

Water Quality for Dialysis

*A monograph based on presentations given at the
AAMI Annual Meeting, June 1992, Anaheim, California,
AAMI Annual Meeting, May 1995, Anaheim, California, and
AAMI Annual Meeting, June 1997, Washington, D.C.*

Abstract: This monograph covers water treatment for hemodialysis, including clinical symptoms of inadequately treated water, microbiological considerations, contemporary reverse osmosis technology, the monitoring of water treatment systems, and regulation of water treatment systems.

Keywords: deionization, reverse osmosis, ultrafiltration, water purification, water treatment

AAMI Dialysis Monograph Series

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Foreword

The Association for the Advancement of Medical Instrumentation (AAMI) is perhaps most widely known for its development of standards and recommended practices for medical devices, including *Hemodialysis Systems* (ANSI/AAMI RD5-1992, 2nd ed.) and *Reuse of Hemodialyzers* (ANSI/AAMI RD47-1993, 2nd ed.). The revision of the second editions of RD5 and RD47 (in progress) will incorporate new information that has been widely accepted in the dialysis field since the publication of the last edition of the two standards. These and other voluntary standards developed by AAMI reflect the collective expertise of health care professionals, representatives of industry, and government officials and must undergo a formal and lengthy national consensus approval process before they are released.

At the same time, standards are not intended to replace professional judgment and, although reviewed and revised periodically (every 5 years), they are static documents applied to a dynamic field. In short, standards are truly useful only when relied on in conjunction with other sources of information and guidance, knowledge about specific situations, and a framework of professional experience.

In this regard, AAMI has annually sponsored two courses—on water quality for dialysis and on dialyzer reprocessing—for more than 15 years. Directed primarily to doctors, nurses, and technicians who specialize in nephrology, the overall goal of the courses is to help dialysis professionals stay current so that they are better able to apply consensus recommendations to real-life situations. Without ignoring the basics, these courses emphasize changes over the previous year, or seen on the horizon, in technology, relevant government requirements and recommendations, and applicable AAMI standards.

The monographs contained in this publication are based on select presentations from courses held in 1992, 1995, and 1997. For AAMI's CD-ROM version, the monographs are provided in two separate files.

Water Quality for Dialysis, the first of the monographs, contains eight papers and addresses the microbiologic qualities of water for hemodialysis, aspects of pre- and post-treatment reverse osmosis membrane technology, monitoring of hemodialysis water treatment systems, and FDA regulation of water purification systems for hemodialysis.

Current Concepts in Hemodialyzer Reprocessing, with nine papers, covers the history of reprocessing, microbiologic considerations, monitoring and anticoagulation strategies, personnel and quality assurance issues, and AAMI guidelines for HCFA compliance.

Comments on this publication are welcome and should be sent to Technical Programs, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201. For information concerning future dialysis courses, contact the same department.

NOTE—Chapters of this publication were written by individual experts and reflect the authors' personal views and expertise. Although based on 1992, 1995, and 1997 presentations, it should be noted that authors had an opportunity in 1998 to review and update their edited papers, prior to publication of this document.

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Overview of Water Treatment for Hemodialysis¹

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In the 1960s, the requirement for any type of water treatment for hemodialysis was only vaguely related to success in therapy. The tendency was to think more of protecting the dialysis machines from suspended solids or particulate (25-micron [μ] sediment filtration) and scale (softening to remove hardness factors) than the patients. In fact, the developmental status of the hemodialyzers (e.g., KiiI and coil hemodialyzers) and delivery systems then used fell far short of necessity, creating so much "background" difficulty in patient therapy that the untoward features of water went largely unnoticed. But, in the late 1960s and early 1970s, case reports began emerging that forewarned of concerns such as "hard-water syndrome" (calcium/magnesium overload), hemolysis (caused by exposure to excessive chloramines), heavy-metal intoxication (hemolysis associated with excessive copper and dementia/bone disease associated with excessive aluminum), and bacterial sepsis with shock. The science of water purification began to take shape.

By the late 1960s or so, the notion of chemically purifying water, in terms of the removal of charged, inorganic solutes (e.g., the sodium, calcium, magnesium, and iron salts of chloride, sulfate, and phosphates) was imported from industry in the form of mixed-bed deionization (DI) resins. Increasingly, then, in the 1970s, water for dialysis was not only undergoing sediment filtration, but also was being chemically purified by granular activated carbon filtration (to remove chlorine, chloramines, and trihalomethanes), followed by DI, followed by 1 μ sediment filtration (to remove resin fines) and 0.2 μ particle filtration (to remove bacteria but not their endotoxin). In the late 1960s, reverse osmosis (RO) was just being validated for use in dialysis.

By the late 1970s, RO filtration with cellulose acetate membranes to purify water began to take hold, conjunctive to DI purification. Cellulose acetate membranes, though, were fettered by their degradation by bacteria and excursions in supply water pH and by their generally inadequate flux and rejection characteristics.

By the early 1980s, then, efforts were afoot to more comprehensively approach water purification with means such as pretreatment (10 μ depth filtration to remove suspended particles, followed by softening, activated carbon filtration, and carbon fines filters); treatment (reverse osmosis with cellulose acetate membranes to reduce loading on downstream DI resin, used more often now for "polishing" the RO purified water), and post-treatment (ultraviolet [UV] irradiation and particulate and bacterial filtration). The availability of thin-film-composite (TFC) RO membranes (both bacteria- and pH-resistant, with high-flux and high-solute rejection characteristics) opened the way to purify water for dialysis without using DI polishing. This stood true, provided that total dissolved solids (TDS), critical elements such as aluminum and fluoride, and pH could be maintained within reliably safe limits. Critically, in recognition of continuing problems with bacteria, the need for distribution loops absent "dead legs" to convey purified water was becoming accepted. Purified water storage vs no storage is debated.

Thin-film-composite membranes were widely used. Recognition of the need to better control bacterial growth throughout the entire water treatment system and, specifically, the access by endotoxin to the water being conveyed to patients became the accepted "norm." There followed, then, less dependence on DI as a primary means of chemically purifying water and more emphasis on post-treatment of TFC RO purified water with UV followed by cross-flow filtration with molecularly retentive ultrafilters (UFs). The idea became established that, if UV is used to kill bacteria, then UV must be followed by UFs to remove any resulting bacterial endotoxin. Loop distribution and the total absence of "dead legs" is accepted.

The widespread and growing use of high-flux dialysis and sodium bicarbonate for base replacement in patients literally mandates that attention be focused on endotoxin removal in generating prescription water for dialysis. Debate over storage vs no storage of chemically purified water continues. Common sense, however, mitigates that

¹ Presented at "Water Treatment Considerations in Hemodialysis Therapy," a short course held on 22 May 1995 in conjunction with the 1995 AAMI Annual Meeting, Anaheim, California.

storage is acceptable, often preferable, if properly executed and preventively maintained against intrusion by bacteria and their endotoxin. The requirement for preventive sanitation becomes an axiom.

There are new modes of water treatment, delivery, and sanitation on the horizon. Will these prove to be better and safer? We'll let the Food and Drug Administration tell us, and we'll await new AAMI standards for the emerging technologies.

Clinical Symptoms of Inadequately Treated Water for Hemodialysis ¹

Rebecca L. Amato, BSN, RN, CNN

"Til taught by pain, men really knew not what good water's worth."

Lord Byron in *Don Juan*

INTRODUCTION

Water for hemodialysis is a prescription item; it is the main ingredient of the dialysate. Therefore, the physician is ultimately responsible for determining not only the dialysate composition, but also the final water quality delivered to the patient. Historically, doctors and nurses have had little involvement with water treatment decisions, even though there are many clinical risks involved; the task has rested mainly upon the technicians' shoulders. This trend is changing. With the Food and Drug Administration (FDA) regulations being more strictly enforced, the Health Care Finance Administration (HCFA) becoming more interested in water treatment, and the Association for the Advancement of Medical Instrumentation (AAMI) rewriting its guidelines, water is in the forefront of all dialysis professionals' minds.

Like dialysis machines, water treatment equipment for hemodialysis is regulated by the FDA as a class II medical device. Simple devices such as Band-Aids™ and tongue depressors are categorized as class I and are subject to minimal FDA requirements. Devices such as internal pacemakers and high-flux dialyzers are categorized as class III and are subject to strict premarket approval, tracking, and documentation requirements. These requirements are also applicable to class II medical devices but not to the same degree as class III.

What makes the quality of the water so critical for hemodialysis? The exposure factor. The average person drinks approximately 14 liters (L) of water a week in a variety of forms. Toxic substances that might be in the potable water are excreted through the kidneys, and the blood is indirectly exposed to such contaminants via the gastrointestinal (GI) system, where, to a great degree, the contaminants can be selectively absorbed or disposed of. On average, hemodialysis patients are subjected to 360 liters of water per week. Their diminished renal function makes it impossible for them to excrete the toxins in urine, and their blood is directly exposed to contaminants via the dialyzer membrane, where the contaminants can be transferred directly into circulation without the protection of the gastrointestinal barrier (Klein 1986, Luehmann et al. 1989).

Contaminants in the water are related to geographic regions and the type of water utilized. Water comes in two different "flavors": ground and surface. Ground water or well water has been sieved through the earth, which acts as a natural depth filter, removing particulates from the water while the water takes on the characteristics of the surrounding rock. Typically, ground water is higher in ionic content and much lower in microbial life than surface water. Surface water is exposed to the environment and is generally higher in bacterial levels. Industrial chemicals, pesticides, solvents, and other pollutants are also more likely to inhabit surface water. More disinfection, filtration, and flocculation usually are required by the municipal water supplier that uses surface water.

Contaminants in the water can be inorganic or organic. Trace minerals, heavy metals, and chemicals make up the inorganic contaminants, while bacteria, viruses, and organic matter comprise the organic category. Radionuclides, a third category, can occur naturally, or they can be man-made radioactive material; there have been no reports, to date, of radionuclides causing incidents in the hemodialysis setting.

¹ Presented at "Water Treatment Considerations in Hemodialysis Therapy," a short course held on 8 June 1997 in conjunction with the 1997 AAMI Annual Meeting, Washington, D.C.

REGULATIONS AND GUIDELINES

Finding it necessary to regulate contaminants found in the drinking water, the Environmental Protection Agency (EPA) mandated the "Safe Drinking Water Act" in 1974. Eight years later, AAMI published guidelines for the maximum allowable levels of contaminants in water for hemodialysis (AAMI 1982) and other aspects of water quality. These guidelines were based on three criteria:

- 1) Where there were no reported adverse effects for a contaminant, 10% of the EPA's specified maximum level in drinking water was recommended as the maximum allowable level in water to be used for dialysis. This recommendation was based on the assumptions that the feed water meets the requirements of the Safe Drinking Water Act, and that the water purification system (e.g., reverse osmosis [RO]) is capable of removing at least 90% of the contaminants in the source water.
- 2) Where there had been reported incidents, the recommended maximum allowable level was set at 50% of the lowest concentration associated with toxicity or, as with calcium, fluoride, and others, at a level below that known to cause physiologic complications.
- 3) For selenium, the maximum limits recommended by AAMI were set at the "no-transfer" level into the blood. For these contaminants, the AAMI limits are actually higher than the maximum levels allowed by the EPA.

Ironically, some contaminants added to drinking water, such as aluminum and chloramine, are not yet regulated by the EPA, but are well known to be dangerous to the dialysis patient. Therefore, AAMI has established maximum limits for those contaminants. Current AAMI and EPA limits on water contaminants are shown in Table 1. Current AAMI recommendations for disinfectant levels and bacteriological quality are shown in Table 2.

Contaminant	AAMI Maximum for Dialysis Water (mg/L) (AAMI 1993)	EPA Maximum for Drinking Water (mg/L) (EPA 1996)	Lowest Concentration Associated with Dialysis Toxicity (mg/L)
Calcium	2 (0.1 mEq/L)	Not regulated	88
Magnesium	4 (0.3 mEq/L)	Not regulated	
Sodium	70 (3.0 mEq/L)	Not regulated	300
Potassium	8 (0.2 mEq/L)	Not regulated	
Fluoride	0.2	4.0	1.0
Chlorine	0.5	4.0*	
Chloramine	0.1	4.0*	0.25
Nitrate	2	10	21
Sulfate	100	400/500*	200
Copper	0.1	1.3**	0.49
Barium	0.1	2	
Zinc	0.1	5*	0.2
Aluminum	0.01	0.05-0.2*	0.06
Arsenic	0.005	0.05	
Lead	0.005	0.015**	
Silver	0.005	0.10*	
Cadmium	0.001	0.005	
Chromium	0.014	0.10	
Selenium	0.09	0.05	
Mercury	0.0002	0.002	

*Unenforceable maximum contaminant level goal

**Action level at 90th percentile.

Table 2 -- Limits on Disinfectant Residues and Bacterial Contamination		
Disinfectant	AAMI Recommended Limit	Manufacturer's Suggested Level
Formaldehyde	<5 mg/L	
Peracetic acid		<3 mg/L
Glutaraldehyde		<3 mg/L
Sodium hypochlorite (bleach)		<0.5 mg/L
Bacteria		
Water	<200 cfu/ml	
Dialysate	<2000 cfu/ml	
Concentrate	<200 cfu/ml	
Endotoxin		
Water for reuse	<1 ng/5 EU	

DETECTIVE WORK

Those who like detective work will find it a challenge to decipher clinical symptoms from the given data. For those who don't, I wish it were easy to distinguish between the normal symptomology of chronic renal failure and insidious water culprits. Unless a patient exhibits an acute or subacute reaction, we may not relate chronic symptoms to water-related problems. We may mistakenly attribute the symptoms to the normal end-stage renal disease process or to the uncommon use of aluminum-containing phosphorous binders, not to water (EPA 1996). To make things more complicated, various water contaminants can produce very similar acute symptoms. For instance, a copper reaction mimics an endogenous (coming from the dialysis system) endotoxin reaction; and calcium, fluoride and sodium toxicities look very much alike.

How do we go about singling out what went wrong? When I talk with facility personnel after an incident, I often find that they have thrown out all the "evidence" (bloodlines and dialyzers). The fluid from the bloodlines and most dialyzers can be tested for chemicals and endotoxin after the fact, so they should be kept. All too often, the only testing performed is blood cultures on the patient. It is rare that a patient will become septic from waterborne bacteria originating from the dialysate because bacteria are too large to cross the dialyzer membrane; consequently, blood cultures will likely be negative. Of course, if there is a ruptured dialyzer membrane (blood leak) or a contaminated reused dialyzer, sepsis can occur, and blood cultures will then be valid. When a reaction is suspected, blood samples should be assayed not only for cultures, but also for chemical analysis (e.g., panel 22, chem. 21), complete blood cell count, and hematocrit. It is imperative to record all clinical symptoms, no matter how insignificant, along with vital signs (Arduino 1997).

In conjunction with the blood samples, bacteria testing should be performed on the dialysate exiting the dialyzer(s) and on the RO product water supply to the dialysis machine(s). Limulus amoebocyte lysate (LAL) testing will identify endotoxin reactions, and chemical testing (e.g., bleach, formaldehyde) may delineate whether or not a disinfectant was present. An AAMI contaminant analysis should be performed on the product water after an incident, especially if the total dissolved solids (TDS) or conductivity of the water treatment system was higher than normal. In a pinch, a water sample or dialysate sample can be sent to a laboratory not specializing in dialysis, and tested for physiologic contaminants (e.g. potassium, copper, sodium). The lab needs to remove the protein bias used for blood sampling when doing these tests. It should be noted that such testing may not detect all contaminants that may be in the water or dialysate, and that the lab equipment may not be sensitive enough. Further testing should involve total chlorine, pH of the dialysate, and conductivity of the dialysate and product water. All sampling should be performed as soon as possible after an incident occurs, or from the fluids retained in the saved bloodlines and dialyzer(s) (Arduino 1997). (See table 3.)

Table 3 — Patient Reaction Data Sheet					
Patient Status	Vital Signs	Time__ BP__ T__ R__ P__	Time__ BP__ T__ R__ P__	Time__ BP__ T__ R__ P__	Time__ BP__ T__ R__ P__
Dialysis start time _____ QB/BFR _____ QD/DFR _____ Dialysis stopped time _____	Symptoms: Onset time of symptoms into dialysis _____	N&V _____ Pruritus _____ Flushing _____ Chills _____ Headache _____ GI distress _____ Other _____ _____	SOB _____ Chest pain _____ Arrhythmia _____ ECG _____ Other _____ _____	Back pain _____ Access pain _____ Abd. Pain _____ Other _____ _____	Neural checks: PERRLA _____ Hank grips _____ Weakness _____ Lethargy _____ Numbness _____ Confusion _____ Other _____ _____
Frank hemolysis seen? Y/N	Blood chemistries: (copies attached)	Na__ K__ Ca__ Cl__ Mg__ CO ₂ __ Gluc. _____ pH _____	CBC__ Hct__ Hgb__ Other _____ _____	Blood culture _____ _____	Other _____ _____
Dialysate	Dialyzer and lines Saved? Y/N	pH _____ Cond _____ Temp _____	Disinfectant test Type _____ +/- _____	Bacteria _____ LAL _____	Other _____ _____
Product Water	Cond/TDS _____ Resist (DI) _____	pH _____ Temp _____	Total chloramine ____ Hardness _____	Bacteria _____ LAL _____	AAMI analysis? Y/N (copy attached)

Unfortunately, accidents continue to occur in dialysis even though we have documented information on how to prevent them. In most reported incidents, either no purification was used or only pretreatment was used. A few deaths have been associated with deionization (DI), and very few incidents have occurred when reverse osmosis was used. By and large, reverse osmosis with proper pretreatment is the safest means of water purification for hemodialysis applications.

The following sections describe clinical symptoms associated with various hemodialysis water contaminants. The clinical symptoms listed may be incomplete and are limited to ones reported to the FDA or published in subsequent articles.

INORGANIC CONTAMINANTS

ALUMINUM

Aluminum is added to the drinking water supply when colloidal matter is high. Colloids are undissolved, sub-micron-sized, suspended particles that interfere with the filtration process and make the water turbid. Aluminum sulfate or alum acts as a coagulant that aggregates the colloids together. The colloids are then stirred or else a synthetic polyelectrolyte is added so that the "flocs" can settle or be filtered out (Luehmann, et al. 1989). As mentioned earlier, there is not an EPA standard for the amount of aluminum allowed in the drinking water supply. The community

water supplier attempts to add just enough alum to bind with the colloids so that all of them are filtered or settled out. But, aluminum sulfate is typically added by shovelfuls until the water looks right—which is not very scientific.

Aluminum is amphoteric in nature, meaning that it is neutrally charged in a pH of around 7.0 units. Removal of a contaminant via deionization requires a charge; therefore, aluminum is weakly attracted to DI at a near-neutral pH level and may not be eliminated adequately from the water.

Several incidents involving aluminum have been reported. The most recent was in 1992, when three patients died of hyperaluminumemia because an aluminum pump was utilized in an acid concentrate delivery system (FDA 1992). The pump was relatively small, but acid concentrate is extremely corrosive to metal; hence, the aluminum levels climbed high enough to kill patients. Other aluminum incidents that have occurred were specific to the water supply; they did not result from the aluminum-containing phosphorous binders that once were popular, nor were they related to aluminum accidentally placed in the hemodialysis system (Rosenthal 1997, Schreeder, et al. 1983).

Symptoms related to hyperaluminumemia include neurological deterioration ("dialysis dementia"), involving tremors, speech abnormalities, and an abnormal EEG; anemia, both microcytic and hypochromic; osteomalacia; and osteodystrophy (Elliot, et al. 1978, Pierides, et al. 1980, Schreeder, et al. 1983).

CALCIUM

Calcium hydroxide and other lime-softening agents are added to the community water to increase the pH in order to form a thin protective film inside the piping, thereby reducing corrosion. By increasing the pH, the amount of lead and copper leached from the plumbing into the water supply is minimized (Cartwright 1993, Peterson, et al. 1991). Calcium also can be naturally occurring, as can magnesium; together with an alkaline pH, they cause the water to be "hard." Hard water forms scale on RO membranes and can cause them to prematurely fail unless the water is softened and/or the RO membranes are routinely cleaned.

Acute symptomology of hypercalcemia includes nausea and vomiting, headache, muscular weakness, flushing, lethargy, pruritus, tachycardia, severe hypertension leading to vasodilation, and coma. Chronic symptoms appear as abnormal bone mineralization, soft tissue calcifications, and pancreatitis (Drukker 1969, Evans, et al. 1975).

FLUORIDE

Fluoride is added to the municipal water supply to prevent dental caries. In November 1979, a valve at the Annapolis water treatment plant was not closed completely, and 1,000 gallons of 22% hydrofluosilicic acid were released into the water supply before anyone noticed (*Maryland Communicable Diseases Newsletter* 1980). Eight patients at a local dialysis facility were affected, and one death ensued. More recently, in the summer of 1993 in Chicago, three deaths were associated with over-fluoridation caused by an exhausted DI tank (FDA 1993a, 1993b).

Deionization works on an exchange basis, trading cations and anions for hydrogen ions (H⁺) and hydroxyl ions (OH⁻), which bond to form water (H₂O). The DI resin stores all removed ions until the resin sites are near depletion, at which time a resistivity monitor should alert the user. If the DI system is used past this point of exhaustion (< 1 megohm-cm resistivity), all the stored ions will be released in great numbers, resulting in high contaminant levels in the effluent stream.

The personnel at the Chicago facility were familiar with a monitoring system that used a single amber light. When the old tank was near exhaustion (<2 megohm-cm resistivity), the light extinguished. The new system had a dual light monitor, one green and one amber. In this system, illumination of the amber light meant that the DI resin was near exhaustion, but the facility staff were waiting for the light to go out and so continued to use the tank. The light never went out and the concentration of fluoride in the dialysate reached 15 to 25 mg/L (as compared to the AAMI-recommended maximum of 0.2 mg/L). If all the staff had been properly trained on the new device, this incident would not have occurred. Fluoride is weakly attracted to DI resin when the pH of the supply water is outside of a neutral range (just the opposite of aluminum). Therefore, when DI resin exhausts, weakly attracted ions like fluoride and aluminum are the first to go (Wathen, et al. 1993).

Acute signs of fluoride toxicity are shortness of breath, chest pain, nausea and vomiting, diarrhea, hypotension, headache, weakness, numbness, and pruritus. Chronic symptoms may appear as osteodystrophy and parathyroid disease (only seen in animals) (*Maryland Communicable Diseases Newsletter* 1980, FDA 1993a, Wathen, et al. 1993).

SODIUM

Hypnatremia from sodium overexposure has occurred in two incidents (Nickey, et al. 1970, Personal communication 1995). In each case, only pretreatment was utilized, and the softener head malfunctioned. The indicator in the softener head was in the "home" position, which normally means that the softener has been completely regenerated and rinsed. For some reason, the indicator moved to the home position without being rinsed of the concentrated sodium chloride solution that is used for softener regeneration. The type of dialysis machines used did not sense chloride ions; therefore, the conductivity was read as normal by the dialysis machines and they did not go into dialysate bypass mode. If secondary checks had been in place, such as a handheld conductivity meter for the dialysate and the product water, and if RO or DI had been used in addition to the pretreatment, these incidents could have been avoided.

Acute symptoms of hypnatremia present themselves as increased thirst, nausea and vomiting, headache, confusion, hypertension, pulmonary edema, shortness of breath, and tachycardia. Seizure, coma and death can ensue if the concentrations of sodium are high enough (Robson 1978).

SULFATES

Sulfates occur naturally and also are added to the water as compounds. They have been known to cause nausea and vomiting and metabolic acidosis in dialysis patients (Comty, et al. 1974).

COPPER

Copper leaches from copper and brass piping, especially in the case of acidic feed water and purified product water. It is well known that copper piping should not be installed after the RO or DI water purification equipment, but accidents do occur. For instance, a plumber who is not familiar with the consequences for hemodialysis, replaces a broken T section in the loop. He doesn't have polyvinylchloride (PVC), stainless steel, or another inert type of piping material on hand, so he plumbs in a piece of copper or brass. Purified water can be thought of as a magnet or as an aggressive solvent. It will grab on to or leach whatever is in the piping because it has many empty sites to bind with.

Even the short exposure consequent to the leaching of copper from a small piece of piping can cause severe reactions in patients. Copper toxicity mimics an endotoxin reaction, with flushing, chills, headache, and vomiting but without the temperature spikes. Methemoglobinemia leading to hypoxia and cyanosis has also been seen with copper exposure. Methemoglobin is found in the blood following poisoning by certain substances. It is related to oxyhemoglobin, but has no oxygen-carrying ability because the iron has been converted from divalent (Fe^{++}) ferrous sulfate to trivalent (Fe^{+++}) ferric acid. In worst-case scenarios, the blood will appear brown from the precipitation of iron.

Along with methemoglobinemia, other documented acute and subacute symptoms are chills, flushing, headaches, projectile vomiting, gastrointestinal problems including abdominal cramps and diarrhea, hypotension, leukocytosis, hemolytic anemia, metabolic acidosis, and myoglobinemia resulting in muscle pain. Chronic symptoms become evident as liver damage and pancreatitis (Manzler, et al. 1970, Eastwood, et al. 1983).

IRON

Iron, which can leach from galvanized pipes or occur naturally, accumulates on the RO membrane. To a lesser degree, softeners will also remove low levels of iron, along with calcium and magnesium. Iron fouling an RO membrane reacts with peracetic acid disinfectants and damages the membrane, resulting in poor product water quality. Long-term exposure to high levels of iron in dialysis patients can lead to liver damage, and, as with all heavy metals, acute exposure will result in hemolytic anemia.

LEAD

Lead is a potentially lethal heavy metal, although there are no documented incidents associated with lead in water for dialysis. Lead solder can leach from fittings and was used to connect copper piping as recently as 1986, when it was mandated that solder must contain less than 0.2% lead. Lead pipes may be in houses predating 1920, and lead is still used in some faucets. It is estimated that drinking water is accountable for 10% to 20% of the total lead exposure in young children. Therefore, the EPA has imposed more stringent lead (and copper) rules on public water suppliers, making municipalities responsible for the water quality in the homes they supply, regardless of the type of piping each house has (Peterson, et al. 1991, Cartwright 1993). In response to these new requirements, municipalities in some regions have been increasing the pH of drinking water to as high as 10.5 units (ZyzaTech Water Systems, Inc., experience), which will reduce pipe corrosion and in turn decrease the amount of lead and other metals in the water.

Dialysis patients' safety could be jeopardized in the following scenario: If the pH is high (more than 9.0) and if chloramines are present in the incoming water, pretreatment capabilities and RO product water quality will be diminished. In excessive alkalinity, the ammonia group disassociates from the chlorine molecule; the ammonia gas crosses the RO membrane and causes the pores to enlarge, resulting in decreased percent rejection and diminished water quality (Luehmann, et al. 1989). Moreover, the chloramine/chlorine may not be fully adsorbed (a chemical reaction) by the carbon tank. If the pH situation is rectified immediately (by, for example, acid injection before the RO membrane), the RO membrane typically reverts to its original operating parameters and the pretreatment will perform as before. (The RO membrane is altered, but not damaged, while the ammonia is present.) (ZyzaTech Water Systems, Inc., experience)

It is imperative to assess incoming source water pH and chlorine/chloramine levels on at least a weekly basis in order to prepare for alterations in the water supply.

The symptoms of plumbism (chronic lead poisoning) are neurological damage and fatal hemolysis.

ZINC

Zinc leaches from galvanized iron and brass pipes. Excessive exposure has caused nausea, vomiting, fever, and chronic anemia due to hemolysis. This can also look much like the flu or an endotoxin reaction (Gallery, et al. 1972).

NITRATES

Nitrates can be high in farming communities, due to defiling of the water by animal excrement, bacteria, and fertilizers. Reported acute and subacute symptoms of hypernitremia include hemolytic anemia, persistent hypotension, nausea and vomiting, lethargy, weakness, confusion, and methemoglobinemia leading to cyanosis (Carlson, et al. 1970, Salvadori, et al. 1984).

CHLORINE/CHLORAMINE

Chlorine and chloramine are added to the water for disinfection purposes. For public water suppliers, chloramine (combined chlorine) has become the disinfectant of choice over free chlorine because it is more stable and less likely to dissipate, thus allowing lower concentrations to be used. Also, there is a danger of free chlorine combining with organic chemicals found in the water and forming trihalomethanes, which are known to be carcinogenic; the formation of trihalomethanes does not occur with chloramines. Both chlorine and chloramine are damaging to thin film RO membranes and harmful to dialysis patients. No chlorine events have been reported, but there have been numerous incidents involving chloramines (FDA 1988, Kjellstrand 1974, Yawata, et al. 1973, Eaton, et al. 1973).

The most notable report was the "Philadelphia incident" of 1987, in which 44 out of 107 patients required blood transfusions and 10 were sent to the emergency department (Ackerman 1988). Initially, a nurse in the facility noticed that an unusually large number of hematocrits were lower than normal. Three patients were transfused. Many patients complained of headaches and malaise and were hypotensive. After 2 to 3 days of symptomology and many more

transfusions, it became obvious that chloramines were the culprit. Fortunately, thanks to careful clinical monitoring, no patients died.

Upon further investigation, it was discovered that the water requirements for the facility had increased and that the water capacity of the RO unit had been expanded three-fold; however, the carbon tanks had not been expanded to accommodate the higher incoming flow. The staff person monitoring the system recorded the chloramine levels accurately as they climbed up to 0.5 mg/L (the AAMI-recommended maximum level being 0.1 mg/L), but was not aware that the results should be reported to someone. Furthermore, no written policy was in place regarding chlorine/chloramine levels, and double-checks were not standard procedure. Also, the staff falsely believed that backwashing the carbon tank would regenerate the carbon media (Ackerman 1988, FDA 1988). In fact, this procedure only exposes unused sides; once the carbon is exhausted, it must be replaced.

Other chloramine incidents have occurred even when the dialysis facilities were warned ahead of time that the water supplier would be switching from chlorine to chloramine (FDA 1988, Luehmann 1997). The facility staff either thought that they were well prepared or did not understand the consequences.

In addition to insufficient carbon filtration, inadequate total chlorine testing measures can leave a facility wide open for problems. In some dialysis units, the only time total chlorine levels are measured is during the water vendor's semiannual visit; this is a dangerous practice. AAMI suggests testing at least once a day, but before every dialysis shift is safer. In other dialysis centers, the staff only test for free chlorine because no chloramine is added to the water. Chloramine can form naturally from the combination of rotting vegetation and chlorine; consequently, it is important always to test for total chlorine, which conveys both free and combined levels. In some facilities, there continues to be inadequate empty-bed contact time within the carbon tanks, which places the patients at risk.

Hemolysis can result from exposure of the blood to many toxic substances, including chloramine. Frank hemolysis appears as bright, "cherry pop" blood exiting the dialyzer and can cause hyperkalemia and cardiac arrest (Klein 1986). Along with hemolysis, other documented signs of chloramine exposure are hemolytic anemia, chest pain, arrhythmia, shortness of breath, nausea and vomiting, and methemoglobinemia leading to cyanosis, with brown blood seen in the most toxic cases (Botella, et al. 1997).

ORGANIC CONTAMINANTS

Bacterial and pyrogenic contaminants are always an issue in water treatment. The ubiquitous waterborne bacteria can live in the most pure water, water that seems to have no nutritional value. An intact RO membrane will remove bacteria, endotoxins, and viruses at a rate of 99% plus. However, RO membranes have been known to "grow through" with bacteria, a phenomenon associated with long periods of down time (White, et al. 1991). In addition, older RO membranes that are worn with holes in them allow for the passage of bacteria. Microbial contaminants can also be introduced any time the system or loop is opened.

Waterborne gram-negative bacteria, such as *Pseudomonas*, produce a lipopolysaccharide form of endotoxin. Once the bacterium dies, the endotoxin is released from the cell wall of the bacterium and can cause pyrogenic reactions among dialysis patients. Gram-negative bacteria are relatively easy to kill unless they form a protective gelatinous covering known as biofilm (glycocalyx), and they grow rapidly. In addition to *Pseudomonas*, gram-negative bacteria genera include *Flavobacterium*, *Acinetobacter*, *Alcaligenes*, *Achromobacter*, *Aeromonas*, *Serratia*, and *Moraxella* (Favero, et al. 1975).

The nontuberculous mycobacteria (NTM) genera of waterborne bacteria do not produce endotoxins, so there is no risk of pyrogenic reactions. The danger with these gram-positive rods is that a longer exposure to disinfectant chemicals is required to kill them and they can be retained in inadequately reprocessed dialyzers. Although NTM grow more slowly than gram-negative bacteria, they can be too numerous to count all too soon. Species of NTM include *M. chelonae*, *M. fortuitum*, *M. goodii*, *M. scrofulaceum*, *M. kansasii*, *M. avium*, and *M. intracellulare* (Carson, et al. 1978).

The severity of a pyrogenic reaction is directly proportional to the amount of endotoxin exposure (Bland 1989), which can arise from the product water, concentrate, dialysis machine or from endotoxin accumulation in

reprocessed dialyzers. Pyrogenic reactions occur from 1 hour to halfway into the treatment, depending on whether high-flux or conventional dialysis is underway. Uncontrollable shaking, chills, temperature spikes, nausea, vomiting, myalgia, and hypotension are typical symptoms of a pyrogenic reaction (Favero, et al. 1974, 1975).

Sepsis originating from the dialysate is an unusual occurrence, because bacteria are too large to cross the dialyzer membrane. In the event of a dialyzer rupture (blood leak), however, bacteria can invade the dialysate. When waterborne bacteria cause sepsis, they usually originate from reused hemodialyzers that were reprocessed with less than sufficient germicide concentrations or exposure time (Carson, et al. 1978). The symptoms of sepsis are the same as a pyrogenic reaction, but they do *not* subside soon after the patient is removed from dialysis.

In an incident in Brazil in February 1996, more than 60 patients died, mainly due to liver failure resulting from endotoxin exposure from extremely toxic blue-green algae (*Nephrology News and Issues* 1996, 1997; Arduino 1997). The drinking-water supply from the lake was hauled by truck to a pumping station, where it was sand-filtered and treated with chlorine and aluminum. (By the way, this is all the treatment done by some drinking-water suppliers here in the United States.) The dialysis facility further treated the water with carbon adsorption, sand filtration and DI. Apparently, the city's treatment plant did not completely chlorinate the water, and the facility was not able to compensate for the lack because it did not use reverse osmosis, which would have removed endotoxin.

Some U.S. facilities continue to use pretreated or tap water as emergency backup to dialyze patients. It is a dangerous practice to put so much faith in the water supplier, even here in the United States. According to the EPA, at least 48 states are failing to enforce existing regulations (Carpenter 1991)

pH/CHEMICAL REACTIONS

pH

A pH of 6.7 in the dialysate was reported to cause excessive clotting of dialyzers, resulting in poor dialyzer performance, decreased reuse, and increased blood loss (AAMI 1993). This phenomenon is due to the inactivation of heparin when dialysate pH is lower than 7.0 units (Eastwood, et al. 1983). Clinical symptoms include itching, nausea, vomiting, and acidosis.

AAMI guidelines suggest a dialysate pH range of 6 to 8 (the wide range is to accommodate acetate dialysate). Most facilities use bicarbonate dialysate; therefore, a dialysate range of 7 to 7.8 is more appropriate. Also, physiologic pH is 7.35 to 7.45, and the limits for life are about 6.9 to 7.8 (Lancaster 1995). Dialysis patients mostly fall on the acidotic side (lower than 7.35), so dialyzing a patient against a physiologic pH bath may aid in providing a more stable dialysis treatment. All dialysis machine and concentrate manufacturers recommend testing the final dialysate pH before every dialysis run. The incident described above might have been averted if pH testing had been done.

Usually, incoming water pH does not affect the final dialysate pH because the acid and bicarbonate concentrates determine the final result. However, it is important to assess the supply water pH on a regular basis in order to make adjustments in pretreatment components as necessary. For instance, granular activated carbon takes longer to adsorb chlorine or chloramine when the pH is elevated. Also, the more acidic the supply water, the more heavy metals it will leach from the pipes, elevating the number of contaminants to be removed by RO or DI.

CHEMICAL REACTIONS

Early in 1989, in New York State, ultrafilters preserved in sodium azide and glycerin (to prevent bacterial growth and desiccation), which were not intended for medical use, were placed after the water system. The filters were not adequately rinsed of the chemicals, and the facility staff were not aware of the hazard. Sodium azide leached from the ultrafilters and caused nine patients to suffer life-threatening hypotension, blurred vision, abdominal pain, headache, and loss of consciousness shortly after treatments began (FDA 1989). Because chemicals are so prevalent in the dialysis setting, this is but one of many documented reactions.

Chemical reactions generally occur within the first 15 minutes of treatment, and the symptoms are more obscure than in pyrogen reactions. Headache, nervousness, pruritus, hypotension, palpitations, access pain (Arduino 1997), visual