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Worldwide water standards for hemodialysis

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Abstract

Contaminants commonly found in tap water are toxic to hemodialysis patients. To prevent patient injury from these contaminants, standards for the quality of water used to prepare dialysate have been developed. These standards are in general agreement concerning maximum allowable levels of inorganic chemical contaminants known to have adverse consequences for dialysis patients. There is less agreement about inorganic chemical contaminants that may be toxic, and most standards omit any requirements for organic chemical contaminants. There are considerable differences between standards regarding the maximum allowable levels of microbiological contaminants, as well as the methods to be used for measuring them. Harmonization of existing standards may improve patient protection by promoting demonstrated best practices. Harmonization will require innovation and compromise to produce a standard that is widely applicable, provides patients with the necessary safeguards, and whose requirements can be routinely achieved within the constraints imposed by local reimbursement practices.

Key words: Hemodialysis, water, standards, harmonization

INTRODUCTION

When hemodialysis was first introduced as a treatment for end-stage renal failure in the 1960s, dialysate was formulated by adding various salts, and often glucose, to tap water. Once the more pressing technical challenges of dialysis, such as blood access, were addressed and patients began to survive for longer times and in greater numbers, it became apparent that dialysate prepared from tap water could contain substances that were harmful to hemodialysis patients or that caused problems with hemodialysis machines.[1] As these substances were identified, individual nephrologists began to change their practices. For example, in areas where municipal water supplies contained high levels of calcium and magnesium (hard water), the fluid pathways of dialysis machines became fouled with carbonate precipitates[2] and some patients developed symptoms of hypercalcemia.[3] Recognizing that these problems were related to high levels of calcium in the municipal water, nephrologists began treating the municipal water with a softener before it was used to prepare dialysate.[2,3]

By the mid-1970s, aluminum, chloramines, copper, and fluoride had been identified as being definitely or probably toxic to hemodialysis patients.[1] For aluminum and chloramines, this toxicity was evident at concentrations commonly found in municipal water supplies. In addition, the incidence of pyrogenic reactions during hemodialysis was observed to correlate with the level of bacteria in the dialysate.[4] Thus, it was clear that the water used to prepare dialysate needed purification to ensure low levels of these contaminants. This realization was the start of the development of fluid quality standards for hemodialysis, a process that continues to the present day. The purpose of this paper is to review the evolution of quality standards for water used in hemodialysis applications and discuss some of the issues that may influence the development of these standards at the beginning of the 21 century.

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In the beginning . . .

The idea of a quality standard for water used in hemodialysis appears to have been considered first in the United States in the late 1960s, when the Association for the Advancement of Medical Instrumentation (AAMI) and the American Society for Artificial Internal Organs (ASAIO) began a collaborative effort to write a standard for hemodialysis machines. A tentative draft of that standard was published for comment in 1970. This initial draft suggested that the quality of water used to prepare dialysate should meet the requirements of the United States Pharmacopoeia for purified water, with an additional limit on heavy metals (<0.01 mg/L) and a minimum resistivity of 1 MΩ cm at 25 °C if deionized water was used. This draft underwent numerous revisions over the next 9 years, and it was not until 1979 that the AAMI Renal Disease and Detoxification Committee finally reached agreement on its content. About the same time, Prakash Keshaviah at the Minneapolis Medical Research Foundation, under contract to the United States Food and Drug Administration, was preparing a report identifying the risks and hazards associated with conventional hemodialysis systems. Because of the potential overlap between these 2 endeavors, the AAMI Renal Disease and Detoxification Committee decided to wait for Keshaviah's report before finalizing their standard. Keshaviah's report appeared in June 1980[5] and many of its recommendations were incorporated into the first AAMI standard for hemodialysis systems, which was finally published in May 1982.[6] A parallel effort took place in Canada, with the Canadian Standards Association publishing a draft standard (CSA Standard Z364.2) in 1978.

The AAMI standard established maximum levels of a range of chemical contaminants and bacteria in the water used to prepare dialysate (Tables 1 and 2), as well as a maximum level of bacteria in the final dialysate. The water quality requirements of the Canadian standard were substantially the same as those in the AAMI standard. The substances covered by these standards could be divided into 4 groups (Tables 1 and 2): substances with documented toxicity in hemodialysis patients; substances normally included in dialysate; other trace elements; and microbiological contaminants. For substances with documented toxicity in hemodialysis patients, the maximum levels were set at values less than the lowest level at which toxicity had been documented. For substances normally included in dialysate, the maximum levels were set so that the water would not significantly affect the final dialysate composition. The other trace elements included in the standard were based on the United States Environmental Protection Agency's *National Interim Primary Drinking Water Standard* published in 1975, which set maximum contaminant levels for substances that had been determined to be hazardous to the health of the general population. Because hemodialysis patients have a much greater exposure to water than a person with normal renal function, because the gradient for transfer from dialysate to blood may be maintained throughout dialysis because of protein binding, and because hemodialysis patients lack renal excretion, the maximum allowable levels for these substances was set at one-tenth of the EPA maximum allowable level for drinking water or the no-transfer level. (The no-transfer level for a solute is defined as that dialysate concentration at which there will be no net transfer of the solute across the dialyzer membrane, given a normal plasma concentration of the solute.) The maximum allowable level of bacteria in the water was based on the observation that the incidence of pyrogenic reactions was significantly increased if the level of bacteria in the dialysate exceeded 2000 CFU/mL.[4] Experience suggested that dialysis machines in use at the time the standard was being developed could amplify the bacterial burden in the water by a factor of 10. Therefore, the maximum allowable level of bacteria in the water was set at 200 CFU/mL.

Current water quality standards and recommendations

In the years since the AAMI standard was first published, many other countries have established standards or recommendations for the quality of water used in hemodialysis. These standards and recommendations have been prepared by standards organizations (e.g., Canadian Standards Association,[7] American National Standards Institute/AAMI,[8] International Organization for Standardization [ISO][9]), pharmacopoeias (e.g., Europe,[10] United States[11]), and professional associations (e.g., European Renal Association-European Dialysis and Transplant Association [ERA-EDTA],[12] Japanese Society for Dialysis Therapy[13]). While there is general agreement concerning the maximum allowable levels of inorganic chemicals with documented toxicity in hemodialysis patients (aluminum, chloramines, copper, fluoride, lead, nitrate, sulfate, and zinc), there are some exceptions. For example, the current edition of the European Pharmacopoeia does not explicitly specify maximum allowable levels for copper or chloramines. In the latter case, the European Pharmacopoeia does specify a maximum allowable level for total available chlorine and provides a test method that will detect both free chlorine and chloramines.[10] As the maximum allowable level for total available chlorine is set

Table 1 Recommended maximum concentrations of chemical contaminants in water used for hemodialysis

Contaminant (mg/L)	AAMI[8]	Canadian Standards Association[7]	United States Pharmacopoeia[11]	European Pharmacopoeia[10]
Substances with documented toxicity in hemodialysis patients				
Aluminum	0.01	0.01	0.01	0.01
Chloramines	0.10	0.10	0.10	—
Free chlorine	0.50	—	0.50	—
Total available chlorine	—	—	—	0.1
Copper	0.10	0.10	0.10	—
Fluoride	0.20	0.20	0.20	0.20
Lead	0.005	0.005	0.005	—
Nitrate (as N)	2.00	2.00	2.00	2.00
Sulfate	100	100	100	50
Zinc	0.10	0.10	0.10	0.10
Substances normally included in dialysate				
Calcium	2	2	2	2
Magnesium	4	4	4	2
Potassium	8	8	8	2
Sodium	70	70	70	50
Other substances				
Ammonia	—	—	—	0.2
Antimony	0.006	0.006	0.006	—
Arsenic	0.005	0.005	0.005	—
Barium	0.10	0.10	0.10	—
Beryllium	0.0004	0.0004	0.0004	—
Cadmium	0.001	0.001	0.001	—
Chromium	0.014	0.014	0.014	—
Chloride	—	—	—	50
Mercury	0.0002	0.0002	0.0002	0.001
Selenium	0.09	0.09	0.09	—
Silver	0.005	0.005	0.005	—
Thallium	0.002	0.002	0.002	—
Total heavy metals	—	—	—	0.10
Total organic carbon	—	0.500	—	—

AAMI = Association for the Advancement of Medical Instrumentation.

at the same value as other standards set for chloramines, there is effectively no difference in quality requirements. In addition, there are some differences in how the various standards treat heavy metals and substances normally included in dialysate (magnesium, potassium, and sodium; Table 1). Some standards (Canada, United States, ISO) specify limits for individual heavy metals, while others (European Pharmacopoeia) set a limit for heavy metals as a group. Also, the range of heavy metals included in the standards has evolved over time. Three additional heavy metals (antimony, beryllium, and thallium) were added to the AAMI standard in 2001 by virtue of their inclusion in the United States drinking water standard. The AAMI Renal Disease and Detoxification Committee expressed some hesitation about adding these elements to their hemodialysis water standard because there were no data documenting their toxicity in hemodialysis patients. The extent to which standards for water used in dialysis applications should continue to be influenced by drinking water standards remains an open question as discussed later in this review. Overall, and with the exception of the omission of copper from the European Pharmacopoeia, there is no compelling evidence of adverse clinical consequences arising from the minor differences between standards in the allowable levels of inorganic chemical contaminants.

Of note, none of the existing standards and recommendations includes limits for specific organic chemical contaminants. The rationale for this omission is that organic chemicals with specific toxicity to hemodialysis

Table 2 Recommended maximum levels of microbiological contaminants in water used for hemodialysis

	Bacteria (CFU/mL)	Endotoxin (EU/mL)
AAMI[8]	200	2
Canadian Standards Association[7]	100	2
United States Pharmacopoeia[11]	100	2
European Pharmacopoeia[10]	100	0.25
Swedish Pharmacopoeia[16]	100	0.25
ERA-EDTA[12a]	100	0.25
Japanese Society for Dialysis Therapy[13]	—	0.25
Italian Society of Nephrology[17a]	100	0.25

[a]Both the ERA-EDTA and the Italian Society of Nephrology recommend that all dialysis facilities aim for ultrapure dialysate.
AAMI=Association for the Advancement of Medical Instrumentation; ERA-EDTA=European Renal Association-European Dialysis and Transplant Association.

patients have not been identified and that carbon adsorption and reverse osmosis should remove most organic compounds. That hemodialysis patients may be at risk from organic compounds is evidenced, however, by recent reports from Italy describing contamination of water by organo-halogenated compounds that were not removed by standard hemodialysis water treatment practices,[14,15] including the use of activated carbon and reverse osmosis. The Canadian standard[7] does include a maximum allowable level for total organic carbon (0.5 mg/L); however, it is not clear that meeting this requirement would protect against toxic levels of many organic compounds.

In contrast to chemical contaminants, there are significant differences in the recommended maximum allowable levels of microbiological contaminants in water used for hemodialysis. These differences involve not only the levels of microbiological contaminants (Table 2) but also the methods used to measure them (Table 3). The original AAMI standard set a maximum allowable level for bacteria of 200 CFU/mL. Subsequently, other standards[7,10,11,16] and recommended practices[12,17] set the level at 100 CFU/mL, which is not substantially different from 200 CFU/mL, given the variability inherent in using plate counts to determine bacterial levels. As discussed later, however, there may actually be significant differences in the allowable level of bacteria, depending on what culturing methods are specified. The original AAMI standard did not set a limit for endotoxin because, at that time, no convenient test for endotoxin was available. In 2001, the AAMI standard was revised to include a maximum allowable level of endotoxin of 2 EU/mL measured using the *Limulus amebocyte* lysate assay. This change took place after a lengthy debate about whether or not there was sufficient clinical evidence to support inclusion of a maximum allowable level of endotoxin. This cautious approach is in marked contrast to the position taken in Europe and Japan, where a considerably lower maximum allowable level of endotoxin (0.25 EU/mL) was introduced during the 1990s. Indeed, many authorities advocate even lower maximum allowable levels for bacteria and endotoxin (0.1 CFU/mL and 0.03 EU/mL, respectively), although so far these levels remain recommendations, rather than requirements. Fluids meeting this more rigorous quality standard are referred to as "ultrapure."[18] Low levels of endotoxin and other bacterial products in dialysate have been implicated in the low-level chronic inflammation observed in hemodialysis patients. Use of ultrapure fluids is believed to ameliorate this inflammation and delay or reduce the severity of long-term complications of hemodialysis therapy, such as malnutrition,

Table 3 Recommended method for determining bacterial levels in water used for hemodialysis

	Culture medium	Incubation temperature (°C)	Incubation time (hr)
AAMI[8]	TSA	35 to 37	48
Canadian Standards Association[7]	TSA, SMA, R2A	35	48
United States Pharmacopoeia[11]	TSA	30 to 35	≥ 48
European Pharmacopoeia[10]	R2A	30 to 35	120
Swedish Pharmacopoeia[16]	TGEA	22	≥ 120
ERA-EDTA[12a]	R2A	20 to 22	144
Italian Society of Nephrology[17a]	TGEA, R2A	20 to 23	120 to 144

[a]Both the ERA-EDTA and the Italian Society of Nephrology recommend that all dialysis facilities aim for ultrapure dialysate.
AAMI=Advancement of Medical Instrumentation; ERA-EDTA=European Renal Association-European Dialysis and Transplant Association; R2A=Reasoner's 2A; SMA=standard methods agar; TGEA=tryptone glucose extract agar; TSA=tryptic soy agar.

β_2-microglobulin amyloidosis, resistance to erythropoietin, and loss of residual renal function.[19]

In addition to differences in the maximum allowable levels of endotoxin, there are important differences between standards in the methods recommended for measuring bacterial contamination. The original AAMI standard allowed the use of tryptic soy agar (TSA), standard methods agar (SMA), or blood agar, with enumeration of colonies after incubation for 48 hr at 37 °C.[6] It was soon realized that the nutrient-rich environment provided by blood agar was not appropriate for culturing organisms adapted to a purified water environment and the use of blood agar was eliminated as an option in subsequent versions of the standard.[8] Later studies also showed that the combination of TSA and incubation at 37 °C for 48 hr was not optimal for recovery of waterborne organisms. Use of nutrient-poor media, such as Reasoner's 2A and tryptone glucose extract agar, and longer incubation times at room temperature resulted in colony counts that were often an order of magnitude higher than those obtained with TSA incubated for 48 hr at 37 °C.[18] These more stringent culturing conditions have been adopted in whole, or in part, by several organizations issuing standards or recommendations for the quality of water used for hemodialysis (Table 3).

Where do we go from here?

Some in the dialysis community believe that the time is right to harmonize existing quality standards for water used in hemodialysis applications. It is suggested that a harmonized standard would help disseminate demonstrated best practices in countries with well-established hemodialysis programs, thereby decreasing the likelihood of both acute and chronic adverse events related to water quality. It could also serve as a guideline for countries where chronic hemodialysis is still in its infancy. Finally, a harmonized standard may contribute to better technology for water purification and distribution by establishing a consistent set of expectations for equipment manufacturers. Current efforts to revise and expand the ISO's standards related to fluids used for hemodialysis may act as an impetus to harmonization. Before harmonization can occur, however, 2 important questions must be answered: Is harmonization desirable and feasible; and, how should the maximum allowable levels of contaminants be determined?

The desirability and feasibility of harmonizing water quality standards depend, in part, on how such standards are used. There is a significant difference between a standard used to provide guidance on demonstrated best practices and a standard that is enforced as a regulation. Both models, as well as various hybrid versions, are currently in use around the world. For example, in the United States, compliance with the AAMI standard for water quality is required if a facility is to receive payment for hemodialysis services from the United States Government's Medicare program and compliance is monitored by periodic inspections of dialysis facilities. In contrast, compliance with standards is either not required or not enforced by inspection in many other jurisdictions. A quality standard enforced as a regulation must be capable of being met routinely by a typical dialysis facility at a cost consistent with local reimbursement practices. In contrast, a standard intended as a guide to best practices may recommend a level of quality that can be met only by commitment of additional resources at the discretion of an individual dialysis facility that believes that level of quality will be of benefit to its patients. A harmonized standard should be capable of serving both functions.

It may be possible for a standard to serve both a regulatory and an advisory role by including 2 grades of water quality in the standard. The first grade would establish maximum allowable concentrations of contaminants based on definitive evidence that higher concentrations of a contaminant would be harmful to patients. The second grade may recommend a lower concentration of a contaminant where there was a suggestion that the lower concentration may be associated with improved patient outcomes. This approach has been used by the ERA-EDTA and the Italian Society of Nephrology, which have adopted the European Pharmacopoeia quality standard for maximum allowable levels of contaminants, but recommend the use of ultrapure fluids.[12,17]

As is evident from Tables 1 and 2, there are some differences in the range of contaminants included in the various standards and recommendations, as well as in the maximum allowable level of individual contaminants. A harmonized standard would require a resolution of these differences.

As mentioned previously, some current standards do not explicitly include chloramines even though their toxicity in hemodialysis patients has been documented repeatedly over 30 years.[20,21] It has been argued that there is no need to include chloramines in a standard for a region where chloramines are not used to disinfect municipal water supplies. However, patient injury has occurred in many parts of the world when municipal water providers began using chloramines with little or no prior notice to dialysis facilities. For this reason, it seems reasonable that a harmonized standard should include all

contaminants with documented toxicity in hemodialysis patients. The benefits of avoiding toxicity almost certainly outweigh the cost of routine monitoring for these contaminants.

Whether or not to include contaminants that have no documented toxicity in hemodialysis patients is a more difficult question. Heavy metals were included in the original AAMI standard because their levels in drinking water were regulated as a matter of public health and because they were thought to pose a greater risk to hemodialysis patients because of the mechanism of exposure and the lack of renal excretion. Other standards have chosen to deal with heavy metals collectively by establishing a maximum allowable level for them as a group. Neither approach is entirely satisfactory. Including a substance in the standard because it is included in drinking water regulations implies that any substance added to the drinking water regulations should be added to the hemodialysis water standard. This situation has arisen in the United States, leading to the addition of antimony, beryllium, and thallium to the hemodialysis water standard in 2001 even though there was no evidence that they posed a particular risk to hemodialysis patients. This open-ended, non-evidence-based approach only serves to increase the cost and complexity of monitoring water for hemodialysis without any apparent benefit to patients. Combining the heavy metals into a single group is attractive as it has the potential to reduce the cost of routine water analyses. However, treating heavy metals as a group implies that the maximum allowable level for the group should not exceed the maximum allowable level for the most toxic member of that group. Currently, maximum allowable levels for 10 heavy metals included in the standards that list each heavy metal individually are below the 0.1 mg/L level set in the European Pharmacopoeia for total heavy metals. At this point, it remains unclear how best to deal with trace contaminants, with no clearly defined toxicity in the setting of hemodialysis.

However this issue is resolved, an effective standard should incorporate a mechanism for promptly adding a new substance that may, in the future, be shown to be toxic to hemodialysis patients. Although candidate toxins are rare, examples have appeared in recent years. Lead, which was included in the original AAMI standard because its levels were regulated in drinking water, was reported recently to be toxic in hemodialysis patients,[22] although the level at which toxicity occurs is not well defined. Strontium contamination of water used to prepare dialysate has been implicated in bone disease in hemodialysis patients,[23,24] although there is still debate about the strength of the evidence for strontium toxicity and the concentration at which it occurs.

Microbiological contaminants present a particular problem in trying to reach consensus on maximum allowable levels of contaminants. As described earlier, current standards differ significantly in the maximum allowable level of endotoxin. Further, even though there does not appear to be a large difference in plate count values, in reality, there may be significant differences in the maximum allowable level of bacteria because of differences in recommended culturing methods. In general, European and Japanese standards set a lower maximum allowable level for endotoxin than the United States standard (Table 2). In addition, there is widespread support for the use of ultrapure fluids in both Europe and Japan, based on a growing literature showing improvements in outcomes such as nutrition and anemia correction when ultrapure dialysate is used. Some in the United States dialysis community argue, however, that the evidence used to support lower levels of endotoxin and, in particular, ultrapure dialysate is not convincing. They cite the absence of controlled clinical trials comparing outcomes obtained with lower levels of endotoxin, including ultrapure dialysate, with those obtained with dialysate meeting the current United States quality standards. They also worry about the cost and feasibility of routinely meeting a more stringent quality standard in a regulated environment where reimbursement is tightly controlled. With regard to water, these arguments may be somewhat moot. It should be remembered that patients are treated with dialysate, not water, and it is the microbiological quality of the dialysate that is important. In general, ultrapure dialysate is prepared by point-of-use filtration of the dialysate immediately before it enters the dialyzer. Clearly, higher quality water reduces the burden on the final ultrafilter; however, currently available point-of-use ultrafiltration systems should be capable of producing ultrapure dialysate from concentrates and water that routinely meet any of the quality standards listed in Table 2. Thus, the cost aspect of ultrapure dialysate shifts from debate about whether or not the quality of the water used to prepare the dialysate should be ultrapure to whether or not to install point-of-use ultrafilters for the final dialysate.

All of these arguments are predicated on the assumption that endotoxin levels are an adequate measure of water quality. Endotoxin testing reveals nothing about the levels of other microbiological contaminants, including yeasts, fungi, peptidoglycans, and fragments of bacterial DNA, all of which have been identified in water used for hemodialysis.[25–27]

SUMMARY

Hemodialysis patients are at risk from contaminants in the water used to prepare dialysate. To mitigate this risk, various organizations have developed standards and recommendations for water quality over the past 25 years. There is general agreement concerning maximum allowable levels of inorganic chemical contaminants known to have adverse consequences for dialysis patients. There is less uniformity when it comes to inorganic chemical contaminants that may have toxicity and an almost complete silence in the area of organic chemical contaminants. Further, there are considerable differences between the various standards and recommendations regarding the maximum allowable levels of microbiological contaminants and the methods to be used for measuring these contaminants. Harmonization of the various standards and recommended practices may help protect patients by promoting demonstrated best practices and providing a road map for those countries where large-scale hemodialysis is still in its infancy. Achieving harmonization will require innovation and compromise to produce a standard that is widely applicable, provides patients with the necessary safeguards, and whose requirements can be routinely achieved within the constraints imposed by local reimbursement practices.

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