THE IMPORTANCE OF WATER TREATMENT IN HAEMODIALYSIS AND HAEMOFILTRATION

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"Till taught by pain, men really knew not what good water's worth"
Lord Byron in "Don Juan"

The need for water treatment

Water, depending on the source, will contain varying amounts of dissolved inorganic and organic substances, particulates (clay, sand, iron, etc.) and microorganisms and pyrogens. Agricultural runoff, mining operations, and industrial and municipal pollution all play a role in the contamination of the water supply. Not all municipal supplies are regulated and while they may be safe for drinking purposes, the majority will require some form of treatment to make them safe for haemodialysis or haemofiltration.

Drinking water regulations are based on a weekly exposure of 14 litres. The patient on haemodialysis is exposed each week to between 300 and 400 litres and the patient on haemofiltration to between 70 and 100 litres. Further, these patients have diminished renal function and therefore, compromised urinary excretion of toxic substances. To compound matters further, the dialysis membrane is less selective than gastrointestinal absorption so that diffusion of toxic substances directly into the patient's blood stream occurs. Some of these toxic substances, such as the heavy metals, bind to plasma proteins thereby sustaining the gradient for diffusion from dialysate to blood so that even small gradients result in a significant toxic load. In the case of haemofiltration, there is direct infusion into the patient's blood without the restriction of a separating membrane.

The requirements for water used in haemodialysis and haemofiltration are, therefore, more stringent than for drinking water, necessitating additional water supply treatment. Some substances documented as toxic in haemodialysis are not regulated in the drinking water, a prime example being aluminium. There are reports from dialysis centres all over the world [1-10] correlating the incidence of 'dementia dialytica' to high concentrations of aluminium in the water used to prepare dialysate. Table I lists those substances which have been
TABLE I. Contaminants with documented toxicity in haemodialysis

<table>
<thead>
<tr>
<th>Contaminants</th>
<th>Toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium</td>
<td>Dialysis encephalopathy, and renal bone disease</td>
</tr>
<tr>
<td>Calcium/Magnesium</td>
<td>Hard water syndrome: nausea, vomiting, muscular weakness, flushed feeling, and hyper/hypotension</td>
</tr>
<tr>
<td>Chloramines</td>
<td>Haemolysis, anaemia, and methaemoglobinaemia</td>
</tr>
<tr>
<td>Copper</td>
<td>Nausea, chills, headache, liver damage, and fatal, haemolysis</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Osteomalacia, osteoporosis, and other bone diseases</td>
</tr>
<tr>
<td>Nitrate</td>
<td>Methaemoglobinaemia with cyanosis, hypotension and nausea</td>
</tr>
<tr>
<td>Sodium</td>
<td>Hypertension, pulmonary oedema, confusion, vomiting, headache, tachycardia, shortness of breath, seizures, coma and death</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Nausea, vomiting, and metabolic acidosis</td>
</tr>
<tr>
<td>Zinc</td>
<td>Anaemia, nausea, vomiting, and fever</td>
</tr>
<tr>
<td>Microbial</td>
<td>Pyrexial reactions – chills, fever, nausea, hypotension, and cyanosis</td>
</tr>
</tbody>
</table>

documented as toxic in haemodialysis and their toxic effects. Exposures to some of these substances in haemodialysis have resulted in fatalities.

As stated earlier, most municipal supplies require additional treatment to make them safe for haemodialysis and haemofiltration. There are variations in water quality that may be seasonal, related to variations in municipal treatment or to the use of multiple water sources. Certain chemicals such as fluoride and aluminium that are added by municipal authorities to make the water safe for drinking make the water unsafe for haemodialysis and haemofiltration. With the addition of such toxic chemicals, there always exists the possibility of the accidental addition of much larger quantities than desired, an accidental over-fluoridation of a municipal supply in Maryland affected eight dialysis patients with one death [11]. In addition the distribution system may itself contribute to contamination, toxic materials such as copper, brass, zinc and lead may leach into the water supply during distribution. All of these factors make additional treatment of the municipal supply essential for the safety of the haemodialysis/haemofiltration procedure. Further, a continuing dialogue between the dialysis centre and the municipal supplier needs to be established in order to anticipate and adequately compensate for variations in the municipal supply.

In this paper we deal with the various water treatment options available to the dialysis practitioner along with details concerning the nature of the treatment, the principles involved, the monitoring necessary and other features of the treatment options. We will also discuss the quality of product water required to
ensure safety of the patient and the monitoring requirements to ensure such water quality. The responsibilities of the manufacturer/supplier as well as those of an informed consumer will also be discussed. It is our hope that this paper will provide the practitioner with some of the basic technical information necessary to make informed choices concerning the type and configuration of water treatment necessary for a given water supply to safeguard the well-being of their dialysis patients.

Water treatment options

The water treatment options available for haemodialysis and haemofiltration include sediment filtration, softening, activated carbon filtration, deionisation, reverse osmosis, ultrafiltration and distillation.

Sediment filtration

Sediment filtration is used to remove large particulates (>1μ) from the water supply. If these particulates are not removed, there exists the possibility of plugging of equipment downstream with patient consequences depending on the mode of equipment failure. Figure 1 is a schematic representation of a sediment filter. Filtration is accomplished by size exclusion as the water percolates through screens, closely packed fibres or a porous matrix. Sediment filters are rated by ‘nominal’ pore size for particulate exclusion and the maximum flow

Figure 1. Schematic representation of a sediment filter
rate at which they may be operated. Once the exclusion capacity of the filter is exceeded, there may be 'break-through' of particulates into the effluent of the filter, as well as decreased flow in the system. It is, therefore, important to monitor the pressure drop across the filter by suitable pressure gauges, filters being discarded once the pressure drop exceeds the value specified by the manufacturer as a criterion for filter replacement.

One problem associated with sediment filters is the growth of microbial organisms on the filter media with consequent contamination of equipment downstream and the possibility of bacteraemias and pyrogen reactions in the patient. Disinfection of the water treatment system regularly and replacement of filters at appropriate intervals will minimise the problem.

In some filters, there may be a tendency for sloughing of the filter medium, thereby defeating the purpose of the filter. Further, it should be ensured that toxic residues are not released into the water supply from passage through the sediment filter. In one case [12], the filter was composed of cotton fibres held together by thermosetting polymers prepared from a resin of melamine and formaldehyde. Formaldehyde leached from the filter causing an outbreak of haemolytic anaemia involving 12 patients.

Sediment filters may be used singly or in series or parallel configurations and may be used at several points in the water treatment system. These include prefiltration of the municipal supply, following carbon filters to protect equipment downstream from particulates released from the carbon filters, at the inlet of the dialysis machine, etc.

**Softening**

As indicated in Table 1, excess calcium or magnesium in the municipal supply may result in the 'hard water syndrome' [13,14]. If the source water is high in
calcium or magnesium, water softening is essential. Water softeners are also used as pre-treatment for reverse osmosis devices to protect the membranes of these devices from scale build up and consequent failure.

Water softeners (Figure 2) are ion-exchangers, the resin of the water softener being a cationic resin that exchanges Na⁺ ions for Ca⁺⁺ and Mg⁺⁺ ions as well as other polyvalent cations such as iron and manganese. When all of the available Na⁺ ions in the resin have been exchanged, the resin is said to be exhausted and has to be regenerated. A brine of sodium chloride is used for regeneration, the ion-exchange process being thus reversed and Na⁺ ions being reinstated on the resin. Regeneration may be accomplished on-site or in a central commercial facility. Water softeners have to be sized appropriately, factors including the degree of hardness of the water, the rate of water consumption, and the ion-exchange capacity of the resin as well as the frequency of regeneration cycles. The effectiveness of the softener may be monitored by measuring the hardness of the effluent using suitable titration kits that have a resolution to 1mg/L.

In water softeners that are regenerated on-site and are not equipped with bypass valves, care must be taken to see that regeneration does not occur during the dialysis event. In a case described in the literature [15], accidental interruption of power to the unit caused a mistiming of the regeneration cycle with the development of hypernatremic symptoms (flushing, thirst, vomiting, back pain, headache, disorientation, etc.). If the water softener is provided with an automatic bypass valve, the supply water will not percolate through the resin during regeneration, thereby preventing the risk of hypernatremia from the brine used for regeneration.

As with sediment filters, the possibility of microbial growth on the softener resin exists. Back washing of the resin during regeneration will minimise this problem. Such back washing will also prevent the accumulation of particulates in the resin bed and consequent loss of ion-exchange capacity.

If the resin is regenerated at a central commercial facility, the facility must ensure no admixing of resin from the dialysis centre with resins of other non-medical users to prevent microbial and toxic contamination of the resin. In one case [16], cross-contamination of the resin between urban and rural users occurred with heavy microbial contamination of the urban user’s resin.

The risk of microbial growth in a water softener is to some extent inherent to the design of the resin bed. The problem may, however, be exacerbated if the effluent flow path incorporates dead ends and areas of flow stagnation. Rigorous disinfection procedures and periodic culturing can alleviate this problem. Ideally, a softener is followed by a membrane process, such as reverse osmosis (vide infra), which effectively removes bacteria from the water.

**Activated carbon filtration**

Activated carbon filters remove chlorine, chloramines, and dissolved organics (60–300 daltons) from the water supply and are used not only to meet the product water standards for these substances, but also as pre-treatment for deionisers and reverse osmosis devices. As shown in Figure 3, activated carbon
has a microporous structure and a very large surface area to weight ratio that facilitates adsorption of chlorine, chloramines, and smaller organic contaminants. The adsorption capacity and the rate of removal varies with the source of the carbon and the nature of the activation process. It is important to recognise this in choosing a carbon filter and in sizing it for a particular water supply. If the adsorption capacity is exceeded, there will be 'spill-over' of chlorine, chloramine, and dissolved organics into the effluent. Monitoring the concentration of chlorine or chloramine in the effluent is, therefore, a convenient method for monitoring the efficacy of a carbon filter. Carbon filters cannot be regenerated effectively and must be used as disposables or be repacked with fresh activated carbon. Activated carbon, because of its microporous structure, has a tendency to release particles of carbon called 'fines'. Sediment filters are, therefore, used downstream of carbon filters to trap these fines and prevent them from plugging equipment downstream.

Chlorine removal is necessary with some types of reverse osmosis membranes. However, removal of chlorine promotes microbial growth. Further, the porosity of activated carbon and its affinity for organics make carbon filters susceptible to microbial contamination. Carbon filters do contribute to increased levels of gram-negative bacteria and endotoxins. Appropriate disinfection of the downstream water treatment system is, therefore, important when carbon filters are used.

Chloramines are increasingly being used as bactericidal substitutes for chlorine in municipal treatment of the water supply because chlorine reacts with human acids and other naturally occurring organic compounds in the water supply to
form trithalomethones which have been shown to be carcinogenic in animals [17]. The US EPA has promulgated a maximum level of 0.1mg/L for total trithalomethone in drinking water necessitating the use of chloramines in municipalities. Chloramine in concentrations as low as 0.25mg/L can cause haemolysis, anaemia, and methaemoglobinemia especially in patients with hexose monophosphate shunt deficiency [18–23]. The improper sizing of a carbon filter or absence of monitoring can therefore be extremely hazardous in situations where chloramines are used as bactericidal agents. As activated carbons have a varying ability to remove chloramines, the choice of the right type of carbon filter is also important in such situations.

Deionisation

Deionisers (Figure 4), as the name implies, are used for the removal of dissolved inorganic ions in order to meet product water standards. As with softeners, ion-exchange is the basis for deionisation. There are two types of resin used, cationic and anionic. Cationic resins exchange hydrogen ions for cations while anionic resins exchange hydroxyl ions for anions. In a mixed bed deioniser, cationic and anionic resins are in a mixture so the exchanged hydrogen and hydroxyl ions combine to form water. Mixed bed deionisers produce water of very high quality, the resistivity of the water (a measure of deionisation efficacy) being in excess of 1megohm-cm. Ion exchange resins are usually made by polymerising a mixture of styrene and divinylbenze to form a polystyrene matrix. Cationic resins result from sulfonation of this matrix while anionic resins are made by chloromethylating and aminating the matrix. A dual-bed deioniser,
unlike a mixed-bed deioniser, consists of two separate resin beds, one cationic, and the other anionic, in series. Such deionisers are less effective than the mixed-bed design. As with softeners, when the exchange capacity of the cationic and anionic resins is exhausted, regeneration is possible. Cationic resins are regenerated with strong acids, while anionic resins are regenerated with strong alkalis. The sizing of deionisers is important and is based on the concentration of dissolved ions in the feed and the volume of flow through the system between regeneration cycles. If the feed water has a high content of total dissolved solids (inorganic), deionisers are expensive to operate. Deionisers are sometimes used to ‘polish’ the product water of reverse osmosis devices when it alone is not adequate for removing certain ions such as fluoride and nitrates. Used thus, the costs of deioniser operation are reduced by an order of magnitude as reverse osmosis typically removes more than 90 per cent of the dissolved solids.

Deionisers are monitored by measuring the resistivity of the effluent. Such resistivity monitors must be temperature compensated for appropriate monitoring of deioniser function. Regeneration of the deioniser is based on the resistivity of the effluent, a value of 1megohm-cm being usually used as the criterion for regeneration.

Deioniser resins are subject to fouling if the organic content of the feed water is high because of the large surface area and porous structure of the resins. As with softeners and carbon filters, deionisers are also susceptible to bacterial contamination. Pyrogenic reactions have been documented in the literature [24–29] consequent to bacterial contamination of deionisers. The potential for microbial contamination must also be considered in deciding sizing and regeneration schedules of deionisers.

When a deioniser is exhausted, previously adsorbed ions may be eluted into the effluent. The ions of lower affinity are the ones most readily displaced. With cations, the affinities are ordered as follows:

\[ \text{Ca}^{++} > \text{Mg}^{++} > \text{K}^+ > \text{Na}^+ > \text{H}^+ \]

With anions, the ordering is:

\[ \text{NO}_3^- > \text{SO}_4^{2-} > \text{NO}_2^- > \text{Cl}^- > \text{HCO}_3^- > \text{OH}^- > \text{F}^- \]

In one incident [30], a defective resistivity monitor resulted in the use of the deioniser beyond the point of exhaustion with very high fluoride concentrations in the effluent. The patient involved developed severe osteomalacia, bone resorption, and decreased bone formation. With the replacement of the faulty monitor and regeneration taking place at 800,000ohm-cm, there was improvement noted in the patient's osteomalacia.

When a deioniser is nearing exhaustion, the effluent water may become acidic because the imbalance between cation and anion exchange capacities usually favours cations. Two types of hazards have been documented as a result of acidic effluents from deionisers. One is that of leaching of copper [31–33] from the piping and components of the dialysis machine with copper-induced toxicity (haemolytic anaemia, nausea, vomiting, chills, anorexia, etc.). The other is inactivation of heparin by acidic dialysate with the consequent clotting of dialysers [34,35].
As with softeners, it must be ensured during commercial regeneration, that resins from dialysis centres are not intermixed with resins of non-medical users. In industry, deionisers are used for recovery of plating metals such as chromium and silver. Traces of these toxic metals may remain bound to the resin and be eluted into the water used for dialysis, with toxic consequences, if intermixing of resins occurs. Further, the chemicals used for regenerating the resins of a dialysis centre must not contain excessive levels of toxic impurities such as the heavy metals. Chemicals used for disinfection must be adequately rinsed from the deioniser before use.

With certain municipal supplies, the effluent from deionisers have been found to contain nitrosodimethylamine [36], a suspected carcinogen. In such situations, the feed water must be appropriately pre-treated or a carbon filter used in combination with the deioniser. Anion resins may also be susceptible to hydrolytic cleavage of amines which are dialysable and may constitute a health risk. As with carbon filters, deioniser resins may slough particles and a sediment filter downstream of the deioniser may be necessary.

Reverse osmosis

This form of treatment is effective for dissolved inorganics, dissolved organics, bacteria, pyrogens and particulates. Reverse osmosis is a membrane process that is based on molecular sieving (>200 daltons) and ionic exclusion with 90–98 per cent rejection of monovalent ions and 95–99 per cent rejection of divalent ions. When two solutions of different ionic concentrations are separated by a semipermeable membrane, solvent flows from the less concentrated to the more concentrated side. This phenomenon is defined as reverse osmosis and osmotic pressure is defined as the pressure that must be applied to the concentrated solution side to prevent such a flow. If the applied pressure is greater than the osmotic pressure, there is reversal of solvent flow with solvent moving from the more concentrated to the less concentrated side. This process is called reverse osmosis.

There are several types of membranes suitable for reverse osmosis – cellulotic, aromatic polyamides, polymimides, and polyfuranes. Thin-film composite membranes have also been recently developed for reverse osmosis. The geometrical configurations of the membrane in the reverse osmosis module include plate and frame, tubular, helical tube, spiral wound, and hollow fibre configurations. The spiral wound (Figure 5) and hollow fibre (Figure 6) configurations are usually used in water treatment for haemodialysis and haemofiltration. However, hollow fibre modules are susceptible to plugging and fibre leaks.

Reverse osmosis membranes are subject to premature failure if the feed water has not been appropriately pre-treated. If calcium, magnesium, iron, and manganese are present in high concentrations, there is scale formation on the membrane with loss of efficacy. Some membranes are sensitive to chlorine and chloramines. Cellulose acetate membranes are sensitive to pH>8. Cellulosic membranes are also susceptible to bacterial degradation. Pre-treatment is, therefore, essential to appropriate performance of the reverse osmosis device. The nature of the
pre-treatment will depend on the quality of the feed water and the type of membrane being used. Reverse osmosis membrane modules are expensive, and once damaged, ability to regenerate the membrane is limited.

While reverse osmosis is effective for removal of bacteria, viruses, and pyrogens, microbial infestation of the reverse osmosis module can occur with microorganisms and pyrogens penetrating small defects in the membrane or leaky seals. Bacterial contamination of the product water is, therefore, possible and appropriate disinfection schedules must be planned to control the problem.

Beyond the initial capital cost, water treatment by reverse osmosis is relatively inexpensive (barring premature membrane failure) and is a mode of treatment that effectively removes all four types of contaminants — organic, inorganic, particulate, and microbial. In situations where the ionic concentrations in the feed are very high (e.g. fluoride, and nitrate), a deioniser may be used to ‘polish’ the product water of reverse osmosis. Such a scheme can create a problem with microbial contamination and a downstream ultrafilter may be required. Reverse osmosis devices are monitored by resistivity measurements of the feed water and product water streams and by calculating the percent
rejection from these measurements. In some instances, the effluent may also be analysed for specific contaminants.

_Ultrafiltration_

Ultrafiltration is a membrane process like reverse osmosis, but the molecular cutoff is much higher, being between that of reverse osmosis and sediment filtration. Ultrafiltration is effective for removing micro-organisms, pyrogens, colloids, and particulates (sub-micron). Thin, polymeric membranes are used in ultrafilters, in a sheet or tubular configuration. Ultrafilters are available in different size ranges, relative to nominal pore size and flow capacity. Their effectiveness may be monitored either by measuring the pressure drop across the filter or by measuring bacterial and pyrogen levels in the effluent filtrate.

Ultrafilters may be used to protect the more expensive reverse osmosis membranes from bacterial contamination and fouling by colloids and particulates. Regeneration by chemical cleaning and back-flushing may be possible with certain ultrafilter designs, others being disposable. Ultrafilters are particularly useful as the last stage of treatment to control bacteria and pyrogens in the product water when upstream devices introduce such contamination.

_Distillation_

Distillation removes non-volatile organic and inorganic substances, particulates, colloids, micro-organisms, and pyrogens. It is an effective but very expensive

Figure 7. Schematic depiction of the distillation process

121
mode of treatment that is not commonly encountered in water treatment for
haemodialysis. Liquid water is converted, with expenditure of energy, to the
vapour phase with subsequent condensation of the vapour back to the liquid
phase by cooling (Figure 7). This form of treatment necessitates the use of
storage tanks and distribution pumps. The overall system may, therefore, be
prone to bacterial proliferation even though distillation, itself, eliminates
bacteria and pyrogens. Monitoring of efficacy is accomplished by measuring
the concentration of relevant species in the distillate for organics and by resist-
ivity measurements for ionic contaminants. Distillation is not effective with
volatile contaminants because of carry-over. Distillation systems are continu-
ously reusable, but maintenance requirements are stringent.

Bacterial contamination of water

As indicated above, sediment filters, softeners, carbon filters and deionisers
may all support microbial growth. The following types of bacteria have been
identified in dialysis systems: pseudomonas, acinetobacter, flavobacterium,
achromobacter, seratia, moraxella, aeromonas, mycobacterium chelonei, fortu-
itum, erwinia and alcaligenes. While bacteria and endotoxins ($10^5 - 10^6$ daltons)
cannot cross intact dialysis membranes, there is circumstantial evidence linking
dialysate contamination and pyrogen reactions. Sudden outbreaks of febrile
reactions have been associated with high levels of gram negative bacteria in
dialysate [24,28]. Antibodies to bacterial endotoxin have been detected in
the blood of dialysis patients [37] and electron micrographs have revealed
bacteria on both blood and dialysate sides of the dialyser membrane [38].
Blood samples of patients with pyrogen reactions during dialysis have tested
positive with the limulus lysate assay [39]. It must be noted that some of these
observations were made with Kiil dialysers. As Kiil dialysers were assembled
with membranes in the dialysis centre, endotoxin contamination of the blood
and dialysate sides of the membrane was usually unavoidable. Some of the
circumstantial evidence may, therefore, be related to dialyser contamination
during assembly rather than water contamination. Bacteria and endotoxins
may enter the blood of the dialysis patient through microscopic defects in the
dialyser membrane. Even with intact membranes, small bacteriologic by-products
such as peptidoglycans and enzymes may cross the membrane.

Some strains of bacteria can grow even in distilled water. Bacterial growth in
dialysate is accelerated not only by nutrients such as glucose in the dialysate but
also by the presence of solutes diffusing out of the patient's blood into the dialy-
sate. The levels of bacteria are, therefore, greatly amplified in the dialysate delivery
system and may reach very high levels towards the end of the dialysis procedure.
This is especially so with recirculating systems. It is, therefore important that the
microbiological growth of the water supplied to dialysate delivery systems be
monitored at frequent intervals and disinfection procedures established.

Water quality standards for haemodialysis

Inorganic substances

These may be divided into three categories – those non-toxic substances normally
included in dialysate, toxic substances described in the dialysis literature and
toxic substances regulated by the US EPA in drinking water [40] which have not yet been implicated as toxic in dialysis. The maximum recommended concentrations for these substances are listed in Table II. These recommendations were formulated by us in a study on the risks and hazards associated with haemodialysis systems under contract to the FDA [41]. They have since been adopted by the Association for the Advancement of Medical Instrumentation (AAMI) and the AAMI standard has been approved by the American National Standards Institute, Inc. [42].

**TABLE II.** Water quality standard for haemodialysis

<table>
<thead>
<tr>
<th>Substance</th>
<th>Maximum Concentration (Mg/L)</th>
<th>Rationale</th>
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</thead>
<tbody>
<tr>
<td><strong>Toxic Substances Described in the Dialysis Literature</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium</td>
<td>0.01</td>
<td>Based on lowest toxic levels</td>
</tr>
<tr>
<td>Chloramines</td>
<td>0.10</td>
<td>reported in the dialysis</td>
</tr>
<tr>
<td>Copper</td>
<td>0.10</td>
<td>literature allowing a margin</td>
</tr>
<tr>
<td>Fluoride</td>
<td>0.20</td>
<td>of safety</td>
</tr>
<tr>
<td>Nitrate</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Sulfate</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Non-toxic Substances Normally Included in Dialysate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Sodium</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Toxic Substances Regulated by EPA in Drinking Water</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
</tr>
<tr>
<td>Barium</td>
</tr>
<tr>
<td>Cadmium</td>
</tr>
<tr>
<td>Chromium</td>
</tr>
<tr>
<td>Lead</td>
</tr>
<tr>
<td>Mercury</td>
</tr>
<tr>
<td>Selenium</td>
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<tr>
<td>Silver</td>
</tr>
</tbody>
</table>

The maximum recommended concentrations for substances normally included in dialysate are based on the allowable margin for error in the final dialysate. The recommended levels for substances identified as toxic in dialysis are based on the lowest toxic levels reported in the dialysis literature with an appropriate margin of safety. For substances regulated in drinking water, one should ideally...
set the level at the 'no transfer' level, the level at which no transfer occurs from
dialysate to blood. 'No-transfer' levels have been established for some of these
substances based on experiments with the radio-isotopes of these substances [43].
Some of the 'no-transfer' levels are below the detection limit of analytical methods
established by the EPA for water [44]. Another approach to setting these limits
would be based on the 25-fold exposure of the dialysis patient to water relative
to drinking water exposure. A 25-fold reduction in the levels of these substances
may be too restrictive in light of the successful application in haemodialysis of
reverse osmosis treatment of water. As reverse osmosis devices typically remove
more than 90 per cent of the total dissolved solids (inorganic) in the feed water,
we have proposed maximum contaminant concentrations that are either one-
tenth of the EPA drinking water concentrations or the 'no-transfer' concentra-
tions, whichever is higher. In addition to the above recommendations, AAMI
has suggested a maximum level of 0.5mg/L for chlorine because of its potential
toxicity.

**Organic and radioactive substances**

The EPA drinking water standards regulate the concentrations of chlorinated
hydrocarbons (pesticides), chlorophenoxys (herbicides) and man-made nuclides
emitting α,β, and photon radioactivity. As adequate information is not available
at this time to set maximum contaminant levels for these substances in the water
used for haemodialysis, no recommendations are possible except to note that
activated carbon filters will remove organic material in a range of 60–300 daltons
and reverse osmosis and ultrafiltration membranes will remove substances with a
molecular weight greater than 200 daltons. A combination of activated carbon
and membrane filtration is therefore recommended for removal of organic
compounds. Radioactive substances are expected to be removed by mechanisms
similar to those for their non-radioactive counterparts.

**Microbiology**

Based on studies conducted by the Centres for Disease Control, AAMI has
recommended a maximum total viable count of 200 CFU/ml for the water used
to prepare dialysate. For dialysate, a maximum of 2,000 CFU/ml at the end of
the dialysis procedure is recommended.

**Special considerations concerning water quality used for haemofiltration**

Haemofiltration involves the ultrafiltration of large quantities of plasma water
(convective removal of uraemic toxins) and replacement with intravenous
quality substitution fluid volumes of 25–35 litres/treatment are required. If
substitution fluid is commercially produced, the cost may be prohibitive. On-site
preparation of substitution fluid has, therefore, been undertaken by several
investigators. Henderson et al [45] first established that substitution fluid could
be prepared by membrane filtration of dialysis-quality fluid to ensure removal
of micro-organisms and pyrogens. Shaldiva et al [46] reduced such a scheme to
practice with the design of appropriate equipment. Our group has established a successful large-scale long-term experience with batch on-site preparation of substitution fluid [47].

While the volume of exposure is less in haemofiltration, the fluid is directly infused into the patient's blood without the restrictive diffusion barrier of the dialysis membrane. As most of the chemical contaminants of concern are small molecular weight solutes and as small solute clearances of haemodialysis are of the same magnitude or slightly higher than in haemofiltration, we are of the opinion that haemodialysis product water standards for chemical contaminants may be safely applied to the haemofiltration setting.

Haemofiltration involves direct infusion of substitution fluid into the patient’s blood, the fluid must be of intravenous quality, sterile and non-pyrogenic. Water treatment processes that include reverse osmosis and ultrafiltration along with membrane filtration of the final substitution fluid can achieve this quality of fluid. Figures 8, 9 and 10 depict schematically the pre-treatment of water, the

![Diagram of Water Treatment System](image)

Figure 8. The water pre-treatment scheme used at the Regional Kidney Disease Program (RKDP), Minneapolis, USA for on-site preparation of substitution fluid for haemofiltration

![Diagram of Central System](image)

Figure 9. Schematic of central system (RKDP, Minneapolis, USA) for preparation of substitution fluid for haemofiltration
central production of substitution fluid, and the delivery of this fluid into the patient’s blood through membrane filters as practised in our haemofiltration programme.

We have reported [47] an incidence of 0.2 per cent for pyrogenic reactions with this scheme of treatment and our total experience with on-site preparation is of the order of 6,000 treatments. The pyrogenic reactions observed were associated with low morbidity and easily resolved with hydrocortisone and Benadryl. The fluid invariably tested negative with the limulus lysate assay, even when a pyrogenic episode occurred, indicating very low levels of pyrogen contamination.

In arriving at a standard for pyrogen levels in substitution fluid, one must consider the large infused volume, the patient’s pyrogenic threshold and the practical aspects of limulus lysate test sensitivity. The commonly cited threshold for pyrogenicity threshold in humans is 1–2ng/kg body weight. Using a substitution volume of 35 litres, 1ng/kg body weight for the pyrogenic threshold and a body weight of 70kg, we arrive at a pyrogen threshold concentration of 0.002ng/ml in the substitution fluid. Most limulus lysate assays are unable to measure pyrogens at this level of contamination. Practical considerations force one to use a higher level of 0.01ng/ml.

We have used limulus lysate assays in our haemofiltration programme with detection limits between 0.006 and 0.013ng/ml. The low incidence of pyrogenic reactions cited above indicates that monitoring for pyrogens at these levels may be adequate.

Monitoring of water quality

In discussing the various water treatment options, we have indicated the methods used for monitoring the effectiveness of each of these treatment options. For monitoring the quality of the final product water and to ensure its compliance with the product water standards, the various contaminant concentrations have to be individually analysed. Analytical methods referenced in the American Public Health Association’s “Standard Methods for the Examination of Water and Waste Water” [48] or the US EPA’s “Methods for Chemical Analysis of
Water and Waste” [44] are recommended. For assessing the microbiological quality of the water, conventional microbiological techniques, such as pour or spread plates or the membrane filter technique may be used. The 1ml calibrated loop technique should not be used. Samples must be assayed within 30 minutes of collection or within 24 hours if stored at 5°C. Standard methods agar, blood agar, or tryptic soy agar may be used for culture media and the colonies should be counted after 48 hours of incubation at 37°C. These methods may have to be modified for mycobacteria.

The frequency of monitoring is an important consideration. Unfortunately, no simple guidelines can be established that are universally applicable. The quality of the municipal supply is variable and the performance of water treatment equipment may change with time. The ideal of very frequent monitoring has to be tempered by the realities of analytical costs. A complete water analysis can cost as much as 300 US dollars. The dialysis unit must consult with state and local agencies to determine seasonal variations and the nature of variability of municipal treatment methods before a monitoring schedule can be determined. Further, the nature and configuration of the water treatment system must be considered in determining the schedule. The manufacturer/supplier of the system should advise the dialysis centre regarding schedules of regeneration and replacement of various components. However, monitoring of water quality is the responsibility of the dialysis practitioner.

AAMI has established some guidelines concerning frequency of monitoring. Such guidelines should be viewed with caution in light of the remarks above. AAMI recommends analysis of chemical contaminants every 12 months if reverse osmosis and/or deionisers are used. A frequency of three months and additional monitoring at times of expected high concentrations is recommended for other types of treatment. AAMI also recommends checks of microbiological quality on a monthly basis and when warranted by pyrogenic reactions or bacteremia. They add that such frequent monitoring may not be suited to the home dialysis setting. AAMI also recommends that, initially, monthly testing should be done and a log maintained of such testing. Once a historical record has been developed, testing can be done less frequently and some discrimination used in deciding which contaminants need to be monitored and how often.

Responsibilities of the manufacturer/supplier of water treatment equipment

In the United States, the FDA has now classified water treatment equipment as medical devices. The Good Manufacturing Practices Act does, therefore, apply to the manufacturer of water treatment equipment. There are additional responsibilities that we feel are incumbent upon the manufacturers.

The manufacturer should obtain a certified laboratory analysis of the feed water from the dialysis centre, local water authorities, or EPA certified laboratories. Based on this analysis, the manufacturer should recommend the type and capacity of the system needed, including any pre-treatment, in order to meet either the product water quality standard or other standards specified by the dialysis centre. The recommendations should consider known or anticipated
seasonal variations. A disclosure document should be prepared indicating expected contaminant concentrations at various points of the treatment system.

In recommending certain components for the water treatment system, the manufacturer should provide details such as inlet water temperature, pressures and flow rates, generic nature of materials contacting water and whether they leach, oxidise, or otherwise alter water composition, chemicals that are not compatible with materials of construction, proof of non-toxicity of chemicals such as flocculants required for the water treatment system, etc.

Upon installation of the system, the manufacturer should validate the system for a duration of time adequate to determine the capacity of components such as filters and deionisers. For compounds that require replacement or regeneration, typical life and schedules for replacement/regeneration should be specified by the manufacturer. Methods of system disinfection should be provided along with maintenance guidelines and schedules, trouble-shooting procedures, and lists of spare parts.

Responsibility of the dialysis centre

Beyond installation and initial validation of the system, everything else is the responsibility of the dialysis centre. This includes monitoring of water quality, periodic disinfection and system maintenance. Untoward consequences resulting from inadequate water quality are ultimately the responsibility of the dialysis practitioner. If the aims of haemodialysis and haemofiltration are to detoxify and purify the blood of the patient, the water used to accomplish these aims cannot be of poor quality without jeopardising the patient’s well-being. The dialysis practitioner should bear in mind the Italian proverb: “Acqua torbida non lava” (Dirty water does not wash clean).

References

1. Alfrey AC, Mischell M, Burke SR et al. Trans ASAIO 1972; 18: 257
Open Discussion

TARABA (Chairman) Thank you Dr Keshaviah for this excellent presentation. I think this showed that this subject is very large and it was impossible to go into all the details which would be very important. In your lecture you did not mention, I think, about iron, do you think it is not important to measure the iron content of the water?

KESHAVIAH I think it is very important because it can foul equipment downstream, such as deionisers, resins and the membranes. I showed a diagram of our own water treatment system and that showed iron filters. Very often if you do not remove iron you will see rust stains in other parts of the downstream equipment.

BONSDORFF (Helsinki) What kind of pipe material should be used to transport the treated water to the dialysis point, glass, steel or PVC?
KESAVIAH Till recently, especially in the USA, PVC was not used for purified water. It was only used for sewage systems, but the codes have now been changed so you can use PVC for transporting pure water. Very often lined glass is used when you use distillation because the high purity of distilled water can attack other substances such as copper and lead. PVC is quite adequate and copper alright as long as you are careful that you do not have acidic water, but brass should be avoided.

SALVADORI (Florence) When you speak about nitrates having a maximum concentration of 2mg/L do you mean as N or as NO₃⁻?

KESAVIAH Yes, as nitrogen.

PECCHINI (Cremona, Italy) Is reverse osmosis able to remove nitrosodimethylamine?

KESAVIAH Yes, you can use reverse osmosis. The DMSO is associated only with deionisers and certain municipal supplies. If you have a system with build up of DMSO in the effluent of the deionisers it is advisable to use reverse osmosis.

FOURNIER (Amiens) Do you advocate ‘finishing’ the treatment of the water after reverse osmosis by deionisation? If so, do you think it is valid with regard to the increased risk of bacterial infection after the reverse osmosis?

KESAVIAH That is a good point. I do not recommend this. I think it may be necessary in some instances such as when there is very high levels of fluoride. If the water supply fluoride is very high reverse osmosis may not be adequate. Similarly if aluminium is very high reverse osmosis may not be adequate. If you monitor the effluent and find high levels of fluoride and aluminium then you are forced to use a deioniser in that situation.

For economy you use it after the RO membrane which introduces the problem of bacteria so you have to follow that up with some form of membrane filtration.

FOURNIER (Amiens) As regards the limit for water aluminium do you think that 10μg/L is a safe limit? According to the protein binding of aluminium you may expect a positive balance until your patients have plasma values of 50μg/L.

KESAVIAH There is no such thing as a safe level really for many of these toxic heavy metals. The reason why 10μg/ml has been specified is that you have to be practical because the detection limit of even the most sophisticated methods is between one and three parts per billion. You can say that it should be less than three, but if you cannot measure it you might as well dream up the numbers. For practical reasons it is best at 10, and if you look at the literature there has been no toxicity reported when water levels have been below
50 parts per billion. There is no such thing as a safe level and the only safe level is the no transfer level.

BRANCACCIO (Milan) If you had to manage a new dialysis centre today what water treatment would you suggest?

KESAVIAH As I stated water supplies are very variable so I wish I could give you a simple answer but I will give you a simple guideline at least. If you were to combine reverse osmosis with activated carbon, the reverse osmosis takes care of most of the contaminants and also the organics greater than 200–300 daltons. The activated carbon takes care of the organics smaller than 200 daltons so that sort of design is very good and usually a very safe system. If you have got high fluoride or aluminium you are forced to add other systems and if you have got high calcium and magnesium you have to add pre-treatment softening. I cannot give you a simple answer but reverse osmosis is a very effective treatment.