease in erythropoietin dose.^{24,27}

Bone Disease

Bone disease is common in hemodialysis patients. Although disorders of calcium, phosphate, and vitamin D metabolism are the primary cause of bone disease, substances derived from the dialysate can exacerbate it.

Aluminum is common in the raw water that serves as a source of drinking water, particularly water derived from lakes, rivers, and reservoirs—so-called *surface water*. Aluminum levels may be increased further in drinking water by the addition of alum as a flocculating agent during municipal water treatment.²⁰ Aluminum is associated with both osteomalacic and adynamic bone disease, which often is accompanied by bone pain, fracture, and muscle weakness.^{29,30} In an epidemiologic study involving 18 dialysis centers in Great Britain, Parkinson et al³¹ showed a strong correlation between the incidence of fractures and the aluminum concentration in the water used to prepare dialysate, with aluminum

levels greater than 50 $\mu\text{g/L}$ being associated with fractures in more than 20% of patients at risk. Although the exact mechanism by which aluminum causes bone disease is not understood fully, aluminum localizes at the bone mineralization front and may interfere with the deposition of new bone mineral.

Fluoride is added to many municipal water supplies at a concentration of about 50 $\mu\text{mol/L}$ as prophylaxis against dental caries. These concentrations result in uptake of 3 to 4 $\mu\text{g/min}$ during hemodialysis.³² Without renal excretion, fluoride concentrates in bone³³ and increased fluoride is associated with impaired bone mineralization and osteomalacia in animal models.³⁴ In the late 1960s, there was concern that fluoride might contribute to bone disease in hemodialysis patients.³⁵⁻³⁷ Patients treated with dialysate prepared from water containing 50 $\mu\text{mol/L}$ of fluoride have significantly greater plasma and bone fluoride levels than normal individuals.^{36,37} However, whether or not these high levels of fluoride contribute to bone disease in hemodialysis patients remains unclear.^{38,39} Moreover, it is uncertain that dialysate serves as an important source of the increased fluoride levels found in the bones of hemodialysis patients because there is no difference in bone fluoride concentration between hemodialysis patients and patients with chronic kidney disease who have never been dialyzed.³⁶

Osteomalacia also has been associated with increased bone strontium in hemodialysis patients,^{39,40} and strontium causes osteomalacia in animal models of renal failure.⁴¹ A multicenter survey of 34 dialysis centers in 23 countries showed that serum strontium concentrations in hemodialysis patients were significantly greater than those in normal subjects and that serum strontium concentrations were greatest in those patients treated with dialysate containing high levels of strontium.⁴² It remains uncertain if strontium plays a role in bone disease in hemodialysis patients. Bone strontium concentrations are reported not to correlate with indices of bone formation.³⁹ Also, increased levels of bone strontium usually are associated with increased levels of bone aluminum,^{40,42} making it difficult to establish an effect of strontium on bone independent of that of aluminum. At present, there is no regulation of the strontium concentration in the water used for dialysis or in the final dialysate (Table 2).

β_2 -microglobulin amyloidosis is a unique complication of end-stage renal disease, often manifesting as carpal tunnel syndrome, bone cysts, or a generalized arthropathy.⁴³ Baz et al⁴⁴ were the first to report an association between dialysate quality and the incidence of β_2 -microglobulin amyloidosis. In a retrospective analysis of 226 patients, these investigators observed carpal tunnel syndrome in 24 of 103 patients treated with dialysate of standard microbiologic purity for an average of 6 ± 6 years, compared with 2 of 84 patients treated with ultrapure dialysate for an average of 6.1 ± 3.2 years. The probability of carpal tunnel surgery was significantly lower in the patients treated with ultrapure dialysis. Another retrospective study determined the prevalence of several clinical manifestations of β_2 -microglobulin amyloidosis in patients treated with the same dialysis prescription for a minimum of 10 years.⁴⁵ The use of dialysate with a median colony count of 65

CFU/mL was associated with a significantly lower risk for developing bone cysts, carpal tunnel syndrome, and arthropathy, than was the use of dialysate with a median colony count of 550 CFU/mL.⁴⁵

Cardiovascular Complications

Hemodialysis patients die of cardiovascular events at a much higher rate than the general population, even after adjustment for differences in age and comorbid conditions, such as diabetes.⁴⁶ Atherosclerotic cardiovascular disease is common in hemodialysis patients,⁴⁷ and Stenvinkel et al⁴⁸ have hypothesized that this atherosclerosis is linked to malnutrition and inflammation. Preliminary data suggest that using ultrapure dialysate may decrease inflammation and, thereby, cardiovascular morbidity. Lederer and Schiff⁴⁹ examined the relationship between cardiovascular events and the serum concentration of CRP in 60 patients; 70% of the patients were treated with ultrapure dialysate. Over 3 years, the incidence of new cardiovascular events was significantly higher in patients with a persistently increased CRP level compared with those with a normal CRP level. Regardless of the CRP concentration, none of the patients treated with ultrapure dialysate experienced a cardiovascular event.⁴⁹

Although the impact of dialysate quality on long-term cardiovascular outcomes in hemodialysis patients is subject to ongoing investigation, it is clear that one common water contaminant can trigger an acute cardiovascular event if present in dialysate at a sufficient level. Fluoride is thought to cause hyperkalemia and hypocalcemia in hemodialysis patients, leading to cardiac dysrhythmias. An accidental leak of hydrofluorosilicic acid into the drinking water supply in Annapolis, MD, in 1979 resulted in a dialysate fluoride concentration of 35 mg/L (1,842 $\mu\text{mol/L}$) at a local dialysis facility, leading to the death of 1 patient and a nonfatal cardiac arrest in a second patient.^{50,51} The patients complained of symptoms of hypotension, nausea, chest pain, diarrhea, itching, and vomiting after about 2 hours of dialysis, with cardiac arrest occurring 12 to 14 hours later.^{50,51} Another episode of fatal cardiac arrest after exposure to dialysate containing high levels of fluoride occurred in Chicago in 1993.⁵² In this case, the fluoride came from an exhausted deionizer and the dialysate fluoride level was measured at $1,027 \pm 109 \mu\text{mol/L}$. Twelve patients experienced symptoms similar to those described earlier; cardiac arrest occurred in 3 patients 4 to 6.5 hours after initiation of dialysis.⁵² Serum fluoride concentrations in the affected patients ranged from 59 to 716 $\mu\text{mol/L}$ compared with less than 1 $\mu\text{mol/L}$ in unaffected patients.⁵²

Intradialytic Complications

Intradialytic symptoms have the potential to impact significantly on the adequacy of dialysis by compromising treatment time, blood flow rate and clearance, and restoration of dry weight. Many water contaminants have been associated with intradialytic symptoms, such as nausea, vomiting, weakness, and hypotension. In some cases, such as copper,

fluoride, and zinc, these events are part of a larger clinical response and have been discussed elsewhere in this article.

In the beginning days of chronic hemodialysis, formulation of dialysate with tap water containing high levels of calcium and magnesium was associated with a constellation of symptoms, termed *hard-water syndrome*. Preparation of batches of dialysate from hard tap water and a concentrate that contributed 1.5 mmol/L of calcium and 0.5 mmol/L of magnesium yielded a dialysate with calcium and magnesium concentrations of 3.7 mmol/L and 1.5 mmol/L, respectively. Patients treated with this dialysate became hypercalcemic (postdialysis plasma calcium concentration of $3.7 \pm 0.6 \text{ mmol/L}$) and exhibited symptoms of vomiting, weakness and lethargy, skin flushing, and either hypertension or hypotension.⁵³ Nitrates and sulfate may cause similar symptoms^{21,54} and, in addition, sulfate may cause metabolic acidosis.⁵⁴

Batch dialysate systems in common use during the 1960s and early 1970s provided an excellent environment for bacterial proliferation.^{55,56} The incidence of pyrogenic reactions, characterized by fever, shaking chills, and hypotension within the first 2 hours of dialysis, increases with the number of bacteria in the dialysate.^{57,58} Pyrogenic reactions are caused by endotoxin or endotoxin fragments from gram-negative bacteria. These substances cross dialyzer membranes from dialysate to blood,^{59,60} or may be introduced directly into the blood compartment of a dialyzer during processing for reuse;⁶¹ septicemia may also occur with the latter route of transfer.⁶² Despite the establishment of a quality standard for the microbiologic purity of dialysate and water used to prepare dialysate in 1982³ and water used to prepare germicide for reprocessing in 1986,⁶³ outbreaks of pyrogenic reactions continue to occur. In the early 1990s, approximately 20% of dialysis facilities in the United States reported at least 1 pyrogenic reaction over the course of a year, and 2% to 3% of facilities reported clusters of pyrogenic reactions.⁶⁴ Detailed reports of outbreaks of septicemia and pyrogenic reactions in patients treated with re-used dialyzers appeared between 1985 and 1995.^{61,65-68} The Centers for Disease Control investigated these outbreaks and reported that, in all but one case, the water used for reprocessing dialyzers did not conform to the AAMI standard for microbiologic quality.

In addition to pyrogenic reactions from endotoxin, dialysis patients are at risk from other bacterial products in water and dialysate. Microcystins from cyanobacteria caused the deaths of 50 hemodialysis patients from acute liver failure in a dialysis facility in Brazil.⁶⁹ More recently, 16 patients became ill with symptoms of chills, nausea, and vomiting after exposure to disulfides in the water used to prepare dialysate;⁷⁰ 2 patients died. The latter case differed from the typical pyrogenic reaction arising from endotoxin; the symptoms occurred later (5 hours after first exposure) and hypotension and fever largely were absent.⁷⁰

Neurologic Disorders

In 1972, Alfrey et al⁷¹ reported a severe encephalopathy syndrome in their patients that was characterized by speech

abnormalities, myoclonus, personality changes, seizures, and disordered encephalograms; progression to death occurred within a few months. Similar findings were reported from other dialysis centers throughout the world.^{72,73} Affected patients had high aluminum levels in their brains, particularly in gray matter.⁷⁴ A causative role for aluminum in this syndrome is not proven in as far as the mechanism by which aluminum acts as a neurotoxin is not understood completely; however, there is a strong correlation between dialysate aluminum levels and the incidence of dialysis encephalopathy syndrome,³¹ and decreasing exposure to aluminum by purifying the water used to prepare dialysate and limiting the use of aluminum-containing phosphate binders greatly decreases the incidence.^{30,75} Indeed, implementation of these measures has made dialysis encephalopathy syndrome a rare event, although episodes linked to failure of water purification systems still are reported.^{19,76}

Nutrition

Low serum albumin concentrations predict mortality in dialysis patients.⁷⁷ Inflammation decreases albumin synthesis, leading to low serum albumin concentrations in well-dialyzed patients who are free of liver disease and infection.⁷⁸ The use of ultrapure dialysate decreases inflammation and the acute-phase response.^{23,24} In a prospective study, Schiffel et al⁷⁹ observed an increase in serum albumin concentration and other markers of nutritional status, including clinically estimated dry body weight and midarm muscle circumference, in 24 patients treated with ultrapure dialysate over a 1-year period compared with no change in 24 patients treated with standard dialysate. A role for dialysate quality in nutritional status is supported by the observations of Kleophas et al,⁸⁰ who reported a serum albumin concentration greater than 4.0 g/dL in 82% of their patients who were treated with ultrapure dialysate, in contrast to only 40% of patients treated with standard dialysate in the study by Owen et al.⁷⁷

Summary

Water quality can have a significant impact on patient outcomes and adequacy of dialysis. Several chemicals commonly found in drinking water were identified as toxic to hemodialysis patients in the 1960s and 1970s, leading to the development of water quality standards for dialysis in the late 1970s. The widespread use of water purification systems to comply with these standards made adverse events related to chemical contaminants rare. It should not be assumed, however, that chemical contaminants are no longer a problem. Adverse events related to known contaminants still occur because of equipment failure, human error, or changes in municipal water treatment practices. Furthermore, municipal water treatment is dynamic, changing as new public health issues are identified and addressed. Some of these changes have had an unforeseen impact on dialysis patients, as described later. This trend is likely to continue. For example, some municipalities are considering chlorine dioxide as a disinfectant because it is effective against *Giardia* and *Cryp-*

tosporidium. In addition to being a potent oxidant, chlorine dioxide yields chlorite and chlorate as daughter products. As yet, little is known about the toxicity of these substances in hemodialysis patients, or if current dialysis water treatment practices will remove them adequately. Although microbiologic contaminants have long been identified with pyrogenic reactions, particularly with dialyzer re-use, the role of microbiologic contaminants in chronic inflammation, and patient outcomes related to inflammation, has become evident only recently. The importance of these processes to the adequacy of dialysis remains a matter of debate and an area of active research. One outcome of this research will be a reassessment of current recommendations for the microbiologic purity of water and dialysate, particularly regarding the benefits of using ultrapure dialysate.

Ensuring Dialysate Quality

The recognition that hemodialysis patients were at risk from water contaminants, and the subsequent development of water quality standards,⁵ resulted in all dialysis facilities installing dedicated water purification and distribution systems. A typical system includes a primary purification process, a pretreatment cascade designed to optimize the performance of the primary purification process, and a purified water storage and distribution system (Fig 1). Reverse osmosis is the most common primary purification process. The alternative is deionization, which also may be used to supplement reverse osmosis in some circumstances. Because municipal water quality can differ markedly from location to location, water purification systems will vary from dialysis facility to dialysis facility. Designing a system for a particular dialysis facility has been addressed elsewhere^{81,82} and is beyond the scope of this article.

At the time of installation, most water purification and distribution systems deliver water adequate for the preparation of dialysate that meets applicable quality recommendations. The challenge, in terms of maintaining dialysis adequacy, is to ensure that water and dialysate quality do not deteriorate thereafter. There are 3 main reasons why water and dialysate quality deteriorate: changes in municipal water treatment practices, inadequate system surveillance and maintenance, and as an unintended consequence of changes to the system. Most patient injuries or decreases in dialysis adequacy can be traced to some combination of these 3 causes, as shown by the examples in the following sections.

Municipal Water Treatment

Changes in municipal water treatment practices have led to patients being exposed to increased levels of chemical contaminants, including some of those identified as being particularly toxic to hemodialysis patients, such as chloramine and aluminum. The result has been marked decreases in the adequacy of dialysis, including less than adequate anemia correction and increased encephalopathy syndrome in the cases of chloramine and aluminum, respectively.

Carbon adsorption is included in the pretreatment cascade of

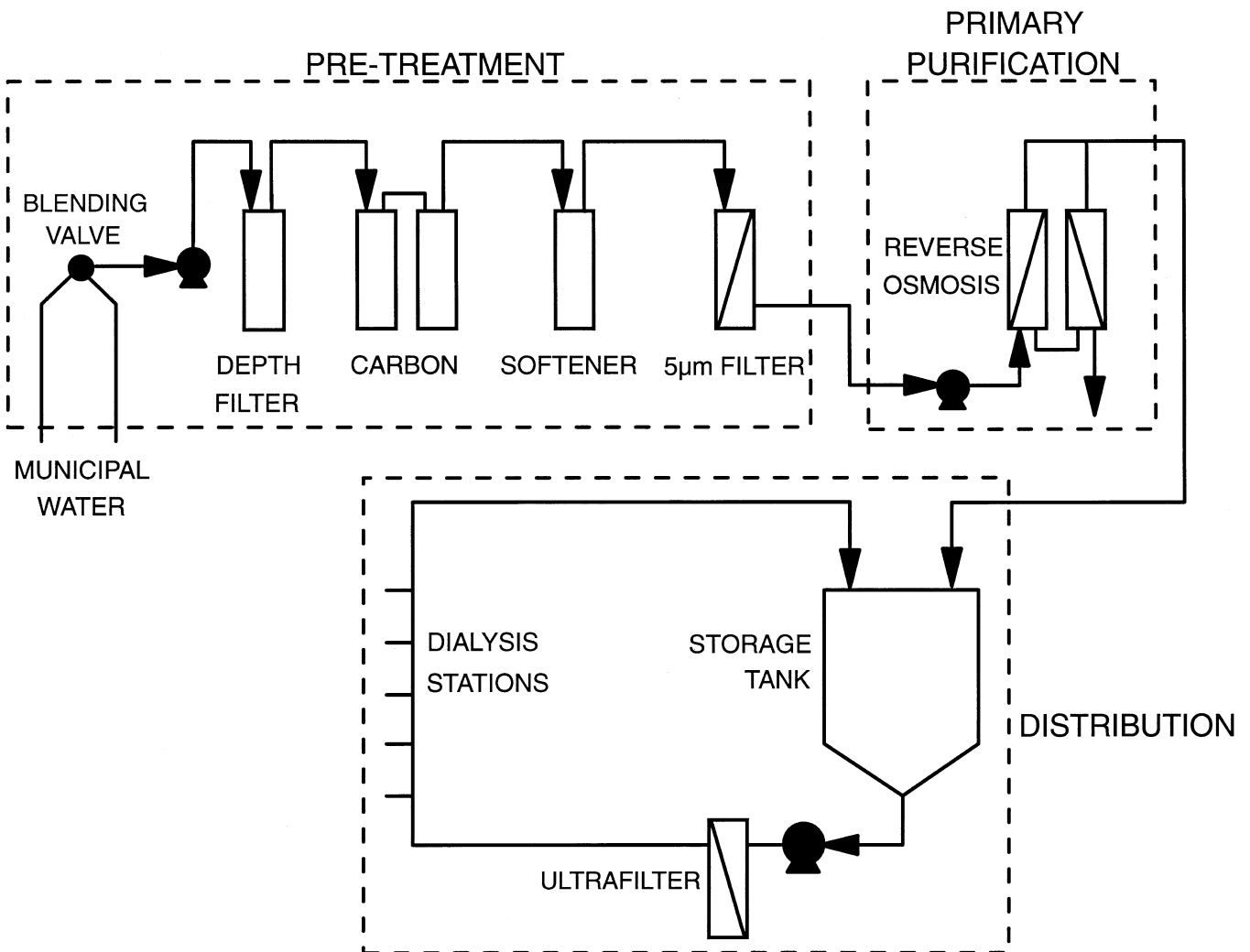


Figure 1 A typical water purification and distribution system for hemodialysis. Actual systems will vary in design depending on the quality of municipal water and the needs of the dialysis facility. Deionization may be used in place of reverse osmosis for primary purification or to polish reverse osmosis water if greater chemical purity is required. When a deionizer is used, it should be followed by an ultrafilter to create a barrier against contamination with bacteria and endotoxins. Whether or not a storage tank is used will depend on the layout of the dialysis facility and the degree of fluctuation in water demand. If ultrapure dialysate is desired, each individual dialysis machine also will be fitted with an ultrafilter for the final dialysate.

water purification systems to remove chlorine and chloramine. In addition to protecting the patient, carbon adsorption prevents chlorine from degrading thin-film composite reverse osmosis membranes and acts as a general scavenger of organic contaminants, some of which are too small to be well removed by reverse osmosis. In general, granular activated carbon has a high capacity for chlorine, but a much lower capacity for chloramine removal. If a municipality changes from chlorine to chloramine for disinfection, or increases the level of chloramine, the capacity of existing carbon adsorption beds may be inadequate for chloramine removal. Anemia correction may be compromised, as evidenced by overt hemolysis or increased resistance to erythropoietin therapy.^{10,12} The ability of granular-activated carbon to remove chloramine depends on the pH level and temperature of the water, and the presence of other substances that may compete with chloramine for active sites on the carbon.

During the 1990s, many municipalities in the United States increased the pH level or added orthophosphate to the water to control corrosion as part of complying with a US Environmental Protection Agency mandate to decrease lead and copper concentrations in drinking water, the so-called *lead and copper rule*. Both increased pH level and orthophosphate concentrations decrease the efficiency of chloramine removal by granular activated carbon. The most serious problem has been with the addition of orthophosphate, which appears to mask active sites on the carbon. When this occurs, alternative strategies such as the injection of sodium metabisulfite may be required to achieve adequate chloramine removal.

Aluminum, in the form of alum, is added to municipal water supplies to flocculate suspended matter and clarify the water. The concentration of suspended matter in surface water changes seasonally and may increase markedly during

droughts. These changes can lead to more intense flocculation and higher water aluminum levels.⁸³ In one instance a higher than usual water aluminum concentration, in combination with inadequate equipment maintenance at the dialysis facility, resulted in the water purification system being overwhelmed. The result was high dialysate aluminum concentrations and the deaths of 18 patients from severe encephalopathy.⁸⁴

System Surveillance and Maintenance

Although most water purification and distribution systems provide adequate dialysate at the time of installation, sustaining that performance requires careful maintenance of the system. Failure to monitor either the performance of individual system components or water and dialysate quality is likely to lead to a deterioration in water and dialysate quality and a decrease in dialysis adequacy.

The most common problems related to poor surveillance and maintenance concern microbiologic contaminants. One of the first steps in purifying water for use in hemodialysis is to remove chlorine and chloramine to protect both the patient and the reverse osmosis membranes that primarily are responsible for removing the remaining chemical and microbiologic contaminants. Removing these disinfectants creates ideal conditions for bacterial proliferation. When the water is being used to process dialyzers for re-use, excessive bacterial contamination has been associated with outbreaks of septicemia and pyrogenic reactions.^{61,67,68} In these cases, high levels of contamination went undetected because surveillance was infrequent,⁶¹ or because inappropriate techniques were used to determine bacterial levels in the water.^{67,68}

Recognizing that low levels of microbiologic contaminants may impact the adequacy of dialysis adversely means placing even greater emphasis on surveillance and maintenance of water purification and distribution systems. Routinely producing ultrapure dialysate is not a trivial task. Dialysate is the product of water purification and distribution, concentrate preparation, and dialysate formulation. Ultrapure dialysate requires that bacterial contamination must be minimized at each of these steps.^{82,85} Maintaining microbiologic quality between the end of the purification cascade and the dialysis machine is usually the weakest link in the chain. If biofilm is allowed to establish on fluid surfaces, it will continually infect the water, concentrate, or dialysate despite regular disinfection. A strategy of regular disinfection to prevent bacterial colonization is required, rather than performing disinfection in response to unacceptable surveillance cultures. Surveillance cultures and endotoxin measurements are limited to verifying the adequacy of disinfection. Nontraditional disinfection processes, such as hot water pasteurization or cleaning with dilute acid before introducing the germicide,^{86,87} may be necessary. Strict attention to preventing biofilm formation appears to create a virtuous circle, in which a decrease in biofilm formation leads to fluids of higher microbiologic purity, which in turn leads to less biofilm formation.⁸⁸

System Modifications

Although they each perform separate functions, the components of a water purification and distribution system must function together as an integrated whole. Changing one component in the system may impact the performance of another component, with unexpected consequences for water and dialysate quality. For example, increasing the output of purified water by installing additional reverse osmosis modules requires that the capacity of the pretreatment cascade, including carbon adsorption, be assessed to ensure that it remains adequate to handle the water requirements of the enlarged reverse osmosis system. Failure to perform such an assessment led to an outbreak of chloramine-induced hemolytic anemia in 1987; 41 patients required blood transfusions.¹¹ In addition to capacity, the impact of changes in the purification system on the performance of existing components must be considered. As discussed previously, an increase in the pH level of the municipal water supply may decrease the efficiency of chloramine removal by carbon adsorption. Some dialysis facilities have added an acid injection system before their carbon adsorption beds to decrease the pH level and maintain the efficiency of carbon adsorption. In one instance, an unacceptably high fluoride level in the purified water was noted during subsequent routine surveillance. Evaluation of the water purification system showed that the acid injection system had decreased the pH level into the range of 5 to 6. In this pH range a significant amount of fluoride is present as nonionized hydrofluoric acid, a very small molecule that is not rejected by reverse osmosis.

Summary

Water purification and distribution systems should be designed professionally based on the quality and seasonal variability of the municipal water and the needs of the dialysis facility. Although such systems will deliver water of adequate quality at the time of installation, their performance will deteriorate over time if they are not maintained adequately. In addition, when the quality of the municipal water changes, the system may no longer operate as intended. Finally, there is the possibility that human error will compromise water and dialysate quality. To prevent water and dialysate quality from compromising the adequacy of dialysis, a dialysis facility must establish a monitoring and maintenance program encompassing the performance of both the individual purification devices and the system as a whole, as well as the quality of the municipal water, the purified water, and the final dialysate. The facility's medical director should oversee the program. Maintenance procedures should be designed to prevent problems, not correct them after they occur. In particular, disinfection protocols should be designed to prevent contamination and biofilm formation, not to eliminate bacteria after the system has been contaminated. An attempt should be made to establish a dialogue with the municipal water supplier, with a request to be notified of changes in municipal treatment practices before they are implemented.

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