

High Quality Dialysate: Its Importance to the Dialysis Patient

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The majority of ESRD patients receiving treatment do so by a technique which removes ingested water and low molecular weight metabolites retained as a consequence of renal failure, and restores electrolyte and acid base balance across a semi permeable membrane contained in an artificial kidney. The procedure is generally performed three times weekly, although currently there is considerable interest in performing more frequent (daily) or longer (nocturnal) treatments. During dialysis, blood withdrawn from the patient flows on one side of the membrane. The other side of the membrane is bathed by dialysis fluid—an electrolyte solution produced from a concentrated electrolyte solution diluted with water. The water used in the preparation of dialysis fluid originates as drinking water (i.e., water that is safe to drink and, in the United States, meets the National Primary Drinking Water Regulations (NPDWR), a legally enforceable standard. A patient receiving regular dialysis treatment for end-stage renal disease is typically exposed to around 360 liters of dialysis fluid per week, roughly 25 times more than the average person drinks in the same period. As the membrane used in the dialyzer is permeable, the water used in the preparation of the dialysis fluid requires additional treatment in the dialysis unit to reduce levels of impurities that may be present at levels below the standards for drinking water. The technology of treatment

for such reduction and the standards to which such water must be prepared are discussed elsewhere. This paper focuses on the effect of dialysis fluid purity on dialysis morbidity and mortality.

Which Contaminants Matter?

Chemical Contaminants

Drinking water is known to contain a variety of chemical contaminants including inorganic, synthetic, and volatile organic contaminants, and pesticides, herbicides, and disinfectants added to neutralize bacteria such as giardia, *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa*. For drinking water, the maximum permitted levels of such contaminants are defined by the Environmental Protection Agency (EPA) (www.epa.gov/safewater/mcl.html).

Chemical contaminants in drinking water may be naturally occurring (e.g., lead and fluoride) or added during the treatment of water for domestic consumption and use. For example, at water treatment plants, particulate matter is removed by the addition of aluminum sulphate and calcium hydroxide, while chlorine or chloramine is added to control bacterial contamination, to make the water less acidic, and reduce corrosion to metal pipes in the distribution network additional lime may also be added.

The maximum permissible chemical contaminant levels in water used in the preparation of dialysis fluid are set by national and international standards, such as the Association for the Advancement of Medical Instrumentation's recommended practices for dialysis water treatment systems (ANSI/AAMI RD52 and ANSI/AAMI RD62). AAMI's system uses three separate categories: 1) substances present in the dialysis fluid (e.g., sodium, potassium, calcium), 2) substances regulated by the Safe Drinking Water Act (e.g., arsenic,

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chromium, lead), whose levels are set at 10% of that permitted in drinking water or at no transfer level, and 3) substances identified as toxic, whose level is set at the lowest level.

In the context of chemical contaminants, a number merit further discussion due to the problems they pose to dialysis patients.

Aluminum is added to drinking water to remove particulates. It accumulates in the bone, resulting in decreased mineralization, and can also cause encephalopathy. Historically, the treatment of water for dialysis was less sophisticated than today, and in the 1970s, outbreaks of encephalopathy (dementia) in various dialysis units were reported, the cause of which was subsequently traced to the inadequate removal of aluminum from water in dialysis units by the then-used water treatment processes (deionizers and softeners). (1) Studies by Parkinson, et al., (2) demonstrated that aluminum removal is only possible by reverse osmosis. Today, reverse osmosis systems provide the first line of treatment for water used in the preparation of dialysis fluid, and this together with the declining use of aluminum-containing phosphate binders has resulted in a decline in abnormal aluminum levels in dialysis patients. The occasional isolated outbreaks of intoxication, however, continue to be reported in the literature. (3-5)

Fluoride is added to drinking water to promote dental health. The EPA has set an enforceable drinking water standard for fluoride of 4 mg/L and a secondary fluoride standard of 2 mg/L to protect against dental fluorosis in developing teeth. The maximum permissible levels in water used for the preparation of dialysis fluid are set at 0.2 ppm (0.2 mg/L). During dialysis, fluoride is removed from the plasma, but the removal rate is less than for other small molecules such as urea and creatinine, resulting in the presence of elevated levels in patients. (6,7) High serum fluoride in dialysis patients is associated with a risk of osteodystrophy and osteomalacia. (8) Deionizers have a limited adsorptive capacity and it is important to understand the possible consequences of operating them beyond their limits. If deionizers are operated to exhaustion, ions previously removed may be released. Such release has been implicated in a fatal fluoride intoxication. (9)

Nitrates are used extensively in fertilizers, and if present in the water can cause methemoglobinemia (blue baby syndrome) in very young children. Glucose-6-phosphate dehydrogenase is involved in the reduction

of methaemoglobin levels in the blood, and a deficiency may predispose some population groups to the development of methaemoglobinemia. For dialysis patients, the maximum permissible levels are less than 2 mg/L nitrate as nitrogen. This level is readily achieved with current water treatment systems and clinical complications in dialysis patients relate to early experiences when less sophisticated water treatment was in use. (10)

Chlorine is added to drinking water to maintain microbiological purity. Chlorine is toxic for humans; it reacts with the body fluids and releases chemical species capable of modifying cellular proteins and lipids, protein denaturation, and hemolysis. The most obvious clinical manifestation of exposure in dialyzed patients is hemolytic anemia arising from the oxidation of bivalent iron in hemoglobin to trivalent iron, leading to the formation of methemoglobin, which is unable to transport either O₂ or CO₂. The presence of methemoglobin leads to the appearance of Heinz bodies, which may be seen when chloramine concentrations exceed 0.5 mg/L. They increase in number and in proportion to the chlorine concentrations and their presence was common during the early years of dialysis, but today it is rare-although it was noted in an outbreak of hemolytic reactions in dialysis patients in 2001. (11-13)

Chloramine is replacing chlorine as a sterilant. Its use is associated with lower levels of disinfection by-products such as trihalomethanes. It is more stable than chlorine and lasts longer in the distribution system. Chloramine, if present in water used for the preparation of dialysis fluid, has the potential to cause anemia or an apparent resistance to erythropoietin by inhibiting the hexose monophosphate shunt, which normally protects red blood cells from oxidative damage, and by oxidizing hemoglobin to methemoglobin. (14,15)

Trace elements such as zinc, copper, and selenium, essential nutrients with a range of physiologic functions, are present in drinking water. Reverse osmosis is able to totally remove such compounds, but a loss over an extended period of time may occur in the dialysis patient, and monitoring of trace metal levels should be undertaken periodically with supplementation for those patients demonstrating deficiency.

Although the most common exposure to chemical contaminants is from the water, occasional exposure can occur from other sources such as the inadequate removal or environmental exposure to chemicals used in the cleaning of the water treatment plant. (16)

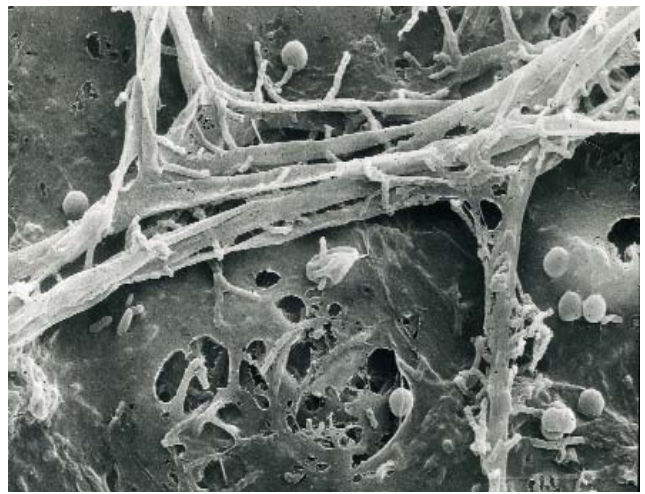
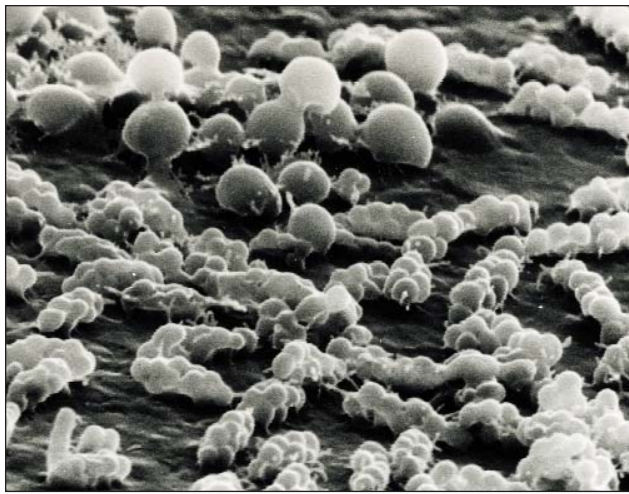


Figure 1. Biofilm on the surface of a water distribution system used in a dialysis unit. (Photographs courtesy of Luc Marchal and Jean Printz. Published with permission from Gambro Lundia AB, Lund, Sweden).

Microbiological Contaminants

Drinking water is treated to minimize bacterial contaminants. Occasional issues from the presence of cyanobacteria can occur in hot summers and are known to affect both dialysis patients and the general population. (17,18)

The commonly used sterilants are ineffective against *Cryptosporidium* oocysts, and their presence in drinking water may cause a problem in immuno compromised patients not receiving dialysis. There are no reports of increased prevalence of *Cryptosporidium* infection in dialysis patients compared to the normal population.

An essential step of water treatment is the removal of chemicals present in the water. Chlorine and chloramines are removed by granular activated carbon, rendering components of the water treatment plant as well as the distribution network prone to the development of biofilm. Biofilm consists of a fine fibrillar meshwork of bacterial origin, with trapped micro-organisms. (Figure 1) The presence of biofilm in dialysis systems is a point of concern, first because biofilms continuously release bacterial components such as peptidoglycans and endotoxins. Moreover, the bacteria present in biofilm are highly resistant against cleaning and disinfection procedures and therefore eradication, once a biofilm is present, is virtually impossible. Recently, however, a new anti-biofilm procedure consisting of a sequential treatment combining enzymes and detergents able to detach adherent cells has been developed. (19)

Bacteria such as those that may be present in the biofilm do not cross the dialyzer membrane, but the

released endotoxin fragments, muramylpeptides, and polysaccharides are able to traverse dialysis membranes (20). Patient exposure to such compounds may have immediate effects in the form of pyrogen reactions, and over the longer period, bacterial DNA fragments can trigger Toll-like receptors on monocytes and induce cytokine production, leading to an inflammatory response. (21) The presence of an inflammatory response in the patient may be signified by the presence of elevated levels of cytokines or C reactive protein, both of which have been shown to be independent predictors in mortality. (22)

Recent evidence demonstrates that chronic inflammation, a non-traditional risk factor that is commonly observed in dialysis patients, can be caused by dialysis-related and unrelated factors. (23,24). The presence of such inflammation can cause impairment of protein catabolism in skeletal muscle and protein-energy malnutrition.

Moving Beyond Today

A number of clinical studies have highlighted the benefits of using ultrapure dialysis fluid in chronic hemodialysis patients. When ultrapure dialysis fluid, defined as fluid with a bacterial count of <0.1 CFU/mL and endotoxin level <0.03 EU/mL, is used, it is associated with improvements in inflammation, maintenance of renal function following the initiation of dialysis, reduction of carbonyl stress, improvement in malnutrition, improvement in iron utilization, and improved erythropoietin response, leading to lower erythropoietin dosage or use. (25-29)

In the United States, the current standards for the microbiologic quality of water and dialysis fluid remain at variance with those suggested in other standards, such as the European Pharmacopoeia.

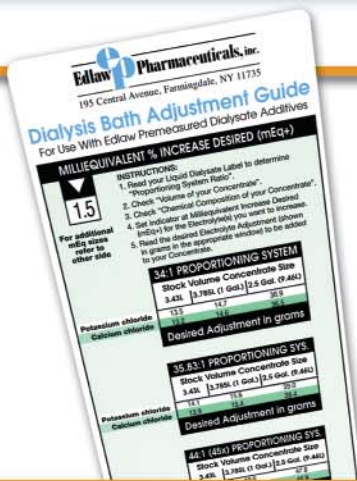
Although it could be argued that there are no data defining the concentration dependence of outcomes on dialysate purity, and randomized clinical trials are lacking, technology exists to routinely provide ultrapure dialysate. The time has now come to take advantage of such innovations to modify clinical practices aimed at decreasing the acceptable microbial contamination levels below that indicated in the current AAMI standards. ■

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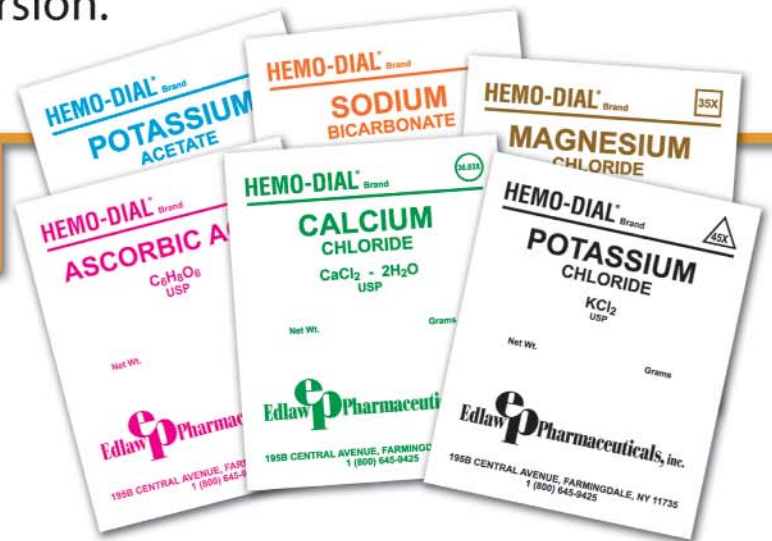
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