Water Research 145 (2018) 1–11

Contents lists available at ScienceDirect

Water Research

journal homepage: www.elsevier.com/locate/watres

Occurrence and fate of endotoxin activity at drinking water purification plants and healthcare facilities in Japan

Dai Simazaki [a, *], Masaaki Hirose [b], Hisashi Hashimoto [c], Shunji Yamanaka [d], Mitsuki Takamura [e], Junya Watanabe [f], Michihiro Akiba [a]

[a] Water Management Section, Department of Environmental Health, National Institute of Public Health, 2-3-6 Wako, Saitama, 351-0197, Japan
[b] Department of Public Health and Medical Affairs, Osaka Prefectual Government, 2-1-22 Ohtemae, Osaka, Osaka, 540-0008, Japan
[c] Water Quality Laboratory, Hanshin Water Supply Authority, 5-11-1 Tanou, Amagasaki, Hyougo, 661-0951, Japan
[d] Nagoya City Environmental Science Research Institute, 5-16-8, Toyoda, Minami, Nagoya, Aichi, 457-0841, Japan
[e] Water Quality Management Center, Morioka City Waterworks and Sewerage Bureau, 86 Aza Sakurayama, Kagano, Morioka, Iwate, 020-0807, Japan
[f] Imabari City Waterworks Bureau, Imabari City Government, 1-4-1 Bekkucho, Imabari, Ehime, 794-8511, Japan

ARTICLE INFO

Article history:
Received 31 March 2018
Received in revised form
3 August 2018
Accepted 4 August 2018
Available online 6 August 2018

Keywords:
Dialysis
Endotoxin
Healthcare facility
Water supply
Water purification

ABSTRACT

Occurrence of residual endotoxin activity (ET) in dialysis water and also tap water as its source is a matter of great concern to medical professionals conducting dialysis therapy at healthcare facilities (HCFs). The present study was performed to determine the occurrence and fate of the ET at selected Japanese drinking water purification plants and HCFs between 2014 and 2016. Chemical coagulation and sedimentation, rapid sand filtration, and membrane filtration were highly effective to decrease both ET dissolved in water (free-ET) and ET bound to cells/particles (bound-ET). Moderate decreases in bound-ET and limited decreases in free-ET were observed by chlorination and ozonation. Bacterial activated carbon filtration was a major cause of significant increases in endotoxin activity during the course of drinking water purification process. Levels of residual ET in water supplied to HCFs were strongly affected by their source waters and the configurations of water purification processes served. Microbial regrowth on the premises, from water tanks to faucets at HCFs could also contribute to ET increases in tap water.

1. Introduction

Endotoxins, or lipopolysaccharides (LPS), are among the constituents of the outer cell wall of heterotrophic gram-negative bacteria and cyanobacteria (Sykora et al., 1980). Endotoxins are known to cause various symptoms in humans typically via intravenous exposure, including fever, diarrhea, and vomiting. Hypotension, shock, intravascular coagulation, and death can also occur at elevated endotoxin concentrations (Anderson et al., 2002, 2003). The lipid component of LPS (lipid A) determines the endotoxin activity and contributes to the pathogenic potential of gram-negative bacteria. Studies on the conformation and activity relationship of lipid A have indicated that its principal structural and conformational diversity in different bacterial species, *e.g.*, type and number of long-chain fatty acids, were closely associated with the endotoxin activity (Tanamoto, 1989; Rietschel et al., 1993). Endotoxin is also known to be very stable in the environment and hardly inactivated by heat, *e.g.*, dry-heat sterilization. The pharmaceutical industry has acknowledged endotoxins as potential pyrogens in parenteral drug products (Gerba and Hou, 1985), and focused a great of attention to prevent endotoxin contamination in their products, *e.g.*, intravenous drugs and injection solvents.

The occurrence of endotoxin or endotoxin activity in the water environments and their fates in water treatment processes and finished water have been attracted a great deal of attention from the research community since the 1970s. In early studies, Luzio and Friedmann (1973) investigated endotoxins in surface water, groundwater, tap water, and various beverages in the U.S., and reported endotoxin levels of 1–400 μg/mL in these samples. Haas et al. (1983) conducted a long-term study at two water treatment and distribution systems in the U.S. over an 18-month period, and endotoxins were observed at levels between 3 and 14 μg/L.

Since the late 1980s, endotoxin concentrations have mostly been reported in endotoxin activity units per volume (*e.g.*, EU/mL) rather than in weight units per volume (*e.g.*, ng/mL), reflecting the fact that endotoxin activity differs between bacterial species.

* Corresponding author.
E-mail address: simazaki.d.aa@niph.go.jp (D. Simazaki).

https://doi.org/10.1016/j.watres.2018.08.009
0043-1354/

Anderson et al. (2002) pointed out that 1 ng/mL was roughly equivalent to 5–10 EU/mL, by estimation from studies reporting a conversion factor. Burger et al. (1989) compared two wastewater reclamation plants in Namibia and South Africa for their ability to remove endotoxins from raw wastewater. Endotoxin activities in the raw wastewater were very high, *i.e.*, up to 2528 and 1350 EU/mL, respectively. Endotoxin activity was effectively decreased in the course of the wastewater reclamation process, particularly in the early treatment stages, including chemical coagulation, breakpoint chlorination, and sand filtration. They also observed significant increases in the levels of endotoxins by up to 50% after activated carbon column treatment. Rapala et al. (2002) investigated endotoxin concentrations in water sources and drinking water purification plants (DWPPs) at the time of 151 cyanobacterial water blooms in Finland. Endotoxin levels in raw water of nine DWPPs ranged from 18 to 356 EU/mL and those in finished water ranged from 3 to 15 EU/mL. At their in-depth studies during the course of water purification processes at two DWPPs, the highest reductions of endotoxin concentrations (83%–86%) were observed in the early stages, including chemical coagulation, sedimentation, and sand filtration. They also found that activated carbon filtration either increased or had no effect on endotoxin concentrations, and chemical oxidation by ozonation and chlorination had little effect.

In recent studies, endotoxin activity by 'free' endotoxins dissolved in water (hereafter described as free-ET) and that by 'bound' endotoxins associated with particles, including cell walls of viable/non-viable gram-negative bacteria (bound-ET), were separated by centrifugation, and differences in their occurrence and fate were discussed. Ohkouchi et al. (2007) reported that the effluent from wastewater treatment plants would be a major source of endotoxin contamination in Yodo River basin in Japan, where the total endotoxin activities ranged from 311 to 2430 EU/mL. They also observed increases in bound-ET after activated carbon adsorption process associated with bacterial regrowth, and that the ratio of free-ET to total endotoxin activity (total-ET) increased by chlorination and ozonation. Can et al. (2013) determined endotoxin contamination at a DWPP in Beijing and its source water from a long water diversion channel between Shijiazhuang and Beijing, China. The total-endotoxin activities in the source water samples ranged from 21 to 41 EU/mL, and those in finished water of the DWPP ranged from 4 to 10 EU/mL, showing a 31% decrease in free-ET and 71% decrease in bound-ET by the entire water purification process. They pointed out that the granular activated carbon filtration and chlorination induced bound-ET and free-ET increases, respectively.

In these days, the occurrence of endotoxins in water supplied to healthcare facilities (HCFs), by public and/or their own private water supply systems, has been a matter of great concern to medical professionals conducting dialysis therapies. This is due to increasing awareness and also an increased need for strict control of microbial and endotoxin contamination in dialysis fluid as well as dialysis water (*i.e.*, solvent of dialysis fluid) in the U.S., European countries, and Japan. It has been reported that microbial contamination of dialysis fluid causes dialysis amyloidosis and malnutrition due to the strong physiological activities of endotoxins (Masakane et al., 2013), and also a nationwide cohort study in Japan concluded that higher facility endotoxin levels in dialysis fluid may be related to increased risk of all-cause mortality among hemodialysis patients (Hasegawa et al., 2015). Moreover, recent progress in an on-line hemodiafiltration (HDF) technique requires ultrapure dialysis water and dialysis fluid served, directly injecting the dialysis fluid into the patient's blood and removing accumulated metabolic products from blood by a combination of diffusive and convective transport through a semi-permeable and high-flux membrane (Tattersall and Ward, 2013; Ase et al., 2017). The Japanese Society for Dialysis Therapy (JSDT) has established the Microbiological Quality Standard for Dialysis Fluid in 2008 along with these trends in dialysis therapy (Kawanishi et al., 2009). Recommended endotoxin level in dialysis water by the JSDT standard is much lower than that by the International Organization for Standardization (ISO) standard revised in 2009 (ISO, 2009) as shown in Table 1. Dialysis therapy at HCFs requires huge amounts of tap water as its raw water. On-site ultrapure water production systems mostly introduced in Japanese HCFs are capable of producing 2–3 m^3 of dialysis water per hour, and typically consist of a prefilter, an ion exchange filter, activated carbon filters, reverse osmosis (RO) modules, an RO permeate storage tank, a UV disinfection device, and UF modules also known as endotoxin removal filters (ETRF) (Ase et al., 2017). Appropriate routine operation and maintenance of the on-site system, including water quality monitoring of the entire process, are crucial for safety management of dialysis therapy and has been recommended by the JSDT standard (Kawanishi et al., 2009). Actually, the level of endotoxin level in dialysis water has been getting better at HCFs in Japan (JSDT, 2017). However, these efforts were solely made by medical professionals at their workplaces and they are not able to control endotoxin before their on-site ultrapure water production systems, *i.e.*, tap water and its source. From the viewpoint of "Water Safety Plan" methodology to control chemical/microbial risks at all steps in water supply from catchment to consumer (or dialysis patients in this case), tap water at HCFs, water purification process at DWPPs, and source water should be also included in the critical control points for ensuring the safety of the dialysis water.

In the present study, the occurrence and fate of both free-ET and bound-ET at selected Japanese DWPPs and HCFs were investigated to identify the key critical control points for the management of endotoxin in water for medical activities.

2. Materials and methods

2.1. Sample collection

Seven DWPPs across Japan were selected for collection of water samples, considering their source water, water purification process, treatment capacity, and location (Table 2). Four DWPPs (DWPP-A1, B2, C, and D) take their source water from the downstream areas of rivers flowing into watersheds that include commercial, industrial, and residential areas. DWPP-B1 takes its source water from a water reservoir, where water quality is seriously affected by the sporadic occurrence of algal blooms. DWPP-A2 withdraws groundwater from a nearby deep aquifer at 200–250 m below the ground surface and minimally affected by external contamination. On the other hand, DWPP-E withdraws groundwater from a shallow aquifer at 10–15 m below the ground surface and is affected by penetration of nearby river water, where trace levels of residual pharmaceuticals and their metabolites have been detected (Simazaki et al., 2015).

DWPP-B1, C, and D employ single or dual ozonation followed by biological activated carbon filtration for removal of trihalomethane precursors and trace chemicals of concern, including taste and odor substances (Table 2). DWPP-A1 and B2 employ conventional chemical coagulation, sedimentation, and rapid sand filtration. Powdered activated carbon is injected at both water intake points on an almost daily basis, to remove taste and odor substances from the raw water. The other two DWPPs withdrawing groundwater employ chemical coagulation followed by direct rapid sand filtration (DWPP-E) or chlorine disinfection only (DWPP-A2). All seven DWPPs use a liquid chlorine agent (*i.e.*, sodium hypochlorite solution) for final disinfection as well as intermittent oxidation. With regard to chemical coagulation, all seven DWPPs use polyaluminum chloride (PAC) solution.