Prevention of hospital-acquired legionellosis

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Purpose of review

The incidence of hospital-acquired legionellosis appears to be increasing. Presence of *Legionella* in the hospital drinking water is the only risk factor known with certainty to be predictive of risk for contracting Legionnaires' disease.

Recent findings

Given the high frequency of infection by nonpneumophila and nonserogroup 1 species, both *Legionella* respiratory culture on selective media and urine antigen testing should be available in the hospital clinical microbiology laboratory. If the drinking water is contaminated by nonpneumophila or nonserogroup 1 species, *Legionella* culture on selective media must be available for patients with hospital-acquired pneumonia. The impact of PCR application for environmental water specimen remains to be elucidated. Its advantage is that it is a rapid test and its weakness is its low specificity. Copper–silver ionization disinfection and point-of-use (POU) filters have proved effective. Chlorine dioxide and monochloramine are under evaluation and their ultimate role remains to be elucidated. Routine *Legionella* cultures in concert with disinfectant levels are the best indicators for ensuring long-term efficacy. Percentage distal site positivity for *Legionella* in drinking water is accurate in predicting risk. Quantitative criteria (CFU/ml) have proven inaccurate and should be abandoned.

Summary

Infection control professionals, not healthcare facility personnel or engineers, should play the leadership role in selecting and evaluating the specific disinfection modality. Proactive measures of routine environmental cultures for hospital water and disinfection modalities allow for effective prevention of this high-profile hospital-acquired infection.

Keywords

disinfection, healthcare-associated pneumonia, legionellosis, nosocomial infections, waterborne pathogens

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Introduction

Hospital-acquired legionellosis continues to be a topical issue. New, important information on laboratory testing, microbiology and methods of prevention have been published within the last several years. In this mini-review, we will touch upon some of the highlights that have relevance to the practicing physician.

Microbiology

Legionella pneumophila serogroup 1 is the most common cause of Legionnaires' disease; however, infections due to nonpneumophila species of *Legionella* and nonserogroup 1 *L. pneumophila* are frequent in hospitals. In an Italian survey of hospitals over 9 years, environmental cultures yielded *Legionella* in 79% (102/129). It was worth noting that *L. pneumophila* serogroups 2–14 were isolated from 55% of the water specimens, whereas *L. pneumophila* serogroup 1 was isolated from only 31% [1•]. In fact, *L. pneumophila* serogroup 6 was found in 60% of the hospitals that yielded *Legionella* in the Italian survey. *L. pneumophila* serogroup 5, serogroup 3 and *Legionella feeleii* were the culprits in three hospital-acquired cases [2–4]. This is pertinent in that the most common diagnostic modality for diagnosis of Legionnaires' disease is the urine antigen. The urine antigen is a rapid point-of-care (POC) test that is sensitive only for *L. pneumophila*, serogroup 1. For the other neglected serogroups and species, the application of *Legionella* culture of sputum becomes most important in diagnosis of hospital-acquired legionellosis. Unfortunately, these infections are easily overlooked and can go untreated because *Legionella* culture is not widely performed or available.

Hospital-acquired outbreaks

Outbreaks are worldwide and have been reported from India [5], Turkey [6], Italy [1•], Taiwan [3,7] and Poland [8]. These outbreaks are usually due to aspiration of

contaminated drinking water, but an oxygen humidifier [9] and a decorative fountain were implicated in two reports. Eight cases occurred in a hospital that had installed a decorative water fountain in the lobby [10]. Two cases of Legionnaires' disease were diagnosed in stem cell transplant patients linked to exposure to a decorative water fountain in a radiation oncology suite [11]. In a French hospital, a case of Legionnaires' disease in a leukemia patient was linked to water from a wash-basin in a hematology unit [2].

The study in India is puzzling [5]. The investigators used a proactive approach to culture the drinking water supply in a hospital in which hospital-acquired legionellosis had not yet been identified. Thirty-three percent of water sites were positive, exceeding the 30% trigger for action in the USA. Disappointingly, no diagnostic tests were applied to patients with hospital-acquired pneumonia, so an opportunity to use the information derived from environmental cultures was not exploited.

A hospital completed construction of a new 12-story addition and 10 cases of hospital-acquired Legionnaires' disease were identified, with one death, within weeks of moving patients onto the wards [12]. *Legionella* can colonize hospital buildings within weeks of water fixtures being connected [13].

Clinical manifestations

In a retrospective study using a Danish national surveillance database, clinical manifestations (fever, headache, diarrhea, hyponatremia) of hospital-acquired Legionnaires' disease were found to be less pronounced than for those with community-acquired Legionnaires' disease [14]. It was noted that about 20% of hospital-acquired cases did not have clear-cut abnormalities on chest radiographs at the onset of symptoms. The time from in-hospital symptoms to diagnosis of legionellosis was shorter for community-acquired vs. hospital-acquired legionellosis. Thirty-day mortality was 12.9% for community-acquired vs. 33.3% for hospital-acquired legionellosis.

Investigators from the MD Anderson Cancer Institute performed a retrospective study on 49 cancer patients with positive *Legionella* culture and direct fluorescent antibody stain over a 12-year period [15]. Eighty-two percent had an underlying hematologic malignancy and 37% were bone marrow transplant recipients. The case fatality rate was 31% despite the fact that most patients received active antimicrobial agents against *Legionella*. Two patients had relapse of Legionnaires' disease following clinical response. There was a trend in improved outcome for severely ill patients who received combination of anti-*Legionella* antibiotics.

Key points

- Hospital-acquired outbreaks of Legionnaires' disease are occurring worldwide and appear to be increasing in frequency.
- Complications, including neurologic, may be a result of an immune-mediated process.
- New laboratory tests or approaches that would assist with management include serum procalcitonin, erythrocyte sedimentation rate, serum ferritin.
- PCR assays are available for environment water surveillance, but false-positive results are problematic.
- Pipe materials affect *Legionella* growth in water distribution systems and biofilms.
- Routine environmental culturing of hospital water even in the absence of known cases is a proactive approach for prevention of hospital-acquired Legionnaires' disease.
- Copper–silver ionization and point-of-use filters have proven effective in prevention. Chlorine dioxide and monochloramine are promising disinfection modalities.

Neurologic symptomatology is common in patients with severe Legionnaires' disease, especially confusion. A patient presented with a 3-day history of fever and chills plus neurological symptoms. The most prominent were facial twitches and tremors, but the patient also complained of severe headache and confusion [16]. Myoclonus and involuntary facial twitching were documented on physical examination. Lumbar puncture chemistries were normal and 1 white blood cell (WBC)/hpf was seen. *Legionella* urinary antigen was positive. All symptoms resolved with levofloxacin therapy.

Two patients with Legionnaires' disease experienced severe neurological deficits and extensive demyelinating lesions were found on central nervous system MRI [17]. A diagnosis of acute disseminating encephalomyelitis was made for both cases. The first patient responded to azithromycin and rifampin. In the second patient, neurologic complications developed following successful ciprofloxacin therapy. High-dose prednisone and nine sessions of plasmapheresis were given. The marked improvement with corticosteroids and plasmapheresis raises the possibility that these complications resulted from an immune-mediated process.

Laboratory diagnosis

Cunha *et al.* [18•] found that elevated erythrocyte sedimentation rates of more than 90 mm/h distinguished Legionnaires' disease from viral pneumonias – a useful diagnostic point given the recently reported occurrence of Legionnaires' disease occurring concomitantly with

influenza. Elevated serum ferritin levels (more than two times the normal) were also found in patients with Legionnaires' disease [19]. Such high levels can be seen in several inflammatory disorders, but have not been reported for other bacterial pneumonias, so the specificity of this test is unknown.

Swiss and Dutch investigators found that procalcitonin test was a useful test for predicting adverse outcomes in legionellosis. Patients with initial procalcitonin values above a cutoff of 1.5 had a significantly higher risk of death and/or ICU admission. The procalcitonin test was actually more predictive of adverse outcome when compared with the use of CURB-65 or Pneumonia Severity Index (PSI) score [20,21]. It should be noted that CURB-65, CRB-65 and PSI scores have been found to be inaccurate in predicting outcome, especially in ICU patients [22]. The modified American Thoracic Society (ATS) score [23] and Pitt Bacteremia Score (PBS) were more accurate for pneumococcal pneumonia (and Legionnaires' disease) in predicting mortality and identifying those patients who would benefit from ICU care [22].

PCR for environmental samples

Molecular diagnostic tests such as PCR for Legionnaires' disease are not yet approved by the U.S. Food and Drug Administration (FDA) for patient care and are available only through research laboratories. On the contrary, PCR assays have been evaluated for environmental sources and are commercially available.

Quantitative PCR (qPCR or real-time PCR) assays have been applied for detection of *Legionella* in environmental water samples (Table 1) [24–31]. At least three assays are commercially available: (GeneDisc System, Pall Co., Port Washington, NY; iQ-Check, Bio-Rad, Hercules, CA; Aqua Screen, Minerva Biolabs, Berlin). In general, the species probe (for *L. pneumophila* only) performs better than the genus probe (for all species of *Legionella*), especially in its specificity. Low specificity and high false-positive rates were found for the PCR test if culture was used as the gold standard [24,25,27,30,32–34]. The high false-positive rate may be due to the presence of viable but nonculturable *Legionella* [34] or the presence of nonviable *Legionella* in water samples [35]. Disinfection of cooling towers and potable water systems for *Legionella* is widely applied. If disinfection was performed, it is likely that the water samples contain nonviable *Legionella*, which were killed by the disinfection measures. The nucleic acids in the dead cells may be amplified by the PCR. This may explain why no correlation was observed between culture and PCR results.

PCR might be useful in outbreak situations when rapid results are needed; subsequent results from culture could

Table 1 Application of quantitative PCR in detecting *Legionella pneumophila* in environmental samples

Author	Country	Site of samples/no. of samples tested	Sensitivity/specificity for *Legionella pneumophila* (%)		Sensitivity/specificity for *Legionella* species (%)		Commercially availability
			Potable water samples	Nonpotable water samples	Potable water samples	Nonpotable water samples	
Lee *et al.* [24]	6 European countries	Potable water (hot and cold)/506 Cooling tower/232	96/32	95/69	99/3	100/7	Y (GeneDisc)
Mietzner *et al.* [25]	US	Potable water (hot)/100	100/85	NA	100/40	NA	Y (GeneDisc)
Yaradou *et al.* [26]	France	Potable water (hot)/132 Cooling tower/46	85/51	100/42	NA	NA	Y (GeneDisc)
Bonetta *et al.* [27]	Italy	Potable water (hot and cold)/76	100/68		NA		N
Guillemet *et al.* [28]	Canada	Spa samples/101		NA		93/36	N
Edagawa *et al.* [29]	Japan	Potable water (hot and cold)/130		NA	25/83	NA	N
Mérault *et al.* [30]	France	Potable water (hot and cold)/209	85/16		NA		N
Felföldi *et al.* [31]	Hungary	Potable water (hot and cold)/NA	qPCR sensitivity > culture		NA		N

NA, data not available; Y, yes; N, no.

be confirmatory and allow definitive identification for epidemiological links. PCR has high negative predictive value (80–100%) when compared with culture results [36]. False-positive readings of *Legionella* samples could lead to unnecessary and expensive emergency decontamination procedures. The PCR results must be interpreted with caution, as the risk of infection may be overestimated. Culture remains the reference standard for detection of *Legionella* in environmental samples. One important advantage is its ability to make epidemiologic links to *Legionella* isolated from patients.

Biofilms

Legionella, like many bacterial species, live in water systems in suspension (planktonic phase) and at the water–surface interface (sessile phase). Biofilms form at the surface and are characterized as close associations of microbes within an organic matrix [37•]. Complex and symbiotic relationships have evolved between *Legionella* and other bacteria and protozoa [38]. These relationships provide *Legionella* with essential nutrients and survival strategies such as intracellular replication and sequestration in amoebae.

The extensive network of pipe surfaces of hospital water distribution systems (particularly hot water recirculating systems) provides ideal conditions for *Legionella* replication [39,40••]. Other sources include decorative fountains, bronchoscopes and ice machines. The presence of *Legionella* in a high proportion (>30%) of outlets has been shown to be predictive of disease [41], whereas quantitative measurements of CFU/ml were shown to be worthless. Quantitation does not correlate with risk due to fluctuations in the recovery of *Legionella* from outlets. Significant differences in *Legionella* concentration were demonstrated with daily sampling from 21 outlets in a hospital water system [42]. The numerical risk threshold used by some regulatory agencies was exceeded on some days but not others, prompting the authors to conclude that the fluctuations invalidated its use in decision making.

Disturbances in water pressure or inadequate levels of chemical biocides create conditions that disrupt biofilms or allow *Legionella* and other waterborne pathogens to multiply. Although often cited as a significant contributor to amplification of *Legionella*, stagnation has not been shown experimentally or in the field to be a major factor in *Legionella* multiplication in water systems [40••,43,44]. There is some indication, however, that pipe materials such as PVC and cross-linked polyethylene (PEX) can affect *Legionella* growth in water systems [45,46]. The concentration of *Legionella* was three times higher on PEX and stainless steel than on copper [45]. Even the type of fixture has been shown to contribute to *Legionella* positivity. Electronic sensor faucets (nontouch) were more likely to be positive for *Legionella* and *Pseudomonas* than standard faucets. The components of the electronic mixing valves and lower temperatures due to thermostatic mixing were suspected of causing the positivity. One report advises against placing these devices in high-risk patient units [47,48].

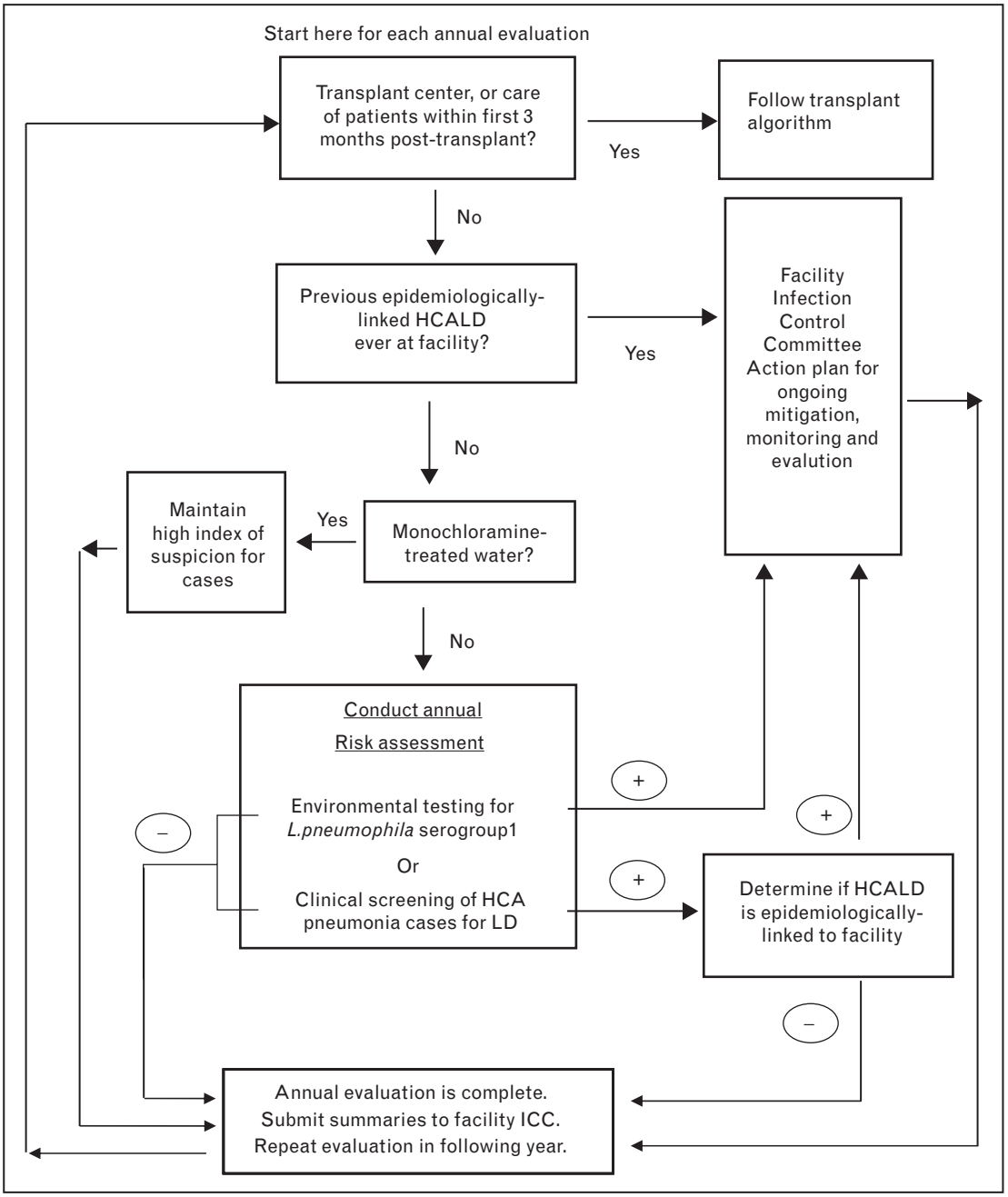
Assessment of risk in healthcare facilities

Surrogate markers for the presence of *Legionella* have been sought and some physiochemical parameters may be predictive. Manganese at more than 6 μg/l was found to be an indicator of *Legionella* contamination, whereas temperatures exceeding 55°C were protective in hot water systems of hospitals and other buildings [49]. Nevertheless, knowledge of *Legionella* positivity in hospital drinking water is the only factor known with certainty to be predictive of risk.

The Allegheny County Health Department, Pittsburgh, Pennsylvania Guidelines assess the extent of *Legionella* contamination of the hospital water system using drinking water cultures as an indicator for the need for *Legionella* preventive measures. This proactive approach differs from that of the U.S. Centers for Disease Control (CDC) by instituting environmental cultures followed by remedial action before the disease strikes. With the exception of hospitals performing transplants, the CDC recommends culturing only after the appearance of one to two cases. Prevention is both life-saving and less expensive in the long run, given the litigation and unfavorable publicity. The proactive approach has now been adopted for all 150 hospitals in the Veterans Healthcare System in the USA (2008). The VA Directive provides an algorithm for performing the risk assessment (Fig. 1) [50]. If more than 30% of outlets tested yield *L. pneumophila* serogroup 1, then an action plan is required for mitigation, monitoring and evaluation.

Risk assessment combined with environmental monitoring has been effective in predicting risk in studies in the USA, Italy, France, Taiwan, Spain and Greece [1•,51–55], and most European countries now mandate routine culturing of the hospital drinking water for *Legionella*. Likewise, U.S. state health departments also mandate such culturing despite lack of support by the CDC. Napoli *et al.* [1•] reported the results of clinical and environmental surveillance for *Legionella* in southeastern Italy from 2000 to 2009. Approximately 60% of private hospitals and 93% of public hospitals were positive for *Legionella* spp. *L. pneumophila* serogroup 1 was the most frequently isolated species. Of the 73 public hospitals, 51% had more than 30% of distal water sites positive for *Legionella* species (C. Napoli, personal communication). The information on hospital drinking water contamination by *Legionella* proved useful for risk assessment

Figure 1 The Veterans Healthcare System Legionella Directive risk assessment algorithm for healthcare-acquired Legionnaires' disease, based on environmental surveillance for Legionnaires' disease



Risk assessment is performed annually and includes testing a minimum of 10 water outlets for *Legionella* and determining percentage of positive outlets. Modified from [50]. HCA, healthcare-associated; HCALD, healthcare-associated Legionnaire's disease.

evaluation. In Taiwan, 63% (10/16) of hospital drinking water systems were positive. Nineteen percent (three of 16) had distal site positivity more than 30% [56].

Disinfection

Copper–silver ionization is the most reliable technology today for disinfection of hospital drinking water [57••,58,59]. Chlorine dioxide has had variable success due to the challenge of maintaining sufficient concentration of chlorine dioxide in hot water systems. Point-of-use disposable filters may be a cost-effective method to control *Legionella* in limited areas (e.g. ICU and transplant units) without the necessity for systematic disinfection; they also can be applied quickly in an emergent situation. Monochloramine disinfection remains under evaluation.

A 10-year experience with hyperchlorination, superheat and flush, chlorine dioxide, monochloramine, installation of electric boilers on the cold water lines and point-of-use filters was reported from an Italian hospital [60•]. Point-of-use filters were the most effective modality and also the most expensive. Chlorine dioxide was the least expensive, but it failed to eradicate *Legionella* from the system. The study was difficult to interpret, as the use of CFU/ml as measure of efficacy is inaccurate.

Given the proliferation of so many commercial firms offering disinfection systems, failures have become commonplace, with patients contracting Legionnaires' disease despite installation of an expensive disinfection system. One consistent finding was observed with all of these failures: the purchase of the disinfection system was made by the engineers from the facilities management team with minimal input from the infection control department. Thus, we strongly recommend that the infection control practitioners, not healthcare facilities personnel, select the disinfection method and the vendor. Infection control practitioners would use evidence-based medicine as criteria for selection. Service and maintenance are necessary for long-term efficacy. Routine environmental cultures performed simultaneously with disinfection concentrations should be performed at regular intervals for the lifespan of the system.

Conclusion

The incidence of Legionnaires' disease appears to be increasing, both community-acquired and hospital-acquired [61,62]. More hospitals are facing the dilemma of hospital-acquired legionellosis as they discover that the drinking water is the source. Prevention is feasible using proactive environmental culturing and disinfection of hospital drinking water.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 399).

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