Hospital-acquired legionellosis: solutions for a preventable infection

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Hospital-acquired Legionnaires' disease has been reported from many hospitals since the first outbreak in 1976. Although cooling towers were linked to the cases of Legionnaires' disease in the years after its discovery, potable water has been the environmental source for almost all reported hospital outbreaks. Microaspiration is the major mode of transmission in hospital-acquired Legionnaires' disease; showering is not a mode of transmission. Since the clinical manifestations are non-specific, and specialised laboratory testing is required, hospital-acquired legionellosis is easily underdiagnosed. Discovery of a single case of hospital-acquired Legionnaires' disease is an important sentinel of additional undiscovered cases. Routine environmental culture of the hospital water supply for legionella has proven to be an important strategy in prevention. Documentation of legionella colonisation in the water supply would increase physician index of suspicion for Legionnaires' disease and the necessity for in-house legionella test methods would be obvious. Legionella is a common commensal of large-building water supplies. Preventive maintenance is commonly recommended; unfortunately, this measure is ineffective in minimising legionella colonisation of building water supplies. Copper-silver ionisation systems have emerged as the most successful long-term disinfection method for hospital water disinfection systems. There is a need for public-health agencies to educate the public and media that discovery of cases identifies those hospitals as providers of superior care, and that such hospitals are not negligent.

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History of hospital-acquired Legionnaires' disease

Legionnaires' disease has been recognised as an important cause of hospital-acquired pneumonia.[1–7] The first reported outbreak of hospital-acquired Legionnaires' disease was in a psychiatric hospital in Washington DC in 1965, in which 81 patients contracted pneumonia, with 15 deaths. Retrospective studies on stored serum samples showed antibody seroconversion for *Legionella pneumophila* in 85% of the patients.[8] The largest outbreak of hospital-acquired Legionnaires' disease occurred at the Wadsworth Veterans' Administration Medical Center (VAMC) in Los Angeles, with at least 218 confirmed cases from 1977 to 1982.[9] Since then, more than 300 reports of hospital-acquired Legionnaires' disease have appeared in peer-reviewed literature and public-health reports.

Mode of transmission

Cooling towers were originally thought to be the main source of legionella after the US Centers for Disease Control (CDC) investigators isolated legionella from a cooling tower near a hospital with cases of Legionnaires' disease.[10] Tracer studies showed that aerosols from the tower could have reached air intake supplying patient rooms. However, the epidemiological investigation showed that cases occurred in hospital wings that had no contact with the air intakes. The hospital water was not sampled for legionella because this outbreak predated the discovery that legionella could colonise water distribution systems.

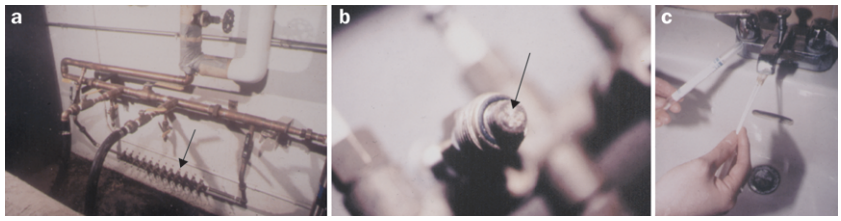

Figure 1. A biofilm sampling device in the hot water recirculating line of a colonised building. (a) Each plug within the row of plugs can be removed for sampling (arrow). (b) Surface portion of one plug that was exposed to flowing water showing a thin layer of biofilm (arrow). Legionella was isolated from within the biofilm at 10^4–10^5 cfu/0·5 cm^2 within 1–2 months from this hospital. (c) The biofilm can be sampled by inserting a swab into the outlet and rotating upwards 3–4 times.

From 1982 to 1985, the pivotal discovery was made that the potable water supply was the actual source of hospital-acquired Legionnaires' disease (figure 1).[11–13] Since this discovery, reported cases of hospital-acquired Legionnaires' disease linked to cooling towers have all but disappeared. It is noteworthy that of hundreds of hospital-acquired outbreaks since 1985 virtually all have been linked to potable water. In only one report since 1985 has a hospital outbreak been linked to a cooling tower,[14] and follow-up needs to be done for this hospital.

In three well-publicised outbreaks at Wadsworth VAMC,[9] Burlington Hospital of Vermont,[15] and Rhode

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Island Hospital,[16] an epidemiological link to the cooling towers was reported. It is not well known that cases of Legionnaires' disease subsequently reappeared in all three hospitals despite disinfection of the cooling towers. Copper-silver ionisation systems were subsequently installed on the water distribution systems at both Wadsworth VAMC and Burlington Hospital. At Rhode Island Hospital, molecular subtyping confirmed that *L pneumophila* in the cooling tower was identical to the *L pneumophila* isolated from cases of hospital-acquired Legionnaires' disease; however, the hospital water was also colonised with legionella of the same subtype as was found in the cooling tower. An outbreak recurred within 1 year, despite disinfection of the cooling towers, and was terminated when the cooling towers were again disinfected,[17] but potable water was also withheld from high-risk patients. Years later, Mermel et al[18] confirmed that cases of hospital-acquired Legionnaires' disease persisted at Rhode Island Hospital despite the fact that legionella could not be isolated from the cooling tower. Molecular subtyping of the clinical and environmental isolates confirmed the hospital water supply as the source.

Aspiration is now known to be the major mode of transmission for hospital-acquired Legionnaires' disease.[2,19–24] Colonisation of the oropharynx by legionella was suggested by one study,[25] but not by another.[26] In a prospective study of patients with head and neck cancer undergoing tumour resection with its postoperative sequelae of aspiration, 30% of postoperative pneumonias were due to *L pneumophila*.[13]

Showering is often thought, erroneously, to be a mode of transmission. We reported a link to showering in a retrospective survey of three hospitals;[27] however, results of subsequent unpublished case-control studies at the three hospitals did not show a link to showering. Similarly, neither further retrospective studies[28,29] nor more rigorous prospective studies designed to assess the role of showering confirmed this association with showering.[2,30] Some of the latter type of study even showed that showering might be protective for Legionnaires' disease.[22,31] The presumed reason for this paradoxical finding is that patients who are able to take showers are ambulatory and less likely to aspirate. As a result, our transplant centre allows patients to shower, and we recommend that the practice of prohibiting showering for fear of acquisition of legionella should be abandoned.

Legionella has been linked to aerosol-generating devices within hospitals that used tap water,[32–34] but the degree of aerosolisation was intense in each of these reports. For example, use of jet nebulisers using contaminated water delivered directly to the patients' airways was a significant risk factor for acquisition of Legionnaires' disease within the University of Chicago Hospital.[35] Nasogastric tubes[21,22,36] and intubation[2,37] have been linked to hospital-acquired legionellosis in several studies; the authors presumed microaspiration of contaminated water was the means of entry.

Underdiagnosis of hospital-acquired Legionnaires' disease

Underdiagnosis of Legionnaires' disease is a major bias in computing its incidence. Accurate diagnosis requires legionella laboratory testing since the clinical manifestations are non-specific. In the USA only 19% of 253 hospitals participating in the CDC National Nosocomial Infections Surveillance System routinely did legionella laboratory testing of patients at high risk for developing hospital-acquired Legionnaires' disease.[38] Moreover, only 21% of the hospitals that had experienced cases of hospital-acquired Legionnaires' disease applied routine legionella testing for respiratory tract specimens in patients with pneumonia. Only 25% of hospitals in Catalonia applied legionella culture for cases of hospital-acquired pneumonia, and only 10% used the legionella urinary antigen test.[39] In the same survey only a single hospital systematically applied legionella testing for all cases of hospital-acquired pneumonia as part of an active surveillance programme.

In the outbreaks reported in the 1980s, the terms "sporadic", "endemic", and "hyperendemic", rather than the term "outbreak", were used to characterise the number of Legionnaires' disease cases occurring in a hospital. Since the discovery that drinking water could be the source, it is now recognised that many cases of hospital-acquired Legionnaires' disease can go undiagnosed,[2,40,41] and that the above terms are a better indication of the intensity of clinical surveillance than an accurate depiction of actual incidence. Discovery of "even a single case of hospital-acquired Legionnaires' disease may be an important sentinel indicating the likelihood of additional (undiscovered) transmission".[40] In a continuing series of outbreaks, hospital-acquired Legionnaires' disease is now being discovered in paediatric hospitals.[42–50] All outbreaks were linked to hospital water contamination.

Risk factors for hospital-acquired Legionnaires' disease

Underlying disease is a major risk factor for acquisition of disease. Since the major mode of transmission is aspiration, patients with chronic lung disease or those who undergo surgery requiring general anaesthesia are at greater risk. The single most important factor is receipt of an organ transplant with heart transplants having the highest incidence,[51–53] and bone marrow transplants having the lowest incidence.[54] The non-legionella species, especially *Legionella micdadei*, are often implicated in bone-transplant recipients.[55–57] Corticosteroid administration is an independent risk factor (figure 2).[2,40,58] AIDS patients do not seem to be at increased risk for hospital-acquired Legionnaires' disease.[59–61]

Clinical manifestations

Clinical manifestations of legionella pneumonia are non-specific,[62–65] although diarrhoea, neurological symptoms—especially confusion—a fever greater than 39°C, hyponatraemia, hepatic dysfunction, and haematuria have been prominent in several comparative studies.[66,67] Community-acquired Legionnaires' disease seems to have more severe clinical manifestations compared with hospital-acquired Legionnaires' disease, probably because of delay of diagnosis in the community setting with concomitant delay in appropriate antibiotic therapy.

Neurological and gastrointestinal symptoms were significantly more frequent in community-acquired than hospital-acquired Legionnaires' disease.[66]

In the earlier reports of hospital-acquired legionellosis, mortality rates were as high as 80%, usually in immunosuppressed patients who did not receive appropriate antibiotics.[68] However, mortality in the USA has decreased from 46% in 1982 to 14% in 1998 with increased awareness and increasing empirical use of quinolones for hospital-acquired pneumonia.[69] Virulence of the strain,[70,71] delay in antibiotic therapy,[72,73] and degree of immunosuppression were the risk factors associated with mortality.[69,74]

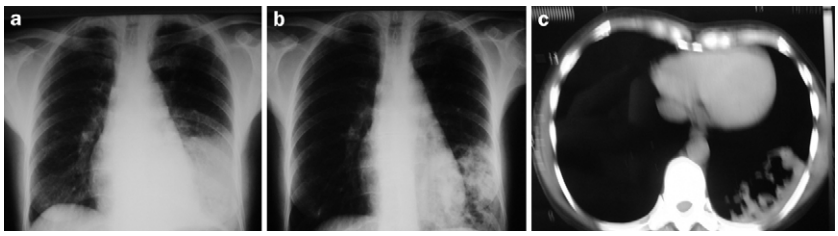

Figure 2. A 5-year-old girl taking prednisone 7·5 mg a day for rheumatoid arthritis was admitted after 36 hours of respiratory tract symptoms (a). (b) Chest radiograph taken 6 days after admission. Legionella pneumophila *serogroup 1 was isolated from sputum. (c) Chest CT scan taken 8 days later showing cavitation.*

Laboratory diagnosis of Legionnaires' disease.

Definitive diagnosis of Legionnaires' disease is established through culture of the microorganism. However, legionella does not grow in the standard bacteriological media used in most hospitals, and specialised selective media are needed. Unfortunately, in most hospitals, such media are not routinely used for patients with pneumonia.[38] For optimum culture of legionella in respiratory tract specimens, multiple media are required, including BCYE-alpha supplemented with antimicrobial agents.[75,76] The addition of dyes facilitates the visualisation of the colonies, and pretreatment with acid or heat prevents overgrowth of competing bacterial microflora.[77,78] The sensitivity of culture with multiple media and pretreatment is 80% and specificity is presumed to be 100%. Culture of respiratory specimens should be routinely available in all hospitals with water supplies colonised by legionella. The isolation of legionella also allows microbiological classification and subtyping by DNA studies to establish epidemiological links to water sources. Detection by urinary antigen has become the most widely used test for diagnosis of Legionnaires' disease.[79,80] The urinary antigen appears early in the course of the disease and usually disappears within 2 months, although its excretion may be longer in patients receiving immunosuppressive treatment or corticosteroids.[81] Concentration of the urine specimen increases the sensitivity of the test.[82] The major limitation of urinary antigen test is that it only detects the soluble antigen of *L pneumophila* serogroup 1. Although serogroup 1 causes 92% of the cases of Legionnaires' disease in the community,[83] the incidence drops to 80% in the hospital setting. Crossreactivity does exist for other serogroups of *L pneumophila*. The sensitivity and specificity of commercial kits for *L pneumophila* serogroup 1 are about 70% and 99%, respectively (Binax, Portland, USA; Biotest AG, Dreieich, Germany; and Bartels, Washington, USA). A rapid immunochromatographic assay (Binax Now Legionella Urinary Antigen, Portland, USA) is now commercially available.[79] The sensitivity and specificity of this test are similar to those obtained with ELISA,[84] but it is more rapid than the ELISA test (15 minutes *vs* 2–3 hours) making it especially useful for small laboratories.

Direct immunofluorescence (DFA) is a rapid diagnostic method, which allows visualisation of the microorganism in the specimen. Large numbers of legionella must be present before they can be readily visualised.[75] Seroconversion is defined as an increase in antibody titres to legionella of greater than or equal to fourfold. Maximum sensitivity of both IgG and IgM antibody seroconversion occurs at 90 days, so convalescent serum samples drawn at 4–6 weeks may give insignificant titres.[85] Serological tests are useful for epidemiological studies but have limited utility in clinical practice. The specificity of serological tests from reference laboratories is high (96%) but is uncertain for laboratories not experienced in legionella testing.

Molecular subtyping has proved useful in delineating the source of Legionnaires' disease. Techniques include monoclonal antibody typing, plasmid analysis, outer-membrane protein profiling, SfiI-macrorestriction analysis, amplified fragment length polymorphism, and arbitrarily primed PCR.[86] However, results must be interpreted in concert with the epidemiological data.[87,88]

Routine environmental culture for legionella in hospitals

The routine use of environmental cultures has emerged as an effective strategy for prevention of hospital-acquired Legionnaires' disease. If legionella colonisation of the water supply is recorded, physician index of suspicion for Legionnaires' disease as a cause of hospital-acquired pneumonia would increase, and the necessity for in-house laboratory methods, especially culture of sputum, would be obvious. Unfortunately, fear of negative media publicity and litigation has been a major obstacle to adopting this approach despite its proven value.

The CDC recommends environmental cultures only in the event of discovery of cases of hospital-acquired Legionnaires'disease.[89] Many European countries have adopted this approach—namely England, Wales,[90] Italy,[91] Switzerland,[92] and Spain[93]. Bureaucratic concerns and not scientific data motivate this passive approach. Several studies have documented that, when the water supply is known to be colonised with legionella, hospital-acquired legionellosis can be uncovered if clinical surveillance for legionella with laboratory testing is initiated for all patients with hospital-acquired pneumonia.[13,39,41,56,94–97] QUOTE "" As

a result, guidelines mandating routine environmental cultures in hospitals have been implemented in Allegheny County[98] and Maryland in the USA,[99] Catalonia, Spain,[100] France,[101] and Denmark.[102]

Antibiotic therapy

The newer macrolides and quinolones are now the antibiotics of choice. Erythromycin is no longer favoured given the fluid volume necessary for intravenous infusion and the relatively high incidence of gastrointestinal side-effects. Fluoroquinolones and azithromycin have the greatest activity against *Legionella* spp in intracellular and animal models.[103,104] Recurrences have been recorded in patients treated with erythromycin. Moreover, time to apyrexia was longer and clinical complications more frequent in patients with Legionnaires' disease treated with erthromycin than in those treated with fluorquinolones in an observational study.[105]

Control of legionella in the hospital water supply

Appropriate maintenance of water distribution systems is often recommended as a critical factor in the control of legionella growth. In reality, such practice has little role in legionella colonisation.[106] The only intervention that is marginally useful in keeping legionella colonisation to a minimum is maintaining hot-water tank temperatures at 50–60°C in the hot-water distribution system. It should be cautioned that even this manoeuvre will have little effect unless a system-wide disinfection process has been done before increasing hot water temperatures.

Emergency measures that can be used during an outbreak include superheat and flush in combination with shock hyperchlorination.[107] The disadvantages are that the process is labour-intensive, and the effects are only short-term (recolonisation will occur in weeks to months).[108] Continuous hyperchlorination is not favoured because of high expense, marginal efficacy, corrosion of piping, and release of carcinogenic byproducts into the drinking water.[107] Copper-silver ionisation systems have been widely implemented in Spain and the USA, and there have been more than 200 installations world-wide. The first 16 installations in the USA have experienced sustained success at 5–11 year follow-up.[109] Other promising methods undergoing assessment include chlorine dioxide and monochloramine, but interpretable results may not be available for several years.

Search strategy and selection criteria

We closely monitored peer-reviewed publications, abstracts of scientific meetings, public-health reports, and lay media communications on hospital-acquired Legionnaires' disease. Medline searches of material since 1996, in all languages, were done bi-monthly using the keywords, "legionellosis", "legionella" etc. This review focused on issues pertinent to decision-making in preventive solutions for hospital-acquired Legionnaires' disease. Thus, articles presenting data on this issue were highly selected. Moreover, general review articles and editorials that provided several references were favoured above older original studies.

Political issues

Legionnaires' disease is a high-profile disease in which political implications can overshadow scientific data. An outbreak of hospital-acquired Legionnaires' disease can precipitate a wave of negative publicity for the hospital concerned, with loss of patients and malpractice suits. The public is not aware that legionella is a common inhabitant of man-made water distribution systems. The incorrect assumption by the media is that legionella is a contaminant of a poorly maintained water system. In a recent European example, the Hôpital Européen Georges Pompidou in Paris experienced 12 cases of hospital-acquired Legionnaires' disease over an 8-month period and was castigated by the lay media.[110] We believe that Hôpital Pompidou was unfairly singled out for blame. A hospital that has a knowledgeable physician staff and in which legionella laboratory testing is available is a hospital that provides superior care. Such hospitals, and their physicians, should be congratulated rather than maligned. In other hospitals, cases of legionellosis go undiagnosed and mortality from hospital-acquired Legionnaires' disease is incorrectly attributed to other causes. Public-health agencies must play an active part in defending hospitals that discover Legionnaires' disease. Fear of media exposure and litigation will prevent enactment of the most effective preventive measure for hospital-acquired Legionnaires' disease—namely, culturing the hospital water supply, identifying the source, and instituting preventive measures.

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