Ultrapure Dialysis Water: Is it really pure?

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The definition of microbiologic quality of hemodialysis (HD) fluid is the maximum allowable levels for bacteria and endotoxin. For dialysis fluid purified by standard methods, the maximum level for bacteria is < 100 colony-forming units (CFU)/ml and for endotoxin concentration using the limulus amebocyte lysate (LAL) essay < 0.5 endotoxin unit (EU)/ml. Ultrapure dialysis fluid is defined as containing < 0.1 CFU/ml and < 0.03 EU/ml. The term "ultrapure" was coined in the early 1980s to denote dialysis fluid that is more purified than the standard purified fluid and can be a surrogate for sterile non-pyrogenic fluid [1,2].

The potential hazard of water impurity is due to the risk of occasional mechanical leak in the dialyzer and routinely occurring back-filtration of dialysate through the dialyzer membrane, which is augmented through larger pores in high-flux dialyzers.

Impurity of the dialysate for contaminants such as bacteria and bacterial endotoxin might contribute to infections and a systemic inflammatory state, which are common in HD patients and affect their usually poor cardiovascular and other outcomes [3-5]. Thus, ultrapure fluid was suggested as "a need for future dialysis" by Canaud and co-researchers already 32 years ago [2]. Ultrapure dialysis fluid has been shown to decrease the chronic inflammatory response and associated surrogate markers, such as reduction in serum albumin level, degree of anemia, and required

dosage of erythropoietin-stimulating agent (ESA) [3-5]. Thus, currently, ultrapure dialysis fluid is required when using high-flux dialyzers and is recommended when possible for all HD patients.

The dialysis water system comprises three steps: (a) pretreatment, whose main components include filters to remove particles and active carbon to remove chlorine, (b) purification, whose main functions include reverse osmosis (RO) and sometimes deionization, and (c) distribution and ultra-purification whose main components include pipes and post-reverse osmosis ultrafilters. Any part of the distribution system can be contaminated by bacteria with formation of biofilm [6], which may not be totally destroyed by repeated disinfections and may be associated with undetected but clinically significant bacterial products.

Ultrapure dialysis fluid can be produced by filtering standard dialysis fluid, after passing purification by the reverse osmosis system, through a submicron bacteria and endotoxin-retentive filter. However, it is important to keep the purified or ultrapure fluid from being contaminated, and cooling the fluid is one way to help achieve this. There are two common methods for water filtering and production of ultrapure dialysis water: additional filters at the end of the distribution system within each machine before the dialysis fluid enters the dialyzer, or an additional ultrafilter after the reverse osmosis at the start of the distribution system before dialysis water is distributed collectively to all dialysis machines. In the latter, the ultrapure fluid may be contaminated downstream in the distribution system. However, the machine-based ultrafilters may also become contaminated. Contemporary dialysis machines are designed such that such submicron bacteria and endotoxin-retentive filters can be

installed as an integral part of the dialysis fluid pathway and can be sanitized whenever the dialysis machines are disinfected. These filters can be added to older dialysis machines that lack this component. They have been validated by the manufacturer to remove bacteria and endotoxin for a given period of time or number of HD treatments. Recently, Di Iorio et al. [7] added an ultrafilter not inside the machine itself but on the wall in front of and adjacent to it. This ultrafilter comprises two serially positioned devices with significant bacterial, viral and endotoxin-retaining capacity [7]. In a prospective crossover study of 29 patients they found that adding the ultrafilter improved dialysis water purity, reduced levels of inflammation markers, and improved hemoglobin concentration with reduced ESA doses as compared to control water.

However, the filters do not remove some small bacterial products, such as fragments of bacterial DNA, which may be clinically significant but are not detected even by the highly sensitive methods performed periodically to determine microbial contaminant levels. Detection of some endotoxins, such as peptidoglycan and other bacterial cell wall components with pyrogenic properties, may be attained by tests that are not generally performed by routine laboratories. Those endotoxins may be detected by their capacity to induce formation of cytokines [8-13]. Gram-negative bacteria remaining in pipes outside the hours of dialysis will proliferate and adhere to wet surfaces, forming biofilms. Biofilm may be present in water storage and distribution systems even when bacteria and endotoxin test results are low, and may be suggested by inconsistent and erratic bacteria testing results since tests detect only organisms suspended in water. When

bacterial contamination persists despite frequent and aggressive disinfection, it may be necessary to determine if biofilm is the cause. In such instances, use of alternative disinfection methods or even replacement of equipment may be required to remediate biofilm [13-16].

In the current issue of *IMAJ*, Grupper and co-authors [17] suggest a third method to produce ultrapure water, namely, adding a RO system after the first commonly used one. They found in a retrospective study of 193 HD patients that an additional ultrapure filter in each dialysis machine does not confer short-term benefits over double RO systems. They compared the same patients in 6 months without the ultrapure filter and in the subsequent 18 months with the ultrapure filter. For a control group they used a historical cohort of 2 years earlier to validate that the effect was not due to time on HD. They found that mean serum C-reactive protein (CRP) increased and serum albumin and systolic blood pressure decreased in the period with the ultrapure filter as compared to that without the ultrapure filter and the controls. The decrease in serum albumin and the increase in CRP were apparent only in patients with arteriovenous access but not in those with a tunneled catheter, possibly due to a higher state of inflammation in the latter patients masking other inflammatory stimuli. CRP levels significantly increased only in patients on high-flux dialyzers, suggesting the possibility of augmented back-filtration of contaminated dialysate. The authors emphasized that their study is the first to assess the effect of an ultrapure filter using a double and not a single RO system, but were aware of its limitation as a retrospective study without an appropriate control group. To explain their unexpected findings, they suggested the increased risk for biofilm formation when ultrapure

filters are not used or rinsed. In contrast, RO systems are in continuous use. The authors raised the concern that their findings may suggest that periodical monitoring of bacterial count and endotoxins may fail to detect variations in water quality or fluctuant bacterial counts due to biofilms. They concluded that in their unit a double RO system to produce ultrapure water is at least not inferior to the use of ultrapure filters [17].

So what is the most appropriate method to produce and protect a true ultrapure dialysis fluid? It seems that it depends on a combination of variables and local factors. These may include water supply, pretreatment, purification and distribution systems, as well as methods and frequency of disinfection of the water system and dialysis machines. Other factors include frequency of changes of the ultrafilter, and frequency and methods for collection and testing of the fluid. Biofilm formation and resistance to disinfection in the water system and possibly in ultrafilters is common and may necessitate replacement of water system components and equipment, especially after failure of repeated disinfections. The inability to detect certain bacteria and bacterial products may be common, and patient follow-up with CRP levels is recommended. A combination of methods such as double RO and an individual machine ultrafilter, though not successful when tried by Grupper et al. [17], seems reasonable.

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"Joy is not in things! It is in us!"

Benjamin Franklin (1706–1790), American statesmen, author, printer and satirist

"In matters of style, swim with the current. In matters of principle, stand like a rock"

Thomas Jefferson (1743–1826), third president of the United States