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BACTERIA AND FUNGI CONTAMINATING WATER AND HEMODIALYSIS FLUIDS: A REVIEW

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ABSTRACT

Hemodialysis is a clinical procedure in which aqueous solutions are used for the purification of blood. Contamination of water or hemodialysis fluids may expose the patient to the risk of infections caused mainly by bacteria or fungi. In this review we examine literature about microbial contamination of water and hemodialysis fluids, relating most bacteria and fungi commonly implicated in infections. This is a bibliographical research that took place in the Bases Virtual Library on Health, Scientific Electronic Library Online (Scielo) and the PubMed portal with the descriptors in health sciences: hemodialysis, infection, water contamination, hemodialysis fluid and microorganisms. Despite multiple efforts to control and avoid problems of healthcare associated infections, microbiological contamination of water remains a challenge for health services. Bacteria and fungi are water contaminants that are also important as infections agents for immunocompromised patients, like those in hemodialysis treatment. Surveillance actions are therefore required to better inhibit the spread of microorganisms, which may reduce or prevent the formation of biofilms on surfaces and pipelines, as well as monitoring infectious agents to prevent the emergence of resistant strains. Microbiological contamination of water is still a worldwide problem, despite the efforts of institutions and other health organizations to control the presence of microorganisms, mainly bacteria and fungi. In addition, biofilmsare the main causes of maintenance of microorganisms in water for hemodialysis.

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INTRODUCTION

Chronic renal failure (CRF) is a kidney disease that leads to loss of kidney function, with a progressive and irreversible process, and patients present multiple signs and symptoms, presenting difficulty in maintaining homeostasis (Romão Jr, 2004). Treatment is by hemodialysis or by peritoneal dialysis, being the first one the most used (Torres-Zamudio, 2003). Hemodialysis is a clinical procedure in which aqueous solutions are used for the purification of blood. The water, or even the solution used, that is the hemodialysis fluids, if contaminated with microorganisms, may expose the patient to the risk of infections (Gueguim *et al*. 2016; Kauffmann-Lacroix *et al*., 2016; Vazquez *et al*., 2018). Hemodialysis machine tubing may show formation of microbial biofilms, so that bacteria and fungi can remain and propagate during hemodialysis sessions (Teixeira *et al*., 2011; Coulliette e Arduino, 2013). Patients in hemodialysis treatment are vulnerable to infectious diseases due to immunocompromising and the exposure to different pathogens such as virus, bacteria, cyanobacteria, mycobacteria, fungi (Gueguim *et al*. 2016; Kauffmann-Lacroix *et al*., 2016; Vazquez *et al*., 2018). Fungi and bacteria can survive under varying environmental conditions and many species are commonly isolated from water (Suleyman *et al*., 2018). The water used in performing medical procedures are treated and undergo strict quality control to eliminate the risk of microbial, endotoxin and chemical contamination. However, evidence has shown that treatment of water intended for medical procedures can present flaws and cause risk of contamination of patients during care procedures (Coulliette e Arduino, 2013; Suleyman *et al*., 2018). Bacteria of different genera and species are the majority contaminant microorganisms of water and hemodialysis fluid. The mainly bacteria related in literature that are recovered from water and hemodialysis fluid are *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Aeromonas* spp.,

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Bacillus spp., *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Burkholderia cepacia, Staphylococcus aureus*, *Enterococcus* spp., *Acinetobacter* spp., among others (Lima *et al*., 2005; Gueguim *et al*., 2016; Vazquez *et al*., 2018). On the other hand, fungi belonging to the genus *Microsporum, Rhizopus, Trichophyton, Fusarium, Epidermophyton, Aspergillus, Penicillium, Sporothrix* (Norton, 1994; Oliveira, 1999). In addition, yeasts in which the genus *Candida* is the main responsible for infections, *C. albicans* species is the most commonly isolated from infections in general (Kemmelmeier *et al*., 2008; Hiller *et al*., 2011; Kollef *et al*., 2012; Colombo *et al*., 2013). In this review we examine literature aboutmicrobial contamination of water and hemodialysis fluids, relating most fungi and bacteria commonly implicated in infections.

MATERIALS AND METHODOLOGY

This study consists of a bibliographical research that was took place in April to September 2018, in the Bases Virtual Library on Health, Scientific Electronic Library Online (Scielo) and the PubMed portal, the Medical Literature Analysis and Retrieval System Online (Medline), from the Association of Descriptors In Health Sciences and Medical Subject Headings (MeSH) by means of the boolean operator "and", with the descriptors: hemodialysis, infection, water contamination, hemodialysis fluid and microorganisms. The inclusion criteria were publications that addressed water contamination utilizing in hemodialysis, published or available online, in the Portuguese, English or Spanish languages.

HEALTH CARE-ASSOCIATED INFECTIONS

Infections that occur in the patient and are related to some medical procedure or general health care, whether in a hospital or outpatient setting, are called Healthcare-Associated Infections (HAIs) (Horan *et al*., 2008; Oliveira *et al*., 2012; Suleyman *et al*., 2018). HAIs are resulted mainly from prolonged hospitalization, contamination of medical materials and devices, prolonged antibiotic therapy, cross-contamination, invasive device insertion, surgical procedures and pre-existing comorbidities (Benedict, 2017). Thus, due to the complexity of care and procedures, health institutions often have difficulty controlling or reducing the presence of pathogenic microorganisms in the environment, thus exposing the patient to the risk of infection (Suleyman *et al*., 2018). Pre-existing diseases and morbidities also collaborate with occurrence of HAIs, since the installation of an infection can harm the treatment that is being performed. In addition, patients debilitated and that are immunocompromised, are more exposed to exogenous and endogenous infectious agents. All this leads the patients to worsen the clinical picture, greater deterioration of the quality of life, as thoseon hemodialysis treatment (Sharif *et al*., 2015; Suleyman *et al*., 2018).

In Brazil, it is estimated that about 5 to 15% of hospitalized patients acquire HAIs, and these infections are the fourth major cause of mortality among patients hospitalized in Intensive Care Units (Leiser *et al*., 2007; Oliveira *et al*., 2011). In other countries, such as Canada, approximately 200,000 patients are annually affected by HAIs, according to the Public Health Agency of Canada (2015). In the United States, HAIs also affects a large number of patients, it is estimated that about 1.7 to 3.5 million patients are diagnosed with health care-related infections annually. This number represents approximately 5% to 10% of hospitalized patients in that country and about 100,000 evolve to death (Anaissie *et al*. 2002a; Klevens *et al*., 2007). In Europe, according to Zingg *et al*. (2017), between 2011 and 2012, from 17,273 patients aged under 18 years in 29 countries, 4.2% of them developed HAIs. In addition to microbial contamination, the problem of resistance of microorganisms to antimicrobials is a worldwide health problem. Governments and health institutions in many countries have sought alternatives to control the spread of resistant microorganisms, given that they pose risks not only to hospitalized patients but to the entire population due to their epidemic potential. For the patient, this condition leads to worsening of the clinical picture, due to several complications, and increases the probability of death (Luepke *et al*., 2017).

CONTAMINATED WATER AS A SOURCE OF INFECTION IN PATIENTS WITH HEMODIALYSIS

The Brazilian Society of Nephrology estimates that about 92% of patients with CRF undergo hemodialysis therapy (Sesso *et al*., 2017). On hemodialysis, water is the most used fluid, constituting about 90% of the dialysis fluids (Pires *et al*., 2010). The water used is treated by several systems, including deionizers, activated carbon filters and reverse osmosis (Bugno *et al*., 2007; Montanari *et al*., 2009; Pires *et al*., 2010). Thus, health institutions around the world strive incessantly to eliminate the risks of water contamination used in medical procedures, but despite efforts to eliminate those contaminants, there are still reports of microbiological contamination even after treatment (Williams *et al*., 2013). It is known that the success of water purification is dependent on the monitoring and maintenance of the treatment system (Bugno *et al*, 2007; Buzzo, 2010; Heidarieh *et al*., 2016). Water quality has a direct impact on the health of the population, so that there are worldwide laws that establish acceptable physicochemical and microbiological parameters. Most water treatment systems are efficient in water purification and waste disposal, however, it is known that some microorganisms such as viruses, bacteria and fungi can remain in the water even after conventional treatment (Heidarieh *et al*., 2016; Shaw *et al*. 2016; Oliveira *et al*., 2018; Suleyman *et al*., 2018).

In hospitals, the compromise of water quality, especially microbiological quality, is a serious public health problem. In the general population the presence of microorganisms in the water may go unnoticed, however, in clinics and hospitals these microorganisms can spread more easily and reach patients vulnerable and to be responsible for infection. In these environments, several factors contribute to the multiplication of microorganisms, such as solutions rich in nutrients, humidity and temperature, which are often ideal for microorganism growth (Suleyman *et al*., 2018). In the last decades several microorganisms have been isolated from waters used in medical procedures; the main agents have been bacteria, however, the emergence of fungal infections resulting from water contamination, mainly water used in hemodialysis therapy has been evidenced (Oliveira *et al*., 2018). Regardless of the treatment system chosen for water purification that should be used in hemodialysis therapy, there are specific parameters and legislation that guarantee its quality. According to Santos *et al*. (2000) the Association for the Advancement of Medical Instrumentation has considered that it is acceptable for water a microbial cell count less than 200 cells / ml in the dialysis liquid ready for use. In Brazil, the acceptable limit for bacteria is also 100 CFU/ mL, according to the standards recommended by National Health Surveillance Agency, according to the legal norm RDC 11/2014 (Brasil, 2014). In view of the seriousness of infections associated with water contamination in a hospital unit, the World Health Organization (WHO) has proposed safety plans that include strategies such as frequent monitoring of water quality and its facilities, evaluation of the HAIs indexes associated with contamination, costs, incidence of microorganisms, education and awareness about the pathogens present in water and its relation with health problems (WHO, 2011).Thus, countries are expected to adopt the plans proposed by WHO and to be more rigorous in controlling water quality and the emergence of HAIs due to microbiological contamination. In the United States, for instance, about $ 28 to $ 45 billion is spent annually on the treatment of HAIs caused by water contamination (Scott, 2012). In contrast to these data, we point to the efficiency of Japan in the microbiological control of water, this excellence directly reflects the health of patients undergoing hemodialysis, with a consequent decrease in mortality and infection rates (Hasegawa *et al*., 2015).

WATER AS A SOURCE OF CONTAMINATION AND DISSEMINATION OF BACTERIA

In Brazil, the problem related to contamination of water used in hemodialysis, became more evident in the 1990s after a contamination of the water used for hemodialysis therapy in Caruaru, a city located in the state of Pernambuco, in the northeast of the country. The incident occurred in 1996 and about 65 patients died due to contamination of the water by a toxin called microcystin, produced by a cyanobacteria (Coelho, 1998). After this, efforts to combat and control water contamination was intensified. In 2004, a study indicated that water and dialysate samples collected in a hemodialysis unit in the city of Ponta Grossa, state of Paraná, southern Brazil, had contamination indexes higher than the standards established by the country's legislation (Borges *et al*., 2007). In 2005, in São Luiz, Brazil, samples of water collected after treatment showed contamination by bacteria and toxins. The main species isolated were *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia, Flavimonas oryzihabitans, Alcaligenes xilosoxidans,* and *Ralstonia pickettii* (Lima *et al*., 2005). Overall, bacteria isolated in waters treated for medical use are of several species, but *Pseudomonas aeruginosa* has been featured (Gomila, 2005).

The reports found in the literature in other countries are similar to the Brazil. In Mexico, in a study carried out in a hemodialysis unit in the city of San Luis Patose, was isolated *Staphylococcus aureus*, *Staphylococcus* spp. coagulase negative, *Escherichia coli, Enterobacter* spp., *Pseudomonas aeruginosa, Acinetobacter* spp., among others (Vázquez *et al*., 2018). In Cameroon, Central Africa, Gueguim *et al*. (2016) reported the isolation of *Pseudomonas* spp., *Staphylococcus* spp., *Aeromonas* spp., *Bacillus* spp., *Klebsiella* spp. and *Pasteurella* spp. from hemodialysis water. In the Asian continent, Heidarieh *et al*. (2016) evaluated the microbiological quality of water intended for hemodialysis in four hospitals and found counts ≥100 CFU / ml in 80 samples of water collected at different points in the distribution system. They accounted 229 isolates of genera*Cocuria, Arthrobacter, Staphylococcus, Mycobacterium, Acinetobacter, Burkholderia, Halomonas, Herbaspirillum, Pseudomonas*, *Sphingomonas* Nazemi *et al*. (2016), in Iran, also isolated and identified *Pseudomonas* spp., *Micrococcus* spp., *Bacillus* spp., *Staphylococcus* spp. and *Legionella* spp. from water and dialysis fluids. Several factors aggravate HAIs, not only the occurrence of infections related to water and hemodialysis fluids, but also the existence of resistant microorganisms. Isolates that are resistant to the most diverse antimicrobial, including multi-drug resistant, directly affects the patient, and burden health services (D'Agata, 2018). In addition, the release of toxins by microorganisms is also the subject of studies. Santos *et al*. (2000) report that dialysis solutions may contain high levels of endotoxin and suggest that this occurs because microbial growth is favored by the presence of substances such as glucose and bicarbonate. Another problem that contribute to the microbial spread by water is the capacity of biofilm formation by some microorganisms, since the water reservoirs, pipes and fittings can favor the microbial adhesion to the surface and forming biofilms.

WATER AS A SOURCE OF CONTAMINATION AND DISSEMINATION OF FUNGI

Water can carry fungi that are opportunistic agents of infections, including water used in health services or in health care procedures. The most of those isolated fungi are potential agents of infections, especially for immunocompromised patients. In recent decades, there have been reports of fungal infections associated with contamination of water used in hemodialysis throughout the world (Arvanitidou *et al*., 2000; Varo *et al*., 2007; Pires *et al*., 2008; Figel *et al*. 2015; Montanari *et al*., 2017). Patients undergoing hemodialysis therapy are vulnerable, with compromised immune systems and, most of those patients with CRF present comorbidities such as diabetes, hypertension and obesity, which may make treatment difficult and worsen the patient's clinical condition.

Studies performed at different places and regions have demonstrated the isolation of different species of yeasts and filamentous fungi from hemodialysis water. Water contamination has varied according to studies between 13% and 77% of samples analyzed, as well as fungus species (Arvanitidou *et al*., 2000, Figel *et al*, 2013; Schiavano *et al*., 2014; Figel *et al*., 2015). In a study carried out in Germany, for example, water samples from 30 hemodialysis units were analyzed, from which the researchers observed that 17.8% of water samples had fungi and bacteria (Bambauer *et al*., 1994). Arvanitidou *et al*. (2000) analyzed treated water from the 85 centers of hemodialysis in Greece, and detected yeasts in 8.2% of the analyzed samples and of filamentous fungi in 77% of the samples. On the other hand, Schiavano *et al*. (2014), in Italy, analyzed 976 water samples, and found 130 (13%) contaminated with fungi, of which 28 were yeasts, 96 were filamentous fungi and sixof both, yeast-like and filamentous fungi.

As can be seen, filamentous fungi and yeasts from different species are isolated from water and hemodialysis fluids, such as different *Candida*, *Aspergillus* and *Fusarium*species (Varo *et al*., 2007; Lepak *et al*., 2011;Schiavano *et al*., 2014; Yapar, 2014; Deorukhkar, 2015; Figel *et al*., 2015; Colombo *et al*., 2017; Epelbaum *et al*., 2017; Montanari *et al*., 2018). Among filamentous fungi, *Aspergillus* spp., *Cladosporium* spp., *Trichoderma* spp., *Fusarium* spp., *Exophiala pisciphila, E. cancerae, E. equine, Rhinocladiella* spp., *Penicillium* spp., *Beauveria* spp., *Acremonium* spp., *Peniophora* spp., *Cladosporium* spp. and *Rhodosporidium* spp., has been isolated from the hospital water system (Varo *et al*., 2007; Figel *et al*., 2013; Figel *et al*., 2015; Xião *et al*., 2015; Edel-Hermann *et al*., 2016). Among the yeasts, *Candida* *parapsilosis*, *C. guilliermondii*, *Rhodotorula mucilaginosa*, *R. glutinis*, *R. rubra* and *Trichosporon inkin* have been reported (Pires *et al*., 2008; Montanari *et al*., 2018). Each of the fungi, genera or species are widely distributed in nature, being found in the soil, in plants, warm-blooded or cold-blooded animals and disseminated by air and water. The genus *Aspergillus*, for instance, is widely found as a water contaminant, and in hospital waters it is associated with the presence of biofilms (Anaissie *et al*., 2003, Williams *et al*., 2013; Oliveira *et al*., 2018). Fungal spores (propagules or conidia) can spread through the air and reach the patients, resulting in invasive aspergillosis, a serious disease that has a high mortality rate (Exner *et al*. 2005; Pappas *et al*., 2010). Among the yeasts, *C. parapsilosis* was the most isolated yeast in a study conducted by Pires *et al*. (2013). This species is often isolated from the environment, being an opportunistic human pathogen, and can be transmitted from one patient to another in the hospital environment, being a colonizer of the human skin (Pires *et al*., 2010). The occurrence of fungi resistant to one or more antifungal agents has increased in recent years (Vieira *et al*., 2017). This is due to several factors, such as indiscriminate and incorrect use of antifungal agents, abandonment of treatment before cure and due to prophylactic use in individuals with risk factors. Abandonment of treatment may occur mainly because the treatment of fungal infections is prolonged and may lead the patient to have side effects (Santos *et al*., 2009; Pfaller *et al*., 2009; Gondim *et al*., 2009). All that emphasizes the importance of the control and elimination of fungi in water and hemodialysis fluids, in order to prevent the diseases to which patients are exposed in dialysis treatment.

BIOFILMS FORMATION

The presence of microorganisms in the systems used for water purification may predispose to the mono- or polymicrobial biofilms formation. It is believed that approximately 95% of the contaminating microorganisms present in drinking water are in biofilm mode (Fleming *et al*. 2013). In devices of hemodialysis machines this issue is aggravated because the water is previously purified and does not contain residues inhibiting the microbial growth. According to Costerton *et al*. (2003), the biofilm can be formed from a community of cells that form microcolonies and are adhered to a substrate, interface, or one another, within an exopolymeric matrix. Microorganisms growth in biofilm mode constitute a form of resistance that is difficult to remove and are provided of protection against host defense mechanisms and hampers the action of antimicrobial agents (Ramage *et al*., 2012). Bacteria within biofilms mode can be up to 1,000 times more resistant to antimicrobials than those in planktonic mode (Vickery, Pajkos, Cossart, 2004). On the other hand, fungi are large biofilm formers, such as species of *Aspergillus*, *Penicillium*, *Pseudallescheria*, *Fusarium*, *Cuninghamella* and *Candida*, that are commonly isolated from hospital water (Mukherjee *et al*., 2005; Pierce *et al*., 2008; Pannanusorn *et al*., 2012; Pires *et al*., 2013; Kauffmann-Lacroix *et al*., 2016). The biofilms formed in the plumbing system of the hemodialysis machines, become continuous reservoirs of release of microorganismsand constitute potential risks of infection to patients under treatment (Oliveira *et al*., 2018). Actions to prevent biofilm formation, eradication and inactivation of those already formed must be continuous processes to be taken to avoid damages to the patient, who are already debilitated and immunocompromised, thus reducing comorbidities and mortality rate.

Conclusion

Microbiological contamination of water is still a world wide problem, despite the efforts of institutions and other health organizations to control the presence of microorganisms, mainly bacteria and fungi. In this matter, infections related to health care due to water contamination are still frequent. Thus, it is necessary to implement more efficient planning and strategies aimed at guaranteeing the quality of the water that is destined to health units. In addition to looking for agents that can control the formation of biofilms in pipes, fittings and reservoirs, since considering that biofilm is the main causes of maintenance of microorganisms in water after treatment, included water for hemodialysis.

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