Water quality in conventional and home haemodialysis

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Abstract | Dialysis water can be contaminated by chemical and microbiological factors, all of which are potentially hazardous to patients on haemodialysis. The quality of dialysis water has seen incremental improvements over the years, with advances in water preparation, monitoring and disinfection methods, and high standards are now readily achievable in clinical practice. Advances in dialysis membrane technology have refocused attention on water quality and its potential role in the bioincompatibility of haemodialysis circuits and adverse patient outcomes. The role of ultrapure dialysate is increasingly being advocated, given its proposed clinical benefits and relative ease of production as a result of the widespread use of reverse osmosis and ultrafiltration. Many of the issues pertaining to water quality in hospital-based dialysis units are also pertinent to haemodialysis in the home. Furthermore, an increased awareness of the environmental and financial consequences of home haemodialysis has resulted in the development of automated and more efficient dialysis machines. These new machines have an increased emphasis on water conservation and recycling along with a decreased need for a complex infrastructure for water purification and maintenance.

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Introduction

Home haemodialysis (HHD) was initially developed in order to overcome the challenges imposed by distance and geographical isolation from dialysis units in certain parts of the world (including Australia and New Zealand). A recent revival of HHD has been driven by the increased number of patients on conventional haemodialysis, and the financial and logistical pressures placed on health-care networks. Furthermore, an increasing body of literature supports possible benefits of HHD with regards to dialysis outcomes and risk of mortality,[1–3] and more tangible improvements to patients' quality of life.[4,5]

Although performed routinely, haemodialysis remains a complex process, given the direct interface between technology and biology. A patient undergoing standard thrice-weekly haemodialysis is exposed to around 400 l of water per week; this value can increase to over 800 l in patients undergoing nocturnal HHD. With only a semi-permeable, synthetic membrane as a barrier between the patient's blood and the dialysate solution, water quality is an essential component in the provision of good dialysis. Water quality is the product of an integrated sequence of purification devices and disinfection measures, and the current standards reflect decades of development, experience and constant refinement. Failure to meet water quality standards has major consequences, with potential for patient morbidity and mortality.

As the majority of patients on HHD use municipal water supplies, many of the issues pertinent to in-centre (hospital-based) dialysis are also relevant in the home setting. In this Review we will outline the evolution of the current standards for the provision of water quality, and recent issues and developments, with a particular focus on haemodialysis in the home.

Water treatment systems

Water supplies in the developed world are generally of a high standard. However, the biochemical profile of municipal water is variable, and numerous chemical and microbiological contaminants are commonly present. Compounds added to improve the quality and safety of the water supply (such as chlorine or fluoride) are potentially hazardous to patients on dialysis. Furthermore, in patients on HHD who live in rural settings and are dependent on a nonmunicipal water supply, the potential exists for contamination from salts and particulate matter, which may occur naturally, or as by-products of agricultural processes (for example, fertilizers and nitrates).

In general, water treatment consists of a sequential system (Figure 1) that contains a pretreatment component, the main purification device and further purification to increase the dialysate quality, the specifics of which are influenced by the quality of the feed water. Pretreatment usually employs a combination of sediment filters, carbon filters and water softeners. Reverse osmosis units—which are able to remove inorganic solutes as well as bacteria and endotoxins—have been widely adopted in water purification systems. Reverse

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P. G. Kerr declares associations with the following companies: Baxter, Fresenius Australia. See the article online for full details of the relationships. The other authors declare no competing interests.

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Key points

- High-quality dialysis water is an essential part of the provision of conventional haemodialysis and home haemodialysis
- Dialysis water can be contaminated by various chemical and bacterial factors, which have the potential to cause morbidity and—in severe cases—mortality
- High-quality dialysis fluid standards are now readily achievable with existing infrastructure and current dialysis fluid guidelines
- Bacterial fragments and endotoxins have been implicated in adverse patient outcomes and the use of ultrapure dialysate has been linked to improved clinical outcomes, but further evaluation is needed
- New technologies and materials will enable the dialysis water infrastructure to be more compatible with newer and more effective disinfection agents
- Home haemodialysis places additional challenges in our ability to translate the existing water purification infrastructure into the home setting, but new developments will allow for simplified and integrated dialysis infrastructure

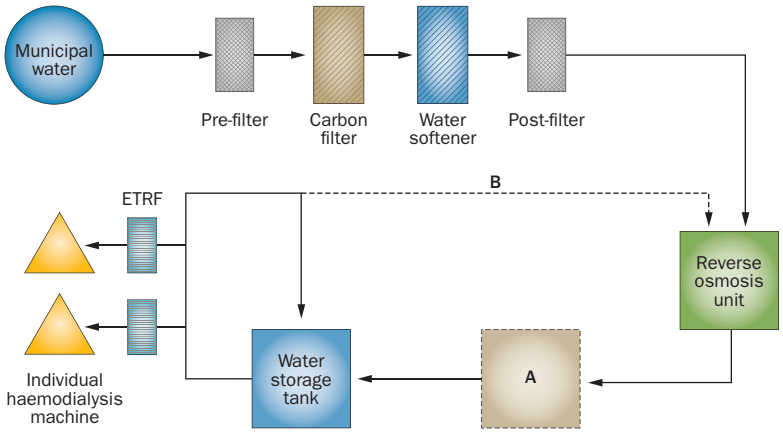

Figure 1 | Typical water purification system for a haemodialysis system. The letter 'A' represents the point in many units where a second reverse osmosis unit or deionizing unit may be used, together with newer methods such as ultraviolet irradiators. The dotted line labelled 'B' indicates where dialysis water may cycle back into the storage tank or be "re-fed" back into the circuit before the reverse osmosis unit. Abbreviation: ETRF, endotoxin-retaining filter.

Table 1 | Common water contaminants and clinical consequences

Contaminant	Clinical toxic effects
Aluminium	Encephalopathy,[10] renal bone disease,[12] anaemia[12]
Chlorine or chloramines	Haemolytic anaemia[17,19,111]
Fluoride	Renal bone disease[15,16,112]
Calcium or magnesium	Hard water syndrome[9] (nausea, vomiting, headache, muscle weakness)
Nitrates	Methemoglobinaemia[113]
Copper	Haemolytic anaemia[114]
Zinc	Nausea, vomiting, fever[115]
Lead	Abdominal pain, muscle weakness[20]

osmosis units use a semi-permeable membrane, where pressurized feed water is directed at the membrane; the portion of water that passes through the membrane—the 'permeate'—is free of contaminants. As reverse osmosis units employ a 'water rejection' principle, most units use large quantities of water, although a degree of water conservation can be incorporated into the reverse osmosis design, which can adjust water production according to flow rates, as well as recycling some of the rejected water into the feed stream.

Reverse osmosis can be the final step in the water purification process, or can be used together with deionizers, which work through an ion-exchange process that removes both cations and anions from the water. Deionizers cannot, however, remove particles without charge; in addition, they have a finite capacity for the removal of contaminants and have been implicated in increasing the bacterial content of the water.[6] For these reasons, deionisers are no longer used alone, and in many centres have been replaced by two-stage reverse osmosis systems.

The use of endotoxin-retaining filters or ultrafilters is common in water purification systems. These filters are located downstream of the reverse osmosis unit, or at individual dialysis machines, and have been shown to reduce levels of bacterial fragments and endotoxins.[7] In areas with known high concentrations of organic matter, anion-exchange resins can be used as pre-filters to protect the carbon filters and reverse osmosis units. The need for this set-up is usually determined by testing the source water for organic content prior to installation.

Chemical contaminants

Improvements in water quality have diminished the incidence of severe chemical contamination, meaning that microbiological contaminants often dominate any discussion of dialysis water quality. However, intermittent case reports of chemical contamination serve as a reminder of the severe consequences of any lapse in standards.[8] Common chemical contaminants and clinical consequences are listed in Table 1.

Particulate matter such as clay, sand and sediment are commonly present in water and are removed using sand-bed or sediment filters. These filters contain multiple layers with variable pore sizes, enabling the entrapment of progressively smaller particles. Hard water (that is, water high in mineral content, especially calcium), is present in many parts of the world, and water softening is required before the water can be used for haemodialysis. This process involves the removal of calcium and magnesium from the water supply by ion-exchange resins. Failure of water softening leads to a cluster of clinical manifestations (such as nausea, vomiting and weakness) collectively referred to as the 'hard water syndrome',[9] and can also exhaust dialysis membranes and damage equipment.

Aluminium is often present in surface water, or is added to clear the water of particulate matter. Its toxicity is cumulative and it has been associated with dementia,[10,11] anaemia and renal osteodystrophy.[12] In most modern dialysis units, aluminium is removed via reverse osmosis; deionization has proven to be a less reliable method.[13] Fluoride is also commonly added to drinking water to prevent dental decay. Like aluminium, its toxicity is cumulative,[14] predominantly affecting bone mineralization,[15,16] and it can be removed effectively by reverse osmosis. Chlorine and, more recently, chloramines are also added to water as disinfectants; both of these

substances are toxic to humans and can result in haemolytic anaemia in patients on dialysis.[17] Chloramines, which have diverse biochemical properties, have a low molecular weight and no charge, and are therefore poorly cleared by reverse osmosis or deionization. They are usually cleared through adsorption by charcoal filters,[18] although ascorbic acid is also sometimes used alone or in conjunction with charcoal to facilitate removal.[19] In the past, lead and copper were commonly used in pipes; these metals are associated with cumulative toxicity, and recent reports indicate that their potential for toxicity persists, through old infrastructure and industrial waste.[20–22] Trace elements are usually removed through reverse osmosis, creating a concentration gradient between plasma and the dialysate, which can potentially result in blood concentrations being different (usually lower) in haemodialysis patients compared with healthy controls.[23]

No current agreement exists regarding the acceptable levels for toxic organic compounds in water used for haemodialysis; the current recommendation is set at a somewhat arbitrary tenfold reduction[24] from the levels recommended for safe drinking water. These compounds are generally removed by a combination of adsorption and reverse osmosis. Recent work demonstrates the potential for these substances to accumulate in components of the water purification infrastructure,[25] and further research is needed to define acceptable levels of what is a heterogeneous group of compounds, in the haemodialysis setting.

Microbiological contaminants

Microbial contamination can occur on either side of the reverse osmosis membrane, as a result of feedwater or dialysate contamination. Regional authorities tightly control municipal water supplies, and most cases of contamination result from deficiencies in the water preparation and distribution. The organisms that survive in dialysis fluids exploit the nutrient-poor, niche environment, and are not the typical pathogens seen in clinical medicine. Contamination can be caused by fungi, viruses or protozoa, although bacterial contamination is the most common form of contamination; such contaminants include water-borne bacteria, Gram-negative bacteria and non-tuberculous mycobacteria (Box 1).[26–28]

The inherent design of water purification systems, distribution pipes and dialysis circuits renders them susceptible to colonization by water-borne bacteria. Bacterial growth is influenced by numerous factors, such as the chemical composition, flow rate, pressure and temperature of the feed water. The nature of the distribution network is also important, with potential hazards including the length of the network, the presence of 'stagnant' spaces and variable flow. Changes in temperature, particularly increases, as well as the choice of dialysate buffer are also important factors affecting bacterial growth. The adoption of bicarbonate buffers has increased the vulnerability of water systems to infection, as these can support endotoxin-producing, Gram-negative bacteria.[29–31] The risk of infection is increased if batches are reused, stored after preparation or handled incorrectly. The risk is likely to be decreased by the increasing use of dry powder concentrates, using prepared batches only once, or the use of commercially prepared batches.

Box 1 | Common bacteria found in dialysis water[26–28,44]

- *Acinetobacter* spp.
- *Flavobacterium* spp.
- *Pseudomonas* spp.
- *Enterobacter cloacae*
- *Serratia* spp.
- *Alcaligenes* spp.
- *Achromobacter* spp.
- *Aeromonas* spp.
- *Burkholderia cepacia*
- *Vibrio* spp.
- *Mycobacterium* spp. (non-tuberculous)
- *Sphingomonas* spp.
- *Ochrobactrum* spp.

Biofilms are polymicrobial aggregates that attach to foreign body surfaces. They harbour a variety of microorganisms, which are enclosed in a self-produced matrix of extrapolymeric substances (lipids, proteins, nucleic acids and polysaccharides).[32] The presence of this matrix renders the biofilm less susceptible to disinfection and antimicrobial agents, and biofilms are implicated in many difficult-to-eradicate human infections.[33] The introduction of reverse osmosis units has greatly reduced the microbiological burden of dialysate, as these units filter bacteria and endotoxins with a molecular weight of >200 kDa. However, the presence of smaller endotoxins and bacterial fragments has been recognized as an important source of contamination and chronic inflammation seen in patients on haemodialysis.[34,35] A degree of biofilm formation is inevitable, especially because following reverse osmosis the water is devoid of disinfectants and other additives, and therefore more susceptible to bacterial contamination. Biofilm only becomes a problem, however, when the bacterial levels become unacceptably high. Prevention is therefore the key, and is achieved through maintenance of water standards, regular disinfection and modern water distribution system design and materials.

Guidelines and quality monitoring

Numerous guidelines on water quality for haemodialysis have been published by local and international organizations.[36] These guidelines commonly differ in the recommended ranges, monitoring recommendations, and methods used for specimen collection and culture. Some progress has been made in achieving consolidation and uniformity, and although many local bodies continue to issue guidelines, these are commonly based on the documents published by the International Standards Organization (ISO) or the American National Standards Institute (ANSI) and the Association for the Advancement of Medical Instrumentation (AAMI). It is important to stress that dialysis water and fluid guidelines have evolved from municipal drinking water standards, and are not based on evidence from randomized

Table 2 | Maximum allowable levels of chemicals and elements in water

Contaminant	Maximum concentration in dialysis water (mg/l)	Drinking water guidelines (mg/l)
Toxic chemicals		
Aluminium	0.01	0.2
Total chlorine	0.1	0.6
Copper	0.1	1.0
Fluoride	0.2	1.5
Lead	0.005	0.01
Nitrate	2	50
Sulphate	100	250
Zinc	0.1	3
Trace elements		
Antimony	0.006	0.02
Arsenic	0.005	0.01
Barium	0.1	0.7
Beryllium	0.0004	NR
Cadmium	0.001	0.003
Chromium	0.014	0.05
Mercury	0.0002	0.006
Selenium	0.09	0.04
Silver	0.005	NR
Thallium	0.002	N/A

Abbreviations: N/A, not available; NR, no recommendation given. Adapted from ISO 13959:2009[24] and World Health Organization guidelines for drinking water.[43]

clinical trials. However, close scrutiny and investigation of febrile reactions in patients on haemodialysis in the USA provided important insights during the evolution of the current guidelines.[37–39] The ISO and ANSI/AAMI guidelines pertaining to dialysis water and fluids, concentrates and equipment were updated through 2009 to 2011 and are referenced throughout this Review.[6,24,40–42]

The current maximum allowable levels of toxic chemicals, electrolytes and trace elements in dialysis water are listed in Table 2, and are contrasted with current maximum levels allowable for drinking water, as mandated by the World Health Organization.[43]

The current maximum levels for total viable microbial count and endotoxin levels for dialysis water, standard dialysate and ultrapure dialysate, are listed in Table 3. Dialysis water refers to water suitable for use in the preparation of dialysis fluids, concentrates and substitution fluid for convective therapies. Dialysis fluid or dialysate refer to fluid that is used during haemodialysis. These solutions differ in the maximum allowable endotoxin level, allowing for an increase in total endotoxin levels following the addition of bicarbonate concentrates and passage through the distribution piping. Current guidelines consider normal dialysate fluid to be a minimum standard. In clinical practice, the levels of microbial contaminants detected are usually significantly lower. The threshold level for action is commonly set at less than 50% of the recommended maximum. Whether or not ultrapure dialysate should be widely used remains a contentious issue, although many authors advocate its use across all types of haemodialysis, given the relative ease of its preparation and proposed benefits (as discussed below).

Monitoring of dialysis fluids

The frequency of monitoring for chemical and bacterial contaminants is commonly not specified in guidelines and is often highly variable.

Monitoring of chemical contaminants

A detailed chemical analysis of the feed water is undertaken prior to the installation of the water purification system, in order to ensure that the water purification infrastructure is adequately suited to the composition and quality of the feed water. The specific components of the water purification system all require regular maintenance and monitoring (as will be discussed). The functional lifespan of the individual devices can be affected by the quality of the feed water; as a result, the maintenance schedule is often specific to an individual facility, and may differ from the manufacturer's recommendations. Monitoring usually occurs at regular intervals, but frequency of monitoring may need to increase during seasonal fluctuations or extreme environmental conditions. The frequency of testing for specific chemical contaminants is also quite variable, with chloramine testing occurring before each dialysis session, and a detailed chemical analysis of the water purification system commonly undertaken on an annual basis.

Monitoring of microbial contaminants

Microbial testing of dialysis fluids should be regarded as a confirmatory measure, affirming the effectiveness of existing disinfection and water quality protocols. Many protocols exist, but most in-centre units carry out testing on a monthly basis. Testing of the dialysate is the most important aspect of antimicrobial testing; if this meets the recommended standard there is no need for more extensive 'upstream' testing. Consequently, tests of multiple sites in the distribution network, as recommended by many guidelines, are usually carried out less frequently.

The diversity of bacteria in dialysis water was highlighted in a study that used molecular, culture-independent identification methods.[44] Heterotrophic plate counts remain the most common means of quantifying the bacterial load in dialysis water. In general, samples should be analyzed as soon as possible after collection; storage prior to plating is not recommended. The bacteria that inhabit distribution systems are often fastidious organisms, adapted to a nutrient-deprived environment. Consequently, standard culture media such as blood and chocolate agars are less suited to the growth of water-borne organisms, and specialized culture media are recommended.[45] Tryptone glucose extract agar (TGEA)[46] or Reasoner's agar 2 (R2A)[47] are the most commonly used culture media, and have demonstrated higher bacterial yields than standard media.[48–50] Specific incubation times (usually 10 days) and temperature (17–24 °C)[48] are also needed, as otherwise the results

Table 3 | Maximum allowable levels for TVC and endotoxins in standard and ultrapure dialysis fluid and dialysis water

Contaminant	Dialysis water		Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Action level (typically 50% of maximum level)	Maximum allowable level	Action level (typically 50% of maximum level)	Maximum allowable level
TVC (CFU/ml)	<100	50	<100	50	<0.1
Endotoxin (EU/ml)	<0.25	0.125	<0.5	0.25	<0.03

Abbreviations: CFU, colony-forming unit; EU, endotoxin units; TVC, total viable count. Adapted from ISO 11663:2009.[40]

may underestimate the total microbial burden of the dialysis water.

The culture of fastidious organisms is time consuming and does not allow for real-time decision-making. Newer techniques such as epifluorescence microscopy may enable more rapid detection times, but lack sensitivity at low cell counts.[51] Heterotrophic plate counts do not provide additional information about the extent of bacterial contamination, and are generally a poor measure of the presence of biofilm. Few techniques are currently available for detecting biofilm, and most rely on physical methods and sampling of a defined area of the water delivery system; the Robbins method[52] is a common example. In our opinion, if water quality and disinfection guidelines are met, biofilm monitoring is not a necessary component of ensuring water quality and in most cases can be safely omitted.

Testing for endotoxin levels and other cytokine-stimulating substances is increasingly common, and routine in many centres. The Limulus amoebocyte lysate (LAL) assay is the only commercially available assay for detecting endotoxin levels. Two types of the assay are available: a gel-clot assay and a kinetic assay.[53] The kinetic assay is more sensitive than the gel-clot assay and uses a spectrophotometer to detect the amount of endotoxin. The gel-clot assay detects the presence or absence of endotoxins at a particular concentration.

LAL testing is limited by the fact that it does not detect endotoxin fragments, peptidoglycans or oligonucleotides, all of which are capable of inducing cytokines and an inflammatory response.[30] More complex bioassays have been developed to detect these compounds, using the silkworm larvae plasma test,[54] or cytokine induction on monocyte cell lines.[55] Although these techniques are more sensitive than LAL testing, they are limited by cost and technical complexity. Endotoxin testing in general remains a considerable challenge.

Maintenance of the purification system

Monitoring and maintaining the integrity of the water purification system is essential. Monitoring procedures have evolved over time and are commonly prespecified in the product-specific manufacturer's recommendations. However, the individual characteristics of each dialysis centre, the feed water and the age and quality of the underlying infrastructure need to be considered. Furthermore, even though institutions have individual well-established monitoring protocols, the protocols need to be reviewed following the installation of new equipment, any change to the water supply or extreme environmental events.

Filters are usually inspected visually. Newer devices use opaque housing, which greatly facilitates inspection. Water softeners require regeneration of the cation resin, which is commonly automated to occur outside of dialysis hours. Carbon filters are prone to bacterial contamination and exhaustion. These are replaced at regular intervals and most in-centre units undertake testing for chlorine and chloramines prior to each dialysis session. Reverse osmosis units vary in terms of their design and setup and installation. Online monitors detect the rejection percentage and water conductivity. Temperature and water pressure can affect the performance of the reverse osmosis unit and also need regular monitoring.

Disinfection

The principle aims of disinfection protocols are to prevent bacterial contamination and to ensure that dialysis fluid standards can be readily maintained. Regular disinfection is also essential in preventing the formation of biofilm. As is the case in many aspects of microbiology, prevention rather than subsequent eradication is their primary focus.

Historically, chemical disinfectants (such as hypochlorites, peracetic acid and formaldehyde) were the main agents used in most dialysis units. These agents can damage pipes, rendering them susceptible to bacterial colonization and difficult to clean. Such agents can also reduce or shorten the efficacy of water purification equipment and dialysis monitors.[56] Disinfectants are commonly combined with a descaling agent, such as acetic acid or citric acid. The use of chemical disinfectants is complex and time consuming, they pose a risk to patients and staff, and their disposal poses a considerable financial and environmental burden. Chemical disinfectants such as hypochlorite or acetic acid may also promote biofilm production.[57,58] As a result, alternatives to chemical disinfection, as well as changes to the design of dialysis water systems have been proposed, but all face numerous challenges.

Ultraviolet irradiators can be used in various stages of the purification process,[59] but their effect on biofilm is limited. Ozone generators[60] and hot water (≥80 °C)[61] disinfectants are very effective at eliminating bacteria, reducing biofilms, and endotoxins, but can only be

used in systems designed from compatible materials. Sodium hypochlorite is a commonly used disinfection agent largely because it can use existing piping infrastructure. Furthermore, chlorine dioxide is commonly used in hospital water systems to combat the spread of potential clinical pathogens such as *Legionella* spp. These agents are associated with the formation of a range of disinfection by-products (chlorite, chlorate and organic compounds),[62] which may persist in the water treatment infrastructure and cause harm to patients; furthermore, organic compounds are poorly removed by existing water purification systems.[63] Newer disinfection techniques such as hot citric acid disinfection may provide a less toxic and more environmentally sustainable solution.[63]

Bacterial contamination can also be minimized by an appropriately designed dialysis water distribution system. A well-designed system should aim to incorporate the smallest possible pipe area, minimization of complex branching and dead-end pipes, and the elimination of stagnant spaces (such as collection tanks between the reverse osmosis unit and the patient) and irregular surfaces (such as at joints between pipes and fittings). The importance of using materials that are compatible with modern disinfection methods (such as polyvinyldene fluoride and cross-linked polyethylene)[56] is also becoming increasingly important. Intermittent or low flow rates within the distribution systems favour bacterial growth and biofilm formation. However, data from the semi-conductor industry, where flow was maintained above a critical threshold (expressed by the Reynolds number) found that this flow increase did not prevent biofilm formation.[64] It is, therefore, difficult to specify a minimal threshold for flow. In addition, continuous flow is not possible in many dialysis centres (which have days when they are closed and times when disinfection occurs) and most HHD machines. As a result, current guidelines do not carry a specific recommendation regarding minimum flow rates.[6]

Biocompatibility and dialysis fluids

A state of chronic inflammation has been well described in patients on haemodialysis, and has been increasingly linked with poor clinical outcomes in this cohort. The presence of bacterial fragments and endotoxins in dialysis fluids has been implicated in the bioincompatibility of dialysis circuits, which has resulted in renewed debate about current water quality standards.

Dialysis membranes

The evolution of dialysis membranes has had important implications on water quality. Early cellulose-based membranes were thin and low-flux, and therefore impermeable to molecules with a molecular weight of more than 5,000 Da.[65] These membranes were highly immunogenic, eliciting an inflammatory response in patients through the activation of complement and cytokine production.[66]

The development of synthetic membranes ushered in the era of high-flux dialysis. Synthetic membranes are thick-walled and offer significantly improved biocompatibility, a reduced inflammatory response and improved middle molecule clearance (in particular clearance of β_2-microglobulin).[67–69] In observational studies these benefits have been linked with a lower incidence of dialysis-related amyloidosis.[70] Furthermore, observational studies[68,71–73] and two randomized controlled trials,[74,75] despite their limitations, suggest a mortality benefit with the use of high-flux membranes.

High-flux membranes are potentially more prone to back-filtration—the passage of dialysate contaminants into the patient's blood—through a mixture of convection and diffusion. The pore size of high-flux membranes is larger than that of low-flux membranes, but the pores are still too small to allow the passage of intact microorganisms, although they do allow passage of endotoxin fragments down to a molecular weight of 3,500–5,000 Da. In reality, endotoxins and other bacterial fragments that are capable of inducing inflammation are much smaller than this and are potentially capable of crossing dialysis membranes (even low-flux ones).[76] It is our opinion that in practice the thick-walled, honeycomb structure of the high-flux membrane actually presents a greater barrier to back-filtration than does the thin wall of the low-flux membrane. Back-filtration has been used as an argument for the universal introduction of ultrapure dialysate standards, but it is difficult to discern how much of the chronic inflammatory response seen is due to bioincompatibility, rather than back-filtration.

Ultrapure dialysate

The term ultrapure dialysate was first used in the early 1990s, in reference to the substitution fluid used for haemodiafiltration. With developments in dialysis membrane technology and renewed scrutiny of water quality, ultrapure dialysate has gained prominence over the past decade. This increased prominence is largely due to the proposed role of dialysis water as a co-factor in the bioincompatibility of haemodialysis systems. The interleukin hypothesis contends that microbial contaminants found in the dialysate and biofilm (for example, endotoxins and polysaccharides) provide chronic antigenic stimulation and propagate a state of chronic inflammation in patients on haemodialysis.[77] This inflammatory state is mediated by the activation of macrophages and other monocytes, with the ensuing production of pro-inflammatory cytokines such as TNF,[78] IL-1[79] and IL-6[80] and the ensuing induction of C-reactive protein.[81] In patients with chronic kidney disease, inflammation is often regarded as the co-factor in the increased risk of morbidities such as atherosclerosis and cardiovascular disease,[82] malnutrition and protein wasting,[83] and erythropoietin resistance.[84]

Although ultrapure dialysate represents an increased standard of water quality, it does not imply sterility, and its provision is influenced by the integrity of the disinfection, microbial monitoring and culture techniques employed. An increasing body of evidence demonstrates the impact of ultrapure dialysis fluid on important clinical parameters.[85] Studies have demonstrated that ultrapure dialysis fluid is associated with a reduction

in inflammatory markers,[86] reduced chronic inflammation,[87] decreased erythropoietin resistance,[88] preservation of residual renal function,[89] a reduction in cardiovascular morbidity,[90] a reduction in β2-microglobulin amyloidosis[91] and decreased levels of advanced glycation end products.[92] The proponents of ultrapure dialysate argue that any treatment that decreases the overall inflammatory burden, and potentially improves the biocompatibility of haemodialysis, should be widely adopted. The ultimate question, however—which is whether these changes translate into improved survival outcomes—remains unanswered, and it is unlikely that a large, prospective randomized trial will ever be undertaken.

Our view is that hard evidence to support the use of ultrapure dialysis is lacking, unless practicing haemodiafiltration; indeed some of the best data on mortality with use of ultrapure dialysate comes from studies of convective therapies.[93–95] In practice, dialysate purity approaching that of ultrapure dialysate is readily achievable with the use of an on-line dialysate ultrafilter.[96] As the large numbers of editorial opinions suggest, it is likely that the wider utilization of ultrapure dialysate is inevitable. Without further studies, the potential benefits must be balanced against infrastructure and equipment costs.

Home haemodialysis

The provision of water for HHD depends on the dialysis system used and the quality of the feed water (municipal water or other sources). Although water and drain-independent systems are likely to become more common, the single-pass system currently accounts for the majority of HHD installations.

Set-up and monitoring considerations

Single-pass dialysis systems require the translation of the hospital-based infrastructure (piping, water filtration, reverse osmosis equipment and backflow prevention) to the home setting. The introduction of reverse osmosis units, often integrated with modern HHD machines, has greatly facilitated the provision of high-quality dialysis water. The majority of patients on HHD have access to municipal water supplies so major deviations from the in-centre treatment paradigm are seldom required. In settings where nonmunicipal water source is used (such as lakes, reservoirs, tank water and bore water), a detailed biochemical analysis is undertaken prior to installation, and the array of filters before the reverse osmosis unit is largely determined by these results. The quality of the feed water can affect the lifespan and effectiveness of reverse osmosis membranes and carbon filters. The size of the carbon filter is usually determined at the initial analysis, and by regular inspection over the first months of use. In areas with a high level of organic contaminants, the addition of an anion-exchange resin can protect the reverse osmosis membranes and prevent early failure. In addition, chlorine levels in the feed-water can vary greatly, with marked seasonal fluctuations, which can exhaust the carbon filters. This potential for chlorine contamination highlights the importance of regular monitoring.

Bacterial contamination is not a major issue in HHD, especially for the majority of patients who use municipal water supplies. The relative simplicity and short length of the pipes obviate many of the issues faced by in-centre dialysis units; however, monitoring of bacterial counts and endotoxin levels should occur regularly, although in practice such monitoring occurs less frequently than it does in-centre.

A number of issues specific to HHD do arise. The operation of the reverse osmosis unit is dependent on both water pressure and temperature. The water pressure must meet the minimum needs of the water treatment systems, and is dependent on the maximum capacity of the household. Water temperature is also an issue, as the operation of the reverse osmosis unit and some components of the filtration system decrease with lower temperatures, thereby reducing their effectiveness; a tempering valve may therefore be required. The drain system should also have a backflow device to prevent any potential contamination. Finally, single-use bicarbonate concentrates are important in minimizing potential bacterial contamination.

As with all aspects of HHD, a degree of patient empowerment is important in maintaining a regular monitoring schedule and preventing complications. In our program, detailed chemical testing of water is performed during installation of the water treatment system (although chloramine testing is performed before every session), and microbial testing is conducted only every 6 months, once a pattern of acceptable water quality is established. Obviously, testing in response to clinical circumstances should occur but in our experience (more than 35 years with an annual average of 50–60 patients on HHD), this requirement is extremely rare.

The question regarding ultrapure dialysate in HHD remains unanswered. As patients on HHD, especially those on nocturnal schedules, are exposed to large volumes of water, intuitively the use of ultrapure fluids should be recommended. In our experience, however, pyrogenic reactions in the HHD setting are extremely uncommon. Furthermore, frequent dialysis and nocturnal HHD (versus conventional dialysis) are associated with less inflammation[97,98] and improved surrogate clinical end points,[99–102] without the use of ultrapure dialysate. The increasing simplicity of the design of the HHD circuit, the provision of newer reverse osmosis membranes that withstand modern disinfection measures, and the availability of ultrafilters on most modern dialysis machines, mean that the standards approaching those of ultrapure dialysate are often easily achieved. However, these modifications do increase the overall cost of setting up and maintaining HHD, and the role of ultrapure dialysate in this setting warrants further study.

Environmental factors and water recycling

Dialysis water generation is an inherently wasteful process, with reject water from the reverse osmosis unit constituting around 70% of total water usage. This issue is particularly relevant to the home setting where long dialysis hours and dialysis frequency can result in even

greater water requirements. The operation of a reverse osmosis unit also requires large amounts of electricity, contributing to a considerable proportion of the overall electricity used in HHD.

In a global climate of increasing electricity costs and growing demand for water, the environmental and financial implications of our current practice are apparent. In Australia, water and electricity costs for patients on dialysis are subsidised by the government, but water and energy conservation are at the forefront of current political debate. It is important to remember that reverse osmosis reject water is water that has already met municipal water standards, and has been further purified before reaching the reverse osmosis unit; it therefore exceeds many international standards for drinking water.[103] Local water conservation programs that recycle reject water for use around the home have resulted in considerable environmental and financial gains.[104] In a similar vein, the challenges of increased electricity demands and environmental sustainability are being explored through solar power generation, which supplies the bulk of electricity in one pilot HHD program in Australia.[105]

New developments

The search for more water-efficient dialysis systems has led to renewed interest in sorbent dialysis systems. A sorbent is a substance that binds other substances, and can exist in a solid or liquid form.[106] Early sorbent dialysis systems evolved using the REDY system (REcirculation of DialYsate),[107] a technique that was later employed in the Allient system, and forms the basis of the revitalized Fresenius sorbent system.[108] The key principle of this system is that dialysis effluent is re-circulated through multiple layers of adsorptive columns, which trap solutes, bacteria and endotoxins.[109] These layers consist of activated charcoal, urease and zirconium phosphate, which act as an ion-exchange column to reconstitute a more favourable electrolyte balance, before the fluid is re-circulated as dialysate. Sorbent systems do not require extensive water purification infrastructure or specific disinfection or quality monitoring. Furthermore, the initial 6 l volume of water required is reused for the duration of each dialysis session, a feature that is particularly attractive with increasing pressure on water resources.

The single-pass system is also being constantly refined, with increasing focus on smaller designs and simplified operation. Systems such as the NxStage System One[110] bypass the need for the installation of complex water purification infrastructure, by integrating this function within the machine. These machines can also be used with batch dialysate or as an on-line module for ultrapure dialysate generation. The use of multiple-pass reverse osmosis systems in the home setting will lead to a considerable reduction in water usage. It is likely that the next decade will see the development of systems that are more compact, energy-efficient and water-efficient, and will eliminate the need for the installation of complex and expensive water purification infrastructure in the home.

Conclusions

High-quality dialysis water is readily achievable in the conventional and HHD settings with currently available technology and guidelines. Human error and complacency pose the biggest risks for water contamination in HHD. Current international guidelines have achieved a degree of uniformity, although debate still continues as to whether ultrapure dialysate should be considered the universal standard for all haemodialysis modalities. The increasing simplicity and automation of HHD machines means that ultrapure dialysate will become readily achievable in the home setting, but whether this change will translate into long-term clinical benefits remains unknown.

Review criteria

Material for this Review was based on a search of the PubMed database using a combination of general search terms that included “dialysis water”, “dialysate”, “ultrapure dialysate”, “haemodialysis”, “home haemodialysis”, “water quality”, “water contamination”, “haemodialysis complications”, “bio-incompatibility”, “dialysis membranes”, “bacterial contamination”, “chemical contamination” and “disinfection”. The references from the lists of identified papers were used for further leads. In addition, relevant international guidelines published by the International Standards Organization (ISO), the American National Standards Institute (ANSI) and the Association for the Advancement of Medical Instrumentation (AAMI) were consulted, and the bibliographies cross-referenced to identify additional articles. No date restrictions were placed on the searches, but searches were limited to articles published in English.

1. Marshall, M. R. *et al.* Home hemodialysis and mortality risk in Australian and New Zealand populations. *Am. J. Kidney Dis.* **58**, 782–793 (2011).
2. Saran, R. *et al.* Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int.* **69**, 1222–1228 (2006).
3. Culleton, B. F. *et al.* Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* **298**, 1291–1299 (2007).
4. Kerr, P. G., Agar, J. W. & Hawley, C. M. Alternate night nocturnal hemodialysis: the Australian experience. *Semin. Dial.* **24**, 664–667 (2011).
5. Masterson, R. The advantages and disadvantages of home hemodialysis. *Hemodial. Int.* **12** (Suppl. 1), S16–S20 (2008).
6. ANSI/AAMI/ISO. *ISO 26722:2009. Water treatment equipment for hemodialysis applications and related therapies* [online], http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=43700 (2009).
7. Tsuchida, K., Nakamura, M., Yoshikawa, K., Minakuchi, J. & Takesawa, S. Current situation of endotoxin retentive filter. *Blood Purif.* **27** (Suppl. 1), 28–35 (2009).
8. Junglee, N. A. *et al.* When pure is not so pure: chloramine-related hemolytic anemia in home hemodialysis patients. *Hemodial. Int.* **14**, 327–332 (2010).
9. Freeman, R. M., Lawton, R. L. & Chamberlain, M. A. Hard-water syndrome. *N. Engl. J. Med.* **276**, 1113–1118 (1967).
10. Dunea, G., Mahurkar, S. D., Mamdani, B. & Smith, E. C. Role of aluminum in dialysis dementia. *Ann. Intern. Med.* **88**, 502–504 (1978).
11. Alfrey, A. C., LeGendre, G. R. & Kaehny, W. D. The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N. Engl. J. Med.* **294**, 184–188 (1976).
12. Parkinson, I. S., Ward, M. K. & Kerr, D. N. Dialysis encephalopathy, bone disease and anaemia: the aluminum intoxication syndrome during regular haemodialysis. *J. Clin. Pathol.* **34**, 1285–1294 (1981).

13. Hoenich, N. A. & Levin, R. The implications of water quality in hemodialysis. *Semin. Dial.* **16**, 492–497 (2003).
14. Johnson, W. J. & Taves, D. R. Exposure to excessive fluoride during hemodialysis. *Kidney Int.* **5**, 451–454 (1974).
15. Lough, J., Noonan, R., Gagnon, R. & Kaye, M. Effects of fluoride on bone in chronic renal failure. *Arch. Pathol.* **99**, 484–487 (1975).
16. Rao, T. K. & Friedman, E. A. Editorial: fluoride and bone disease in uremia. *Kidney Int.* **7**, 125–129 (1975).
17. Eaton, J. W., Kolpin, C. F., Swofford, H. S., Kjellstrand, C. M. & Jacob, H. S. Chlorinated urban water: a cause of dialysis-induced hemolytic anemia. *Science* **181**, 463–464 (1973).
18. Ward, D. M. Chloramine removal from water used in hemodialysis. *Adv. Ren. Replace. Ther.* **3**, 337–347 (1996).
19. Neilan, B. A., Ehlers, S. M., Kolpin, C. F. & Eaton, J. W. Prevention of chloramine-induced hemolysis in dialyzed patients. *Clin. Nephrol.* **10**, 105–108 (1978).
20. Kathuria, P., Nair, B., Schram, D. & Medlock, R. Outbreak of lead poisoning in a hemodialysis unit. *J. Am. Soc. Nephrol.* **15**, 617A (2004).
21. Lin, J. L. *et al.* Blood lead levels, malnutrition, inflammation, and mortality in patients with diabetes treated by long-term hemodialysis. *Am. J. Kidney Dis.* **51**, 107–115 (2008).
22. Davenport, A., Murcutt, G. & Whiting, S. Cross-sectional audit of blood lead levels in regular outpatient haemodialysis patients dialysing in north London. *Nephrology (Carlton)* **14**, 476–481 (2009).
23. Tonelli, M. *et al.* Trace elements in hemodialysis patients: a systematic review and meta-analysis. *BMC Med.* **7**, 25 (2009).
24. ANSI/AAMI/ISO. *ISO 13959:2009. Water for haemodialysis and related therapies* [online], http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=43699 (2009).
25. Poli, D. *et al.* Organic contamination in dialysis water: trichloroethylene as a model compound. *Nephrol. Dial. Transplant.* **21**, 1618–1625 (2006).
26. Borges, C. R., Lascowski, K. M., Filho, N. R. & Pelayo, J. S. Microbiological quality of water and dialysate in a haemodialysis unit in Ponta Grossa-PR, Brazil. *J. Appl. Microbiol.* **103**, 1791–1797 (2007).
27. Klein, E., Pass, T., Harding, G. B., Wright, R. & Million, C. Microbial and endotoxin contamination in water and dialysate in the central United States. *Artif. Organs* **14**, 85–94 (1990).
28. Doern, G. V., Brogden, B. E., DiFederico, J. D., Earls, J. E. & Quinn, M. L. Quantitative microbiological monitoring of hemodialysis fluids: evaluation of methods and demonstration of lack of test relevance in single-pass hemodialysis machines with automatic dialysate proportioning with reverse osmosis-treated tap water. *J. Clin. Microbiol.* **16**, 1025–1029 (1982).
29. Bland, L. A., Ridgeway, M. R., Aguero, S. M., Carson, L. A. & Favero, M. S. Potential bacteriologic and endotoxin hazards associated with liquid bicarbonate concentrate. *ASAIO Trans.* **33**, 542–545 (1987).
30. Lonnemann, G. The quality of dialysate: an integrated approach. *Kidney Int. Suppl.* **76**, S112–S119 (2000).
31. Ebben, J. P., Hirsch, D. N., Luehmann, D. A., Collins, A. J. & Keshaviah, P. R. Microbiologic contamination of liquid bicarbonate concentrate for hemodialysis. *ASAIO Trans.* **33**, 269–273 (1987).
32. Flemming, H. C. & Wingender, J. The biofilm matrix. *Nat. Rev. Microbiol.* **8**, 623–633 (2010).
33. Costerton, J. W., Stewart, P. S. & Greenberg, E. P. Bacterial biofilms: a common cause of persistent infections. *Science* **284**, 1318–1322 (1999).
34. Schindler, R. *et al.* Short bacterial DNA fragments: detection in dialysate and induction of cytokines. *J. Am. Soc. Nephrol.* **15**, 3207–3214 (2004).
35. Navarro, M. D. *et al.* Bacterial DNA prolongs the survival of inflamed mononuclear cells in haemodialysis patients. *Nephrol. Dial. Transplant.* **22**, 3580–3585 (2007).
36. Nystrand, R. Microbiology of water and fluids for hemodialysis. *J. Chin. Med. Assoc.* **71**, 223–229 (2008).
37. Hindman, S. H. *et al.* Pyrogenic reactions during haemodialysis caused by extramural endotoxin. *Lancet* **2**, 732–734 (1975).
38. Bernick, J. J., Port, F. K., Favero, M. S. & Brown, D. G. Bacterial and endotoxin permeability of hemodialysis membranes. *Kidney Int.* **16**, 491–496 (1979).
39. Gordon, S. M. *et al.* Pyrogenic reactions in patients receiving conventional, high-efficiency, or high-flux hemodialysis treatments with bicarbonate dialysate containing high concentrations of bacteria and endotoxin. *J. Am. Soc. Nephrol.* **2**, 1436–1444 (1992).
40. ANSI/AAMI/ISO. *ISO 11663:2009. Quality of dialysis fluid for haemodialysis and related therapies* [online], http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=50660 (2009).
41. ANSI/AAMI/ISO. *ISO 13958:2009. Concentrates for hemodialysis and related therapies* [online], http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=43698 (2009).
42. ANSI/AAMI/ISO. *ISO 23500:2011. Guidance for the preparation and quality management of fluids for hemodialysis and related therapies* [online], http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=45345 (2011).
43. World Health Organization. *Guidelines for drinking-water quality* (World Health Organization, Geneva, 2011).
44. Gomila, M. *et al.* A molecular microbial ecology approach to studying hemodialysis water and fluid. *Kidney Int.* **70**, 1567–1576 (2006).
45. Harding, G. B. *et al.* Bacterial contamination of hemodialysis center water and dialysate: are current assays adequate? *Artif. Organs* **13**, 155–159 (1989).
46. Lonnemann, G. Assessment of the quality of dialysate. *Nephrol. Dial. Transplant.* **13** (Suppl. 5), 17–20 (1998).
47. Reasoner, D. J. & Geldreich, E. E. A new medium for the enumeration and subculture of bacteria from potable water. *Appl. Environ. Microbiol.* **49**, 1–7 (1985).
48. Pass, T., Wright, R., Sharp, B. & Harding, G. B. Culture of dialysis fluids on nutrient-rich media for short periods at elevated temperatures underestimate microbial contamination. *Blood Purif.* **14**, 136–145 (1996).
49. van der Linde, K., Lim, B. T., Rondeel, J. M., Antonissen, L. P. & de Jong, G. M. Improved bacteriological surveillance of haemodialysis fluids: a comparison between Tryptic soy agar and Reasoner's 2A media. *Nephrol. Dial. Transplant.* **14**, 2433–2437 (1999).
50. Harding, G. B., Pass, T. & Wright, R. Bacteriology of hemodialysis fluids: are current methodologies meaningful? *Artif. Organs* **16**, 448–456 (1992).
51. Riepl, M. *et al.* Applicability of solid-phase cytometry and epifluorescence microscopy for rapid assessment of the microbiological quality of dialysis water. *Nephrol. Dial. Transplant.* **26**, 3640–3645 (2011).
52. Kharazmi, A., Giwercman, B. & Hoiby, N. Robbins device in biofilm research. *Methods Enzymol.* **310**, 207–215 (1999).
53. Hurley, J. C. Endotoxemia: methods of detection and clinical correlates. *Clin. Microbiol. Rev.* **8**, 268–292 (1995).
54. Tsuchida, K. *et al.* Detection of peptidoglycan and endotoxin in dialysate, using silkworm larvae plasma and limulus amebocyte lysate methods. *Nephron* **75**, 438–443 (1997).
55. Glorieux, G. *et al.* A novel bio-assay increases the detection yield of microbiological impurity of dialysis fluid, in comparison to the LAL-test. *Nephrol. Dial. Transplant.* **24**, 548–554 (2009).
56. Cappelli, G. *et al.* Water treatment and monitor disinfection. *Hemodial. Int.* **10** (Suppl. 1), S13–S18 (2006).
57. Vincent, F. C., Tibi, A. R. & Darbord, J. C. A bacterial biofilm in a hemodialysis system. Assessment of disinfection and crossing of endotoxin. *ASAIO Trans.* **35**, 310–313 (1989).
58. Morin, P. Identification of the bacteriological contamination of a water treatment line used for haemodialysis and its disinfection. *J. Hosp. Infect.* **45**, 218–224 (2000).
59. Stragier, A. & Jadoul, M. Ultraviolet irradiation to preserve high reverse osmosis water quality. *Clin. Nephrol.* **63**, 35–40 (2005).
60. Tarrass, F., Benjelloun, M. & Benjelloun, O. Current understanding of ozone use for disinfecting hemodialysis water treatment systems. *Blood Purif.* **30**, 64–70 (2010).
61. Pontoriero, G., Pozzoni, P., Andrulli, S. & Locatelli, F. The quality of dialysis water. *Nephrol. Dial. Transplant.* **18** (Suppl. 7), vii21–vii25; discussion vii56 (2003).
62. Chang, C. Y., Hsieh, Y. H., Hsu, S. S., Hu, P. Y. & Wang, K. H. The formation of disinfection by-products in water treated with chlorine dioxide. *J. Hazard Mater.* **79**, 89–102 (2000).
63. Sakuma, K. *et al.* Experience of using heat citric acid disinfection method in central dialysis fluid delivery system. *J. Artif. Organs* **13**, 145–150 (2010).
64. Libman, V. Use of Reynolds number as a criterion for design of high-purity water systems. *Ultrapure Water* **23**, 26–34 (2006).
65. Cheung, A. K. & Leypoldt, J. K. The hemodialysis membranes: a historical perspective, current state and future prospect. *Semin. Nephrol.* **17**, 196–213 (1997).
66. Kerr, P. G. & Huang, L. Review: membranes for haemodialysis. *Nephrology (Carlton)* **15**, 381–385 (2010).
67. Hakim, R. M., Wingard, R. L., Husni, L., Parker, R. A. & Parker, T. F. 3rd. The effect of membrane biocompatibility on plasma beta 2-microglobulin levels in chronic hemodialysis patients. *J. Am. Soc. Nephrol.* **7**, 472–478 (1996).
68. Hakim, R. M. *et al.* Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int.* **50**, 566–570 (1996).
69. Hakim, R. M. Influence of the dialysis membrane on outcome of ESRD patients. *Am. J. Kidney Dis.* **32**, S71–S75 (1998).
70. van Ypersele de Strihou, C., Jadoul, M., Malghem, J., Maldague, B. & Jamart, J. Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. *Kidney Int.* **39**, 1012–1019 (1991).

71. Woods, H. F. & Nandakumar, M. Improved outcome for haemodialysis patients treated with high-flux membranes. *Nephrol. Dial. Transplant.* **15** (Suppl. 1), 36–42 (2000).
72. Port, F. K. *et al.* Mortality risk by hemodialyzer reuse practice and dialyzer membrane characteristics: results from the USRDS dialysis morbidity and mortality study. *Am. J. Kidney Dis.* **37**, 276–286 (2001).
73. Bloembergen, W. E. *et al.* Relationship of dialysis membrane and cause-specific mortality. *Am. J. Kidney Dis.* **33**, 1–10 (1999).
74. Cheung, A. K. *et al.* Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J. Am. Soc. Nephrol.* **14**, 3251–3263 (2003).
75. Locatelli, F. *et al.* Effect of membrane permeability on survival of hemodialysis patients. *J. Am. Soc. Nephrol.* **20**, 645–654 (2009).
76. Schiffl, H. High-flux dialyzers, backfiltration, and dialysis fluid quality. *Semin. Dial.* **24**, 1–4 (2011).
77. Pertosa, G., Grandaliano, G., Gesualdo, L. & Schena, F. P. Clinical relevance of cytokine production in hemodialysis. *Kidney. Int. Suppl.* **76**, S104–S111 (2000).
78. Pertosa, G., Gesualdo, L., Bottalico, D. & Schena, F. P. Endotoxins modulate chronically tumour necrosis factor alpha and interleukin 6 release by uraemic monocytes. *Nephrol. Dial. Transplant.* **10**, 328–333 (1995).
79. Dinarello, C. A. Interleukin-1 and interleukin-1 receptor antagonist production during haemodialysis: which cytokine is a surrogate marker for dialysis-related complications? *Nephrol. Dial. Transplant.* **10** (Suppl. 3), 25–28 (1995).
80. Memoli, B. *et al.* Hemodialysis related induction of interleukin-6 production by peripheral blood mononuclear cells. *Kidney Int.* **42**, 320–326 (1992).
81. Arici, M. & Walls, J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? *Kidney Int.* **59**, 407–414 (2001).
82. Zimmermann, J., Herrlinger, S., Pruy, A., Metzger, T. & Wanner, C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int.* **55**, 648–658 (1999).
83. Stenvinkel, P. *et al.* Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int.* **55**, 1899–1911 (1999).
84. Sitter, T., Bergner, A. & Schiffl, H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol. Dial. Transplant.* **15**, 1207–1211 (2000).
85. Canaud, B. & Granger-Vallee, A. Should ultrapure dialysate be part of standard therapy in hemodialysis? *Semin. Dial.* **24**, 426–427 (2011).
86. Rahmati, M. A. *et al.* The role of improved water quality on inflammatory markers in patients undergoing regular dialysis. *Int. J. Artif. Organs* **27**, 723–727 (2004).
87. Arizono, K. *et al.* Use of ultrapure dialysate in reduction of chronic inflammation during hemodialysis. *Blood Purif.* **22** (Suppl. 2), 26–29 (2004).
88. Hsu, P. Y. *et al.* Ultrapure dialysate improves iron utilization and erythropoietin response in chronic hemodialysis patients—a prospective cross-over study. *J. Nephrol.* **17**, 693–700 (2004).
89. Schiffl, H., Lang, S. M. & Fischer, R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. *Nephrol. Dial. Transplant.* **17**, 1814–1818 (2002).
90. Lederer, S. R. & Schiffl, H. Ultrapure dialysis fluid lowers the cardiovascular morbidity in patients on maintenance hemodialysis by reducing continuous microinflammation. *Nephron* **91**, 452–455 (2002).
91. Lonnemann, G. & Koch, K. M. β_2-microglobulin amyloidosis: effects of ultrapure dialysate and type of dialyzer membrane. *J. Am. Soc. Nephrol.* **13** (Suppl. 1), S72–S77 (2002).
92. Izuhara, Y. *et al.* Ultrapure dialysate decreases plasma pentosidine, a marker of "carbonyl stress". *Am. J. Kidney Dis.* **43**, 1024–1029 (2004).
93. Canaud, B. *et al.* Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int.* **69**, 2087–2093 (2006).
94. Panichi, V. *et al.* Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol. Dial. Transplant.* **23**, 2337–2343 (2008).
95. Jirka, T. *et al.* Mortality risk for patients receiving hemodiafiltration versus hemodialysis. *Kidney Int.* **70**, 1524; author reply 1524–1525 (2006).
96. Penne, E. L. *et al.* Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. *Kidney Int.* **76**, 665–672 (2009).
97. Ayus, J. C. *et al.* Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J. Am. Soc. Nephrol.* **16**, 2778–2788 (2005).
98. Yuen, D., Richardson, R. M., Fenton, S. S., McGrath-Chong, M. E. & Chan, C. T. Quotidian nocturnal hemodialysis improves cytokine profile and enhances erythropoietin responsiveness. *ASAIO J.* **51**, 236–241 (2005).
99. Susantitaphong, P., Koulouridis, I., Balk, E. M., Madias, N. E. & Jaber, B. L. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis. *Am. J. Kidney Dis.* **59**, 689–699 (2012).
100. Weinhandl, E. D., Liu, J., Gilbertson, D. T., Arneson, T. J. & Collins, A. J. Survival in daily home hemodialysis and matched thrice-weekly in-center hemodialysis patients. *J. Am. Soc. Nephrol.* **23**, 895–904 (2012).
101. Chertow, G. M. *et al.* In-center hemodialysis six times per week versus three times per week. *N. Engl. J. Med.* **363**, 2287–2300 (2010).
102. Pierratos, A. *et al.* Nocturnal hemodialysis: three-year experience. *J. Am. Soc. Nephrol.* **9**, 859–868 (1998).
103. Agar, J. W. Conserving water in and applying solar power to haemodialysis: 'green dialysis' through wiser resource utilization. *Nephrology (Carlton)* **15**, 448–453 (2010).
104. Agar, J. W., Simmonds, R. E., Knight, R. & Somerville, C. A. Using water wisely: new, affordable, and essential water conservation practices for facility and home hemodialysis. *Hemodial. Int.* **13**, 32–37 (2009).
105. Agar, J. W., Perkins, A. & Tjipto, A. Solar-assisted hemodialysis. *Clin. J. Am. Soc. Nephrol.* **7**, 310–314 (2012).
106. Agar, J. W. Review: understanding sorbent dialysis systems. *Nephrology (Carlton)* **15**, 406–411 (2010).
107. Gordon, A. *et al.* Clinical maintenance hemodialysis with a sorbent-based, low-volume dialysate regeneration system. *Trans. Am. Soc. Artif. Intern. Organs* **17**, 253–258 (1971).
108. Ash, S. R. The Allient dialysis system. *Semin. Dial.* **17**, 164–166 (2004).
109. Shapiro, W. B. The current status of sorbent hemodialysis. *Semin. Dial.* **3**, 40–45 (1990).
110. Clark, W. R. & Turk, J. E. Jr. The NxStage System One. *Semin. Dial.* **17**, 167–170 (2004).
111. Tipple, M. A. *et al.* Illness in hemodialysis patients after exposure to chloramine contaminated dialysate. *ASAIO Trans.* **37**, 588–591 (1991).
112. Arnow, P. M., Bland, L. A., Garcia-Houchins, S., Fridkin, S. & Fellner, S. K. An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. *Ann. Intern. Med.* **121**, 339–344 (1994).
113. Carlson, D. J. & Shapiro, F. L. Methemoglobinemia from well water nitrates: a complication of home dialysis. *Ann. Intern. Med.* **73**, 757–759 (1970).
114. Manzler, A. D. & Schreiner, A. W. Copper-induced acute hemolytic anemia. A new complication of hemodialysis. *Ann. Intern. Med.* **73**, 409–412 (1970).
115. Gallery, E. D., Blomfield, J. & Dixon, S. R. Acute zinc toxicity in haemodialysis. *Br. Med. J.* **4**, 331–333 (1972).

Author contributions

The authors contributed equally to all aspects of this manuscript.