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NARRATIVE REVIEW

Hospital-acquired *Legionella* infections: an update on the procedures for controlling environmental contamination

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Parole chiave: Legionella, disinfezione, prevenzione, acqua calda sanitaria, ospedale

Abstract

The waterborne healthcare-associated infections are mainly sustained by Legionella and Pseudomonas spp. Various water factors and plumbing characteristics, and the interaction with other water microorganisms are considered to be predictive of Legionella contamination. It is therefore mandatory to organize plans of surveillance, prevention and control in order to avoid disease appearance in immunosuppressed patients, with higher risk of death. Guidelines for the prevention of Legionnaires' disease have been published, benefiting those who face this problem, but definitive standardized solutions do not exist yet.
Here we describe fifteen years of activity, during which our study group gathered interesting data on the control of Legionella contamination. Water disinfection is not generally sufficient to control the risk of infection, but a complex water safety plan should be developed, including system maintenance, training of staff and implementation of a clinical surveillance system aimed at early detection of cases. Concerning the control measures, we evaluated the effectiveness of different treatments suggested to reduce Legionella spp contamination, comparing our results with the current literature data. The performance ranking was highest for the filter, followed by boilers at high temperature, monochloramine and, at a lower level, chlorine dioxide; the effectiveness of hyperchlorination was limited, and thermal shock was even more ineffective.

Legionnaires' disease

Legionella is a waterborne bacterium responsible for pneumonia; currently, the genus *Legionella* consists of 59 species, three subspecies and over 70 distinct serogroups, less than half are opportunistic pathogens (1). The surveillance of Legionnaires' disease carried out by the European Legionnaires' Disease Surveillance Network (ELDSNet) reports 5,851 cases of LD in 2013 by 28 EU Member States, and the 8% of cases were linked to healthcare facilities (2). In Italy in 2014, among 1,456 confirmed cases, 62 (4.1%) were nosocomial acquired, but other 38 (2.5%) involved persons living in nursing or rehabilitation homes (3). Independently on the setting, *L. pneumophila* serogroup 1 was the most commonly identified pathogen, accounting for 83% of culture-confirmed cases in Europe, and 99% in Italy. The most common route of infection is the inhalation of

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aerosols containing the bacteria. Aspiration has also been identified as a route of infection in some hospital-acquired cases associated with contaminated water, food and ice (4, 5). There is no evidence of person-to-person transmission, but a recent letter describes a case of possible inter-human transmission (6). Risk factors for Legionnaires' disease include male gender, heavy smoking and alcohol abuse, chronic debilitating illness (chronic heart/lung disease, chronic renal/ liver failure and diabetes), hematologic malignancies, lung cancer, steroid therapy and other immunosuppressive treatments (7). The pneumonia by *Legionella* has a case fatality of 10%, but up to 30-50% in the hospital-acquired infections, thus the clinicians should conduct an active surveillance on pneumonia cases in order to promptly detect the nosocomial cases and adopt the appropriate therapy, so avoiding a fatal outcome (8-11).

By revising 22 years of international literature on waterborne healthcare-associated bacterial infections, 48 articles describing *Legionella* infections and 77 involving other bacteria were published, suggesting that they represent the tip of an iceberg (12). Also in this case, *L. pneumophila* serogroup 1 was the predominant bacterium causing hospital outbreaks (66.7% of outbreaks), followed by serogroup 6 (13, 14) and 3 (15, 16), whereas *Legionella* non *pneumophila* was described only in one article (17). Indeed, patient characteristics are the main risk factor, thus healthcare operators should adopt any preventive measure in order to avoid water exposure of high-risk patients. Furthermore, special attention should be devoted to children, who are rarely affected by waterborne infections of community origin; 9 articles reported as hospitalized neonates, in some cases premature and/or receiving corticosteroids, got *Legionella* pneumonia directly from water or from mechanical ventilation (12).

Preventive and control measures

In hospital, hot and cold water systems are the main sources of infection (18). Factors such as water temperature, configuration and age of the water distribution systems, physicochemical constituents of the water, and plumbing materials encourage legionellae growth (19-21). Old components of the pipeline system, areas of stagnation or low flow, dead-legs and storage tanks allow their survival and development (22). The ability to enter in a viable but not culturable (VBNC) state and the presence of biofilm and protozoa are additional important factors for *Legionella* growth (23, 24). In addition, respiratory devices and nebulizers may also be the source of nosocomial Legionnaires' disease (25, 26). The control of *Legionella* spp contamination is relevant in healthcare settings where patients, mostly with compromised immune systems, are at increased risk of disease and of fatal outcome. For this reason, national and international guidelines advocate the adoption of preventive measures to control *Legionella* water contamination (27-29). The *Legionella* prevention should start from a correct design and construction of water networks, in order to make the colonization and multiplication of the bacterium in hot water distribution systems unlikely (27). During renovations or new construction, the pipe runs should be as short as practical. When recirculation is employed, the pipe runs should be insulated and long dead-legs avoided. New shower systems should be designed to permit mixing of hot and cold water near the showerhead (30, 31). The World Health Organization (WHO) suggests that developing a water safety plan (WSP) is the preferred approach to the management of specific health risks of exposure to *Legionella* from water systems (32). A WSP has 10 steps that fit within the three main areas of system assessment, identification and monitoring of control measures used to ensure water safety, management and communication. All healthcare facilities should have specific WSPs as part of their infection control program. These plans should address issues such as water quality and treatment, cleaning of respiratory equipment and control of microbial growth in water systems. A preliminary stage in developing a WSP is to appoint a team of experts with a thorough knowledge of design and operating characteristics of the water system in order to identify hazards and to prioritize risks. Risk factors for growth of legionellae or for exposure to legionellae in piped water systems include poor water quality and treatment failures, stagnation and low flow rate, construction materials that contribute to microbial growth and biofilm formation, ineffective disinfection, water temperature in the range 25–50°, presence of biofilm and aerosol formation (27). The steps involved in the monitoring phase are to identify and to monitor control measures and validate effectiveness of WSP. Control measures are activities or processes applied to a system to prevent a hazard from occurring and any WSP would be based on a combination of different control methods. Keeping water temperature outside the ideal range for legionellae is an effective control measure for both hot and cold water systems. Guidelines recommend that hot water should be stored above 60° and circulated at a temperature of at least 50°, whilst the recommended temperature for storage and distribution of cold water is below 20° (27, 29, 33). Where temperature controls cannot be maintained, an alternative mean of control needs to be implemented. The available disinfection methods for controlling the contamination of *Legionella* spp in piped water systems are numerous but all present advantages and disadvantages related to ease of implementation, cost, maintenance issues, and short- and long-term effectiveness (27, 34, 35). Among physical methods, circulating water at 60°, such that the temperature at each outlet reaches at least 50° and preferably 55°, is the method most commonly used to control legionellae in hot water system (36-39). This procedure has the possible disadvantage of increasing energy consumption and the risk of scalding (27, 28).

Superheat-and-flush is carried out by raising the temperature inside the hot water storage heater at 70-80° then by flushing sequentially all the distal sites with water at 60-65° for minimum 5 minutes, but preferably 30 minutes, for up to three days (27-29). Superheat-and-flush can still be the first choice of disinfection method in an outbreak situation because it requires no special equipment and can be implemented immediately. However, this technique is not suitable for large buildings where temperatures > 60° at each outlet cannot be maintained (40-42). From our experience in a 765-bed hospital, superheating is the most unreliable method because disinfection is only temporary and re-colonization rapidly occurred (Figure 1, Panel A). Furthermore, this procedure requires considerable energy, manpower and stringent safety measures to prevent scalding. Among thermal disinfection systems, we successfully experimented the use of small electric boilers that were installed on the cold water line in the hospital rooms in order to produce hot water at the point of use (43). The boilers serving 2 adjacent rooms housing high risk patients guarantee the absence of contamination when the temperature is maintained >58°. However, the boilers have to be replaced every five years due to hardness of the groundwater in our municipality.

Point-of-use (POU) filters (0.2-μm pore size) have been used for prevention of nosocomial infections due to *Legionella* spp and *Pseudomonas aeruginosa*, particularly in high-risk areas, such as intensive care and transplant units (44-48). POU filtration acts as physical barrier in a way that 100% negative samples are achieved, provided that protocols are developed in order to ensure filters are replaced regularly (49). Furthermore, retrograde contamination may occur either by splash water from the water basin during use or by direct contact with contaminated hands. Adequate staff and patient training whit respect to the appropriate use, maintenance and replacement of POU filters is recommended (34, 50). During an outbreak POU filters can be installed immediately and are cost-effective compared with the alternative of restricting showering and providing bottled water (51).

Ultraviolet (UV) light irradiation (254 nm) has proven effective close to the point of use but not at distal sites because the lack of residual effect (52). The efficacy of UV disinfection is optimized if the lamp is installed in a virgin building from the first moment of water flow into the plumbing system, if it is combined with another systemic disinfection method and if the area of disinfection is limited (44, 53, 54). The advantages of the UV light include easy installation, low cost and no adverse effects on water or plumbing system (28).

Among chemical disinfection methods, the most popular are continuous systems such as copper and silver ionization, hydrogen peroxide, and chlorine-based biocides. The efficacy of copper and silver ionization in controlling *Legionella* spp contamination has been largely documented when used either alone (55-59) or in combination with other systemic disinfection strategies (60, 61). The advantages of copper and silver ionization include easy installation, residual activity against early recolonization and effectiveness at high water temperature (35, 62). However, this method requires continuous monitoring of copper and silver ions in order to avoid that concentrations exceed the limits for drinking water or they go below the recommended values (0.20-0.80 mg/L and 0.01-0.08 mg/L for copper and silver ion, respectively) (60, 63). Furthermore, water parameters such as hardness, pH and presence of sediments may influence the effectiveness of ionization (55, 64).

Continuous treatment with stabilized hydrogen peroxide is a technique quite recent and requires additional field trials in order to confirm its effectiveness (65-67).

Chlorination is corrosive to pipes (68), produces potentially carcinogenic Disinfection By Products (DBPs) and provides only temporary results (27, 69-72). The shock hyperchlorination is performed injecting chlorine - usually in the form of sodium or calcium hypochlorite - in order to have a free residual chlorine of 20–50 mg/L at distal sites. After a contact period of 1–2 h the water is drained and replaced with fresh water until the concentration of chlorine returns to around 0.5-1 mg/L. An alternative is continuous chlorination with a residual disinfectant between 1 and 2 mg/L. In our experience, this is an expensive and unreliable disinfection procedure, due to the fact that many persons are required to monitor chlorine concentration at the distal sites, and reduction of positive points is limited (43). In our hospital, twelve hyperchlorination procedures were carried out over seven years, but the re-colonization occurred after 1-2 months, sometimes at levels higher than before the treatment (Figure 1, Panel B). Shock hyperchlorination can be used as an emergency disinfection method in hospitals where superheat-and-flush cannot be practicable (35).

Chlorine dioxide is a gas in solution that is generated on site at the facility and it has been largely used to control legionellae in hot water systems (73-75). In our hospital chlorine dioxide is produced *in situ* by using hydrochloric acid and sodium chlorite (Sanipur S.r.l., Brescia, Italy) and injected in continuous to reach a residual disinfectant concentration between 0.3 and 0.5 mg/L at distal points (76). This method reduced contamination to low levels (<100 cfu/L)

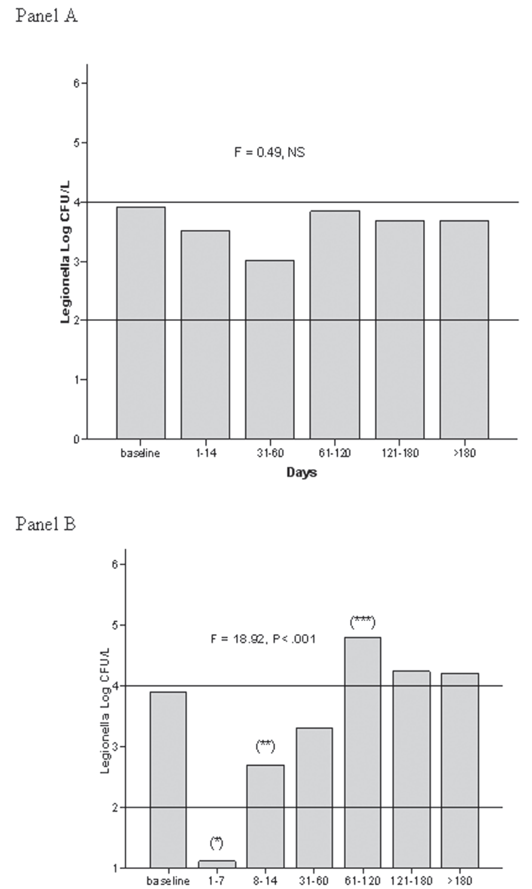

Figure 1 - Time trend of *Legionella* spp contamination after superheating and flush (Panel A) and shock hyperchlorination (Panel B); (*) P < 0.05 *vs* all others, (**) P < 0.05 *vs* others except 31-60 days, (***) P < 0.05 *vs* previous groups. The figure in the panel B has been extracted from reference n. 43.

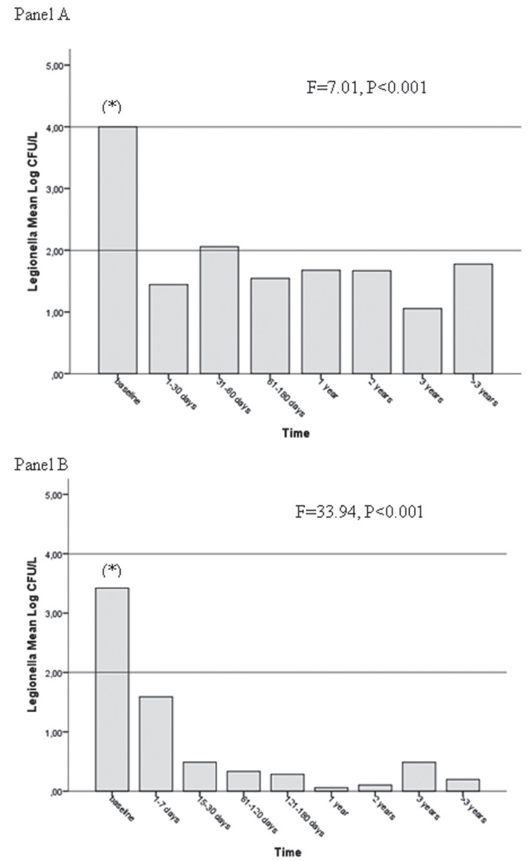

Figure 2 - Time trend of *Legionella* contamination before and after continuous treatment with chlorine dioxide (Panel A) and monochloramine (Panel B). (*) P< 0.05 *vs* all others.

during a three-year period, but did not eradicate *Legionella* (Figure 2, Panel A). This is due to the inadequate penetration of the biocide into biofilms and the resistance of the bacteria to chlorine, as observed by other authors (77, 78). Furthermore, problems with corrosion of pipelines may appear, and the formation of DBPs into the drinking water poses health concerns (79, 80). A guideline value for chlorine dioxide has not been established, but the taste and odor threshold for this compound is 0.4 mg/L and the maximum residual disinfectant level suggested by EPA is 0.8 mg/L (30).

Monochloramine is a well-known disinfectant for drinking water, largely used in United States (81, 82). Few studies describe the use of monochloramine on a small scale for controlling *Legionella* colonization in hospital water systems (83-86). To the knowledge of the authors, we pioneered in Italy to test a commercially available monochloramine plant installed on a hospital hot water system for *Legionella* disinfection (76, 87). In our experience, monochloramine was generated *in situ* by reaction between a stabilized chlorine-based precursor and an ammonium salt (Sanipur S.r.l., Brescia, Italy) and used at concentrations between 2.0 and 3.0 mg/L, according to WHO and EPA guidelines which suggest a maximum residual disinfectant level of 3 and 4 mg/L respectively (30, 88). Monochloramine resulted effective in reducing *Legionella* counts from 97.0% to 8.3% in the first month of its application (Figure 2, Panel B). After three years, only 9 out of 95 samples (9.5%) were positive, and no sample exceeded 10^4 cfu/L versus 59.4% at baseline. The increase of other microorganisms (*Mycobacterium* species), and the formation of nitrogen by-products with carcinogenic activity have been suggested as possible adverse effects of the continuous use of monochloramine (30, 75).

We have a study in progress on other devices that use different methods of monochloramine production/injection: the preliminary results confirm the effectiveness of monochloramine in controlling *Legionella* spp, and no production of undesirable toxic substances such as N-nitrosamines (89).

In Table 1, we compare the effectiveness of different measures adopted in our hospital to control *Legionella* contamination, both in terms of reduction of positive points and of points exceeding 10^4 cfu/L compared to pre-treatment, with information on their cost.

The WHO recommends to perform cultures for *Legionella* every three months to verify the effectiveness of the procedures adopted (27). Monitoring points should be identified throughout the network on the basis of system design, operating parameters and high-risk areas. Particular attention should be given to areas where control is most difficult to achieve, and areas where *Legionella* are most likely to grow. The suggested number of outlets to be sampled for a 500-bed hospital is a minimum of 10 distal sites plus the hot water storage tanks.

Conclusion

We highlight that continuous disinfection of hot water may be an effective tool for reducing *Legionella* contamination, but we emphasize that all systems must be continuously monitored since none eliminates the bacteria once the water network is contaminated, and adequate levels of biocides should be selected in order to obtain the best effect with the minimum damage for pipes. Each disinfection method differs in design and application, and the choice of an appropriate cost-effective measure requires careful analysis and planning. The selection

Table 1 - Cost-effectiveness of various measures adopted in hospital water networks for controlling *Legionella* spp contamination.

Method	Mode of use	% reduction positive points	% reduction points $\geq 10^4$ CFU	Euro/year/ 100 water points
Filter	Change monthly	-100%	-100%	16,000
Electric boiler One for room	Change every 2-5 years >58°	-94.3%	-100%	8,000
Monochloramine	2-3 mg/L at point of use	-86.3%	-100%	3,650
Chlorine dioxide	> 0.3 mg/L at point of use	-46.2%	-82.3%	3,063
Shock hyperchlorination	20-50 ppm free chlorine at point of use, for 1-2 hours, then flush	-3.8%	-83.5%	7,526
Superheating and flush	>60° at point of use for 3 days	+30.5%	-17.9%	3,710

of the vendor for installation of a systemic disinfection method requires accurate consideration with intense scrutiny. About this, the recommendations and feedback of other hospitals with experience of the system under consideration could be useful. The choice also depends on the building characteristics, the water parameters and the characteristics of water distribution systems (for example pH, temperature, turbidity, plumbing material). Furthermore, healthcare facilities should apply the following recommendations: water that is used to rinse and to clean respiratory apparatuses should be sterile; birthing pools should be designed for the purpose, and should be physically cleaned and disinfected both before and after birth; in high-risk areas, such as transplant centers and intensive care units, point-of-use filters are needed at the outlets.

Riassunto

Legionellosi di origine nosocomiale: aggiornamento sulle procedure di controllo della contaminazione ambientale

Le infezioni da *Legionella* spp nelle strutture ospedaliere sono prevalentemente associate all'acqua calda sanitaria. Vari fattori, quali le caratteristiche dell'acqua e delle tubazioni, oltre all'interazione con gli altri batteri acquatici, contribuiscono a favorire la contaminazione da *Legionella* spp. Per tale motivo, è importante organizzare piani di sorveglianza, prevenzione e controllo per evitare la comparsa di casi in pazienti immunodepressi, per i quali il rischio di morte è elevato. La disinfezione non è generalmente sufficiente da sola a controllare il rischio di infezione, ma occorre mettere in atto un complesso piano di sicurezza dell'acqua che includa operazioni di pulizia e disinfezione, formazione del personale e implementazione di un sistema di sorveglianza clinica per individuare prontamente i casi. Numerose Linee Guida nazionali e internazionali sono state pubblicate per affrontare al meglio il problema, ma soluzioni standardizzate e definitive non sono tuttora emerse. In questa rassegna, descriviamo quindici anni di esperienza sul campo, durante i quali abbiamo potuto verificare vantaggi e svantaggi di diversi sistemi di disinfezione applicati alla rete dell'acqua calda sanitaria dell'ospedale, confrontandoli con i dati di letteratura. La maggior efficacia protettiva è garantita dai filtri assoluti installati nei terminali, seguiti dai boiler mantenuti a temperature intorno ai 60°, e dai sistemi in continuo, in particolare la monoclorammina seguita a distanza dal biossido di cloro, mentre i metodi shock sono risultati poco efficaci o addirittura inefficaci anche nel breve periodo.

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