Is dialysis water a safe component for hemodialysis treatment in São Paulo State, Brazil?

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Failure on the water treatment poses hemodialysis patients at risk of injury and death. Identifying if the patients are exposed to water quality related microbiological risks is an important objective to reduce the mortality for chronic renal patients and is the main issue of this study. We evaluated the microbiological water quality used by 205 dialysis services in São Paulo State, Brazil between 2010 to 2016. The study included heterotrophic bacteria count, total coliforms research, and bacterial endotoxin determination in 1366 dialysis water samples. The number of unsatisfactory clinics for at least one microbiological parameter decreased 16.0% between 2010 to 2015 but increased 57.2% in 2016. In 2010, the most frequent unsatisfactory parameter was related to heterotrophic bacteria count (54.8%) followed by endotoxin determination (45.2%). However, in 2013 an opposite situation was observed: endotoxin determination as the parameter of the higher incidence of nonconformities. Total coliform was verified at a lower frequency. We highlighted the importance of regular monitoring of dialysis water quality to prevent infections caused by dialytic procedures and to ensure that the water is a safe component of the treatment.

**Keywords**: Hemodialysis water. Endotoxin. Microbiological water quality. Hemodialysis.

**INTRODUCTION**

Dialysis water quality is the product of an integrated sequence of purification systems and disinfection steps. Failure on the water treatment poses hemodialysis patients at risk of injury and death. Biofilm formation can occur due to the presence of microorganisms in the water system and, once established, acts as a permanent source of bacteria and endotoxins (Linde et al., 1999; Menezes et al., 2015). When present in the dialysis water, endotoxins may enter the blood compartment and potentially activate monocytes to produce pro-inflammatory cytokines, related to several distinct acute and chronic problems of hemodialysis patients (Linde et al., 1999; Garcia, Benitez, 2000). The frequency of pyrogenic reactions associated with contamination of the hemodialysis treatment system is about 0.7 per 1000 sessions (Linde et al., 1999).

From 1969 to 2008, the Center for Disease Control and Prevention (CDC) investigated 20 outbreaks, involving 377 patients, associated with the microbiological contamination of the water used in patients undergoing dialysis. The results indicated that 10 outbreaks were related to the presence of bacteria (145 patients), 06 outbreaks to the presence of endotoxins (177 patients) and 04 outbreaks to the presence of bacteria and endotoxins (53 patients) (Roth, Jarvis, 2000; Coulliette, Arduino, 2013).

International studies carried out in Morocco, Nigeria, and Iraq (Al-Naseri, Mahdi, Hashim, 2013; Asserraji et al., 2014; Braimoh et al., 2014; Okunola, Olaitan, 2016) showed a high bacterial contamination of dialysis water in the dialysis units evaluated though do not reference endotoxin determination and total coliform research. Instead better water quality was observed by Totaro et al. (2017) in a study with satisfactory results for 78% of the dialysis water samples evaluated monthly in nine Italian hospitals from 2015 to 2016. No contamination with heterotrophic bacteria was observed by Shahryari et al. (2016) in the dialysis water samples collected from 2011 to 2012 in five hospital dialysis centers in Iran.

The incidence of outbreaks related to microbiological contamination in hemodialysis water conducted domestic and international governments to establish more restrictive
standards in the last decades (Pouria et al., 1998; Roth, Jarvis, 2000; Coulliette, Arduino, 2013; Upadhyay, Jaber, 2016). Brazilian Health Regulatory Agency (Anvisa) published a new regulation (Brasil, 2014) to establish the good operating practices requirements for the dialysis services. The new quality standard for dialysis water decreased in eight times the maximum permitted level of endotoxin and halved the total number of heterotrophic bacteria count in hemodialysis water, the same standard proposed by the Association for the Advancement of Medical Instrumentation (AAMI), a world reference for the quality of hemodialysis water (AAMI, 2014).

In Brazil, epidemiological data show a gradual increase in the number of chronic renal patients under dialysis treatment during the last years, with direct costs of US$ 970 million per year (Sesso et al., 2016). The Southeastern region has the highest incidence rates of patients (51%) and the largest number of dialysis services in the country (Menezes et al., 2015; Sesso et al., 2016).

Studies conducted in different regions of Brazil to evaluate the microbiological water quality of dialysis services are available in the literature (Simões, Pires, 2004; Lima et al., 2005; Borges et al., 2007; Pires-Gonçalves et al., 2008; Montanari et al., 2009; Buzzo et al., 2010; Marcatto, Grau, Muller, 2010; Marchetti, Caldas, 2011; Figel, Dalzoto, Pimentel, 2015; Ramirez et al., 2015).

Three studies are related with the monitoring of a specific unit (Montanari et al., 2009; Borges et al., 2007; Pires-Gonçalves et al., 2008) and two with the water quality of hospital dialysis units (Simões; Pires; 2004; Lima et al., 2005). The papers published by Buzzo et al. (2010), Marcatto, Grau and Muller (2010), Marchetti and Caldas (2011), Figel et al. (2015) and Ramirez et al. (2015) aimed to monitor the microbiological water quality of dialysis services, in Brazil, used for the treatment of chronic renal patients in São Paulo State (for the first two references), the Federal District, the city of Curitiba and Rio de Janeiro State, respectively.

Since 2000, our group and the Sanitary Surveillance Center of São Paulo State (CVS/SP) have worked on the evaluation of dialysis water quality used by hemodialysis services in São Paulo State, Brazil. The first results of this partnership indicated unsatisfactory quality water for 36.9% of the clinics in 2000 and 28.7% in 2009 (Buzzo et al., 2010; Marcatto, Grau, Muller, 2010).

Ramirez et al. (2015) obtained a similar percentage of unsatisfactory services (27.3%) from the monitoring program for the quality water in Rio de Janeiro state from 2008 to 2010 for 22 dialysis units.

Monitoring and maintaining the integrity of the water purification system is essential to ensure the microbiological quality of the dialysis water and the safety of the patient. The non-compliance with the guideline standards published by local and international organizations for the dialysis water quality can transmit infections, the main cause of morbidity and mortality in patients on hemodialysis, and pyrogenic reactions due to the presence of endotoxins (Ferreira et al., 2013).

The objective of the study was to identify if the patients under hemodialysis treatment are exposed to microbiological risks related to the water quality used by 205 dialysis services in São Paulo state, Brazil, between 2010 to 2016.

**MATERIAL AND METHODS**

Between 2010 and 2016, 500 mL of dialysis water from 205 hemodialysis services located in all mesoregions of São Paulo State, Brazil, were aseptically collected in a sterilized flask and sent to the laboratory under refrigerated temperature (2-8 ºC) to be processed on the same day. All active and registered clinics in the health surveillance of São Paulo State were evaluated in the period.

Initially 1209 dialysis water samples were collected at the water distribution system point at the dialyzer processing rooms in the dialysis units. Clinics with an unsatisfactory result for at least one parameter evaluated were notified and advised by actions from the Health Surveillance System. These units had a new sample collected and tested, resulting in 157 additional samples. The study included heterotrophic bacteria count, total coliforms research, and bacterial endotoxin determination for 1366 treated water samples.

Heterotrophic bacteria counts were determined by pour plate technique on Reasoner’s 2A media agar (Oxoid, Lenexa, Kansas, EUA) with incubation in an inverted position at 35.0 ± 0.5 ºC for 48 hours (APHA, 2005; APHA, 2012). Undiluted and diluted (1:10 v/v) samples were evaluated in duplicates. Colonies were counted after incubation.

Qualitative presence-absence coliform test understood the presumptive and the confirmatory phase (APHA, 2005; APHA, 2012). In the first one, 100 mL of the sample was inoculated into 200 mL of presence-absence broth (Merck, Darmstadt, Darmstadt, Germany) with subsequent incubation at 35.0 ± 0.5 ºC for 48 hours. The bottles were inspected for gas and acid production (indicated by a color change of the indicator dye) and 1 mL of the media was transferred to brilliant green lactose bile fermentation broth (Oxoide, Lenexa, Kansas, EUA) containing an inverted Durham tube for confirmation.
Formation of gas in an amount in the inverted vial after 48 h at 35.0 ± 0.5 ºC was related to a coliform occurrence. Bacterial endotoxin test was performed using diluted (1:2 v/v) samples and a gel-clot method (Brasil, 2010). The sensitivity of the Limulus Amebocyte Lysate (LAL) reagent (Charles River, Écully, Ródano, France) was 0.125 EU/mL. Sample and control standard endotoxin (Charles River, Écully, Ródano, France) dilutions were freshly prepared for each assay using LAL reagent water (Charles River, Écully, Ródano, France). The test was conducted in duplicates, adding 100µL of the diluted sample in 100µL of the LAL reagent. Tubes were placed in a 37 ± 1ºC bath for one hour. If, after this time, the gel had formed and remained intact in the bottom of the tube after an inversion of 180°, the test was considered positive. Any other state of the reaction mixture indicated a negative test.

RESULTS AND DISCUSSION

The first part of the study was the analysis of all active and registered clinics for chronic dialysis in São Paulo State between 2010 to 2016. In this period, 1,209 dialysis water samples were collected in 205 different clinics located in all 15 macroregions of São Paulo State, Brazil (Figure 1). The distribution of the units evaluated annually is displayed in Figure 2.

We verified an average increase of approximately 2.2% per year in the number of dialytic services operating...
in the State during the period studied, a similar result (2.8%) observed for Brazilian Society of Nephrology in a country-wide study between 2011 to 2014 (Brasil, 2014; Sesso et al., 2014).

After the tests were performed, we evaluated the sample results according to the maximum allowed value defined by Brazilian regulations (Brasil, 2004; Brasil, 2014) (Table I).

**TABLE I – Microbiological quality standard for hemodialysis water in Brazil**

| Parameter               | Maximum allowed value |
|-------------------------|-----------------------|
|                         | RDC 154/2004<sup>a</sup> | RDC 11/2014<sup>b</sup> |
| Heterotrophic bacteria count | 200 CFU/mL          | 100 CFU/mL          |
| Total coliforms         | Absence in 100 mL    | Absence in 100 mL   |
| Endotoxin               | ≤ 2.0 EU/mL          | ≤ 0.25 EU/mL        |

<sup>a</sup>Used to evaluate the collected samples from 2010 to March 2014 (Brasil, 2004); <sup>b</sup>Used to evaluate the collected samples from April 2014 to 2016 (Brasil, 2014).

The percentage of unsatisfactory clinics for at least one microbiological parameter in the first collection decreased 16.0% from 2010 to 2015 but increased 57.2% from 2015 to 2016 (Figure 3). In 2013 the highest level of satisfactoriness already recorded by the monitoring program was obtained. Compared to the data by Buzzo et al. (2010) from 2000 to 2009, the reduction is even more significant: from 36.9% in 2000 to 7.2% in 2013. The maintenance of the microbiological monitoring procedures implemented had a positive impact on the treatment units and was an effective measure of infections prevention caused by dialytic procedures.

A study in a hemodialysis unit located in São Paulo State, from 2004 to 2006, showed that all samples presented satisfactory results for the total bacterial count, despite the identification of different groups of bacteria, mainly the genus *Pseudomonas* (Montanari et al., 2009). These data are related to the microbiological evaluation of only one dialysis unit and do not include the evaluation of all parameters established by the legislation in Brazil.

After evaluating six dialysis services in Curitiba, Parana, Brazil, from 2009 to 2010, Figel et al. (2015) concluded that more than 95% of the water samples were in compliance with the heterotrophic bacteria count, all samples presented satisfactory results for total coliform research and 15% of the samples showed unsatisfactory results for endotoxin determination. However, the study does not present the sample conclusions considering the three parameters evaluated. Whereas the sample is considered reproved if the result of one parameter is out of the limit established for the legislation, not less than 15.0% of these samples are unsatisfactory, a similar percentage verified at the beginning of our study in 2010 (16.2%).

The study performed by Marchetti and Caldas (2011) showed that 21.8% of the dialysis water samples evaluated from 2009 to 2010 in Distrito Federal, Brazil, were not in compliance with the national standards; 96.2% of them in 2010. These percentages are lower than those found by Simões and Pires (2004) in Piracicaba, São Paulo, Brazil. In their study, 44% of the 200-dialysis water samples analyzed had heterotrophic bacterial count.

**FIGURE 3 – Percentage of unsatisfactory results for the water sample collections in São Paulo State, Brazil, from 2010 to 2016.**
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in disagreement with the current legislation in 2003, and also by Marcatto et al. (2010) in 2007 and by Buzzo et al. (2010) from 2000 to 2009, either in São Paulo State.

In our study, the percentage of satisfactory results obtained from 2010 (83.7%) to 2015 (86.3%) were higher than the percentage verified in Distrito Federal from 2009 to 2010 (Marchetti, Caldas, 2011) and Rio de Janeiro from 2008 to 2010 (Ramirez et al., 2015): 79.2% and 72.7%, respectively. These data demonstrate the long-term results evolution in monitoring the microbiological quality of dialysis water in São Paulo State and corroborate the performed actions based on the study results since 2000 helped meeting the quality standards established in Brazil.

After the incident in Caruaru, Pernambuco, Brazil, when 47.6% of the patients under dialytic treatments died after exposure to high concentrations of microcystin present in the dialysis water (Pouria et al., 1998), Anvisa has updated the regulation to establish more restrictive standards for water used in hemodialysis procedures. In early 2014, Anvisa published the last microbiological quality standard for dialysis water in Brazil (Brasil, 2014). This regulation decreased in eight times the maximum permitted level of endotoxin and halved the total number of heterotrophic bacteria count, the same standards proposed by AAMI (AAMI, 2014), the world reference in hemodialysis water quality.

Achieving a high-quality standard of water was a challenge for the clinics, which were forced to make changes in the water treatment systems used. The percentage of unsatisfactory results verified in 2014 demonstrated the impact in a short-term: the number of non-compliant clinics in the first collection almost doubled in 2014 (14.2%), compared to the previous year (7.2% in 2013). Long-term actions, as high financial investments, validation and implementation of new processes and analytical methods, as well training of health professionals involved, contributed to the scenario repetition in 2015; a slight improvement in the quality of dialysis water was verified.

In 2016 the difficulty of clinics in keeping the process under control was notorious, since there was a considerable increase in the number of unsatisfactory units (21.5%), related mainly to endotoxin levels greater than 0.25 EU/mL (Figures 3 and 4). The difficulties may be related to maintenance or disinfection failures of hemodialysis machines, the use of inadequate cleaning protocols for the water treatment system as well as errors in the preparation and distribution of the treated water. The biofilm formation in the water system is another factor that may have compromised the microbiological quality of water in the clinics. An established biofilm causes recurrent contamination and is very difficult to remove with the current disinfection procedures (Glorieux et al., 2012; Isakozawa, Migita, Takesawa, 2016).

A profile of non-compliance results for the first dialysis water collection can be seen in Figure 4. At the beginning of the study, heterotrophic bacteria count was the highest unsatisfactory parameter (63.0%, n=17) followed by endotoxin determination (51.9%, n=14). However, from 2013 an opposite situation began to be observed: endotoxin determination as of the parameter of the higher incidence of nonconformities. An expressive number of clinics presented unsatisfactory results for endotoxin determination and for heterotrophic bacteria count throughout the assessed period. Total coliform with an unsatisfactory result was verified at a lower frequency.

FIGURE 4 – Profile of unsatisfactory results for the first water sample collection in dialysis units located in São Paulo State, Brazil, from 2010 to 2016.
From 2010 to 2012, heterotrophic bacteria count was the parameter with the largest percentage of non-compliance samples as well as in the research performed by Marchetti and Caldas (2011), either demonstrating the effectiveness absence of the dialysis water treatment process.

From 2013 to 2016 a change in the profile of non-compliance results was observed. The unsatisfactory results related to heterotrophic bacteria count decreased, even with the period in which the maximum allowed value had been reduced to half the previously established value.

Endotoxin levels above allowed by legislation (Brasil, 2004; Brasil, 2104) demonstrated high prevalence throughout the study, with unsatisfactory percentages even more critical from 2013, when 72.7% of the unsatisfactory units in the first water collection had more than 2.0 Endotoxin Units (EU)/mL in 2013 and 92.7% of the unsatisfactory units presented more than 0.25 (EU)/mL in 2016. Figel et al. (2015) presented lower percentages (15%) in a study performed at six dialysis services in Curitiba, Parana, Brazil, from 2009 to 2010.

Brazilian studies of dialysis water quality using the new microbiological quality standard published in 2014 were not found in the literature.

The second part of the study evaluated all the clinics with an unsatisfactory result for at least one parameter assayed in the first part of the study. A new sample collection was performed in 157 units. The suspension or the closure of the activities in 19 clinics did not allow an extra collection at these sites. The results (Figure 3) for the second sample collection from 2010 to 2016 indicated a microbiological quality improvement in 63.7% (n=100) of the clinics. The data demonstrate the unit’s commitment to solving the pointed problems with the aim of reducing risks for the patients. Figure 5 presents a profile of unsatisfactory results for the second dialysis water collection in the study.

Higher frequencies of unsatisfactory results for counting heterotrophic bacteria from 2010 to 2011 and for bacterial endotoxin from 2014 to 2016 were also seen in the second water sample collection. Instead, in 2012 the unsatisfactory results for endotoxin levels for the second sample water collection presented higher frequency when compared to the first collection. In 2013 the presence of total coliforms in one sample was the only non-compliance result for the second sample collection. Endotoxin was the most prevalent unsatisfactory parameter throughout the study.

The percentage of unsatisfactory units after the second collection samples demonstrated the improvement of the dialysis water quality in São Paulo State between 2010 to 2015, except for 2014 when the microbiological standard was modified and the dialysis units were under adaptation (Figure 3).

Chronic exposure of hemodialysis patients to unsatisfactory levels of cytokine-inducing microbial components, as endotoxin, can significantly contribute to the micro-inflammatory status of these patients (Linde et al., 1999; Garcia, Benitez, 2000). The use of dialysis water not in compliance with microbial quality standards proposed by the Brazilian legislation can increase morbidity and mortality for chronic kidney disease patients due to the risk of bacterial infections.

According to the last released data by the Environmental Company of São Paulo State (CETESB, 2015; CETESB, 2016), the excessive growth of

![FIGURE 5 – Profile of unsatisfactory results for the second water sample collection in dialysis units in São Paulo State, Brazil, from 2010 to 2016.](image-url)
cyanobacteria in reservoirs used for public water supply was observed in some from 2014 to 2015, damaging the water quality offered to the population.

Cyanobacterial endotoxins are generally less toxic than endotoxins from heterotrophic gram-negative bacteria (Weise, Drews, 1970) but they imply serious risks for dialytic patients (Pouria et al., 1998). It was observed gram-negative bacteria colonize the mucilage surrounding colonies of cyanobacteria during blooms thereby indirectly increasing endotoxin concentrations in the water (Worm, Søndergaard, 1998).

High concentration of microorganisms and endotoxins in the water can promote an early saturation of filters used for dialysis water treatment, showing the need to reduce the periodicity of disinfection processes or change filters and prefiltered. If the systems are not frequently sanitized, there is a chance that developing biofilm could release detectable endotoxin when killed by periodic sanitization. Therefore, the presence of high amount of cyanobacteria in the public water supply can be related to the high numbers of unsatisfactory results from 2014 to 2016, mainly for endotoxin.

Many water sources, despite their apparent clarity, contain large amounts of suspended particulate matter that can adversely affect the water treatment system. If not removed, these particles can clog the carbon and softener tanks, destroy the reverse osmosis pump, and foul the reverse osmosis membranes. Tap water containing a high amount of calcium and magnesium forms scale or mineral deposits on reverse osmosis membranes and eventually fouls the membranes, resulting in a decline in the product water quantity and quality. Thus, understanding the supply water characteristics on the dialysis unit is paramount to ensure that the validation of the water treatment system is conducted in the proper manner to allow the achievement of water in compliance to the established quality standards.

In general, microbial contamination is associated with deficiencies in the production and/or inadequate maintenance of the water treatment and distribution system. Bacterial growth in water purification system is influenced by several factors, such as the chemical composition, design of distribution pipes, flow rate, pressure and the temperature of the feed water (Roth, Jarvis, 2000; Coulliette; Arduino, 2013; Suman et al., 2013).

Most dialysis services use pretreatment components together with the reverse osmosis process to produce purified water. The pretreatment is responsible to remove sediments, organic materials, mineral substances and chlorine/chloramine from the incoming water. After this first step, a hydraulic pressure moves the water across a semi-permeable membrane from a solution with a higher solute level to a solution with lower solute level, in a process named reverse osmosis (Payne, Curtis, 2018).

The system used varies in terms of design, setup, and installation. The reverse osmosis membranes are subjected to scale by suspended or soluble material present in the feed water and need to be sanitized or replaced at regular intervals because they are prone to bacterial contamination, as well as some elements of the water production system as water softeners and carbon filters. Changes in pressure and temperature, particularly increases, may also damage the reverse osmosis membranes and pretreatment components (Payne, Curtis, 2018).

The biofilm formation in the water system can occur because following reverse osmosis the water is devoid of disinfectants and others additives, and therefore more susceptible to bacterial contamination. Regular disinfection, the use of modern materials and design in the water distribution system, associated with monitoring water quality, are the best options to prevent the emergence of this problem. However, the individual dialysis unit characteristics, the feed water, the age and quality of the underlying infrastructure need to be considered. Furthermore, even though institutions have individual 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.

To conclude, the study evidenced the improvement of the dialysis water quality in São Paulo State from 2010 to 2015, with except for 2014 when the microbiological standard was modified and the dialysis units were under adaptation. Despite the increase in the unsatisfactory units in the first water collection observed in 2016, 57.9% of the units presented satisfactory results in the second water collection in the same year. The percentage of unsatisfactory samples from the first to the second sample collection in the study was reduced by 63.7%. Endotoxin was the most prevalent unsatisfactory parameter throughout the study.

CONCLUSION

The study highlights the improvement of the microbiological quality of treated water for dialysis from 2010 to 2015, demonstrating the water is a safe component of the treatment. Furthermore, it emphasizes the importance of continuing regular monitoring of the production and the water system distribution of the dialysis services to assure the microbiological quality standard for the dialysis water in order to prevent infections caused on
chronic renal patients. Compliance can be increased by upgrading the disinfection protocols, frequent disinfection of the water system and validation of the water treatment system to achieve the most recent quality standards established for dialysis water in Brazil.

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Received for publication on 03rd January 2018
Accepted for publication on 23rd October 2018