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Title:	International journal of hygiene and environmental health
Title Abbrev:	Int J Hyg Environ Health
Citation:	2008 Jul;211(3-4):229-34. Epub 2008 Apr 11
Article:	Cooling towers and legionellosis: a conundrum with
Author:	Yu V
NLM Unique ID:	100898843 Verify: PubMed
PubMed UI:	18406666
ISSN:	1438-4639 (Print) 1618-131X (Electronic)
Fill from:	**Any format**
Publisher:	Urban & Fischer, Jena, Germany :
Copyright:	Copyright Compliance Guidelines
Authorization:	JAR
Need By:	N/A
Maximum Cost:	**Free**
Patron Name:	Wagener, Marilyn
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Int. J. Hyg. Environ. Health 211 (2008) 229–234
International Journal of Hygiene and Environmental Health
www.elsevier.de/ijheh

EDITORIAL

Cooling towers and legionellosis: A conundrum with proposed solutions

Introduction

Community outbreaks of Legionnaires' disease attributed to cooling towers have commanded an impressive amount of resources and concern. A number of countries have mandated that surveillance cooling towers for Legionella colonization be enacted. The high costs of investigating a Legionella outbreak linked to cooling towers have been documented (Lock et al., 2007).

In this issue of the International Journal of Hygiene and Environmental Health, Engelhart et al. describe a case of hospital-acquired Legionnaires' disease attributed to a cooling tower (Engelhart et al., 2008). The authors suggest that cooling tower aerosols were favored by meteorological conditions with thermal-inversion. Their study is important and a number of strengths should be acknowledged. Molecular subtyping was available for both Legionella isolates from the patient and the cooling tower underscoring the epidemiological importance of isolation of Legionella from patient specimens. The culture methodologies and molecular methodologies were state-of-the-art. Despite genetic variability, in limited geographical areas, the same molecular subtype may be seen over a wide geographic area limiting its discriminative ability (Lawrence et al., 1999; Drenning et al., 2001). This investigation used both sequence-based typing and monoclonal antibody typing. Engelhart et al. (2008) correctly noted that the infectious dose and environmental concentrations of Legionella necessary for spread of disease remain elusive despite numerous investigations.

The current approach to Legionella in cooling towers remains haphazard with nonstandard approaches in culturing, arbitrary interpretations of infectious dose, inconsistent approaches in disinfection, and unsatisfactory endpoints for measuring success of preventive measures given the variation of counts over time (Ragull et al., 2007; Bentham and Broadbent, 1993). Engelhart et al. (2008) discussed the problems of both the variability of the quantitation of Legionella and the non-evidence-based use of heterotrophic plate counts as a marker for Legionella colonization. They suggested that more frequent culturing of a cooling tower water might lend stability to the data with improvement in interpretation.

Hospital-acquired legionellosis

In contrast to the uncertainties and the conflicting data with respect to cooling towers, it is relevant to assess the status of Legionella prevention with respect to water distribution systems. The scientific method has been more successful for prevention of legionellosis contracted from drinking water systems than for cooling towers. The key issue of infectious dose in water distribution systems in hospitals has been elucidated and validated. Quantitation of numbers of Legionella (cfu/ml) from water sites has not proven predictive; however, the degree of colonization as measured by percent distal site positivity for Legionella correlates directly with risk for infection (Kool et al., 1999; Sabrià et al., 2004; Boccia et al., 2006; Stout et al., 2007). Reliability and reproducibility of various disinfection technologies and measures have been devised and tested. This has led to consistency and predictability of risk when key parameters are known. Formulation of rational guidelines can then be assessed and ultimately be evidence-based. Consensus has been reached on some management issues and the process of monitoring and application of disinfection technology is orderly.

Background for cooling towers

The source of Legionnaires' disease is not as clear as one might expect. The cooling tower theory originated from the first-described hospital outbreak in Memphis, Tennessee in which cooling towers were implicated as the source by CDC investigators (Dondero et al., 1980). It followed that aerosolization was the presumed mode of transmission.

Meterologic data similar to the Engelhart study suggested air currents from the cooling tower could

1438-4639/$ - see front matter
doi:10.1016/j.ijheh.2008.02.003

enter the vents of the hospital. Numerous limitations beyond the scope of this commentary were conceded by the CDC investigators themselves in this seminal article; however, one key point should be noted: the hospital drinking water was not cultured.

Subsequent to the discovery that Legionella could be in the drinking water (Stout et al., 1982; Best et al., 1983), the epidemiology of Legionnares' disease has taken and interesting if not curious and controversial course. Although outbreaks of Legionnaires' disease continue to occur in hospitals, virtually all of them have been linked to water distribution systems after 1985. Prior to this time, outbreaks were consistently linked to cooling towers. In the current era, cooling tower sources have generally been confined to community-acquired outbreaks, in contrast to water distribution systems which have been consistently linked to hospital as well as community-acquired outbreaks (Bhopal, 1995; Joseph et al., 2004). (A similar occurrence has occurred for hotels. In the early years of EWGLI surveillance, outbreaks from hotels were linked to cooling towers; over time, once drinking water sources were also cultured in hotel outbreaks, cooling towers were rarely implicated.) So, this report by Engelhart is of notable interest since the investigators concluded the cooling tower was the source for a hospital-acquired case.

Overview of pathogenesis of pneumonia

In order to appreciate the reasoning behind this commentary, a review of the pathogenesis of pneumonia is summarized. Pneumonia is an infection of the lung and Legionnaires' disease is one form of bacterial pneumonia. Pneumonia can be contracted from an exogenous source. For example, Legionnaires' disease is contracted from water colonized by Legionella. *Mycobacterium tuberculosis* and influenza viruses are spread by aerosolized droplets from infected individuals. On the other hand, pneumonia is more commonly contracted from an endogenous source, i.e. from microbes that are part of the normal human flora in the mouth. For example, pneumococcal pneumonia and *Haemophilus influenzae* pneumonia, the two-most common causes of community-acquired pneumonia, infection is initiated with colonization of the oropharynx. The mechanism of infection for an endogenous source is aspiration of the colonizing microflora into the lung, or in the case of Legionnaires' disease, aspiration of water containing Legionella.

The major risk factor in community-acquired pneumonia associated with aspiration is cigarette smoking while the major risk factor for nosocomial or hospital-acquired pneumonia is also aspiration. Hospital procedures involving oropharynx manipulation (gastric tubes) or respiratory tract manipulation (endotracheal tubes for anesthesia and surgery) are the precipitating causes. The major underlying disease associated with aspiration is chronic obstructive pulmonary disease (COPD) in which the protective function of the respiratory tract is compromised.

Epidemic presentation is the hallmark of respiratory pathogens that are aerosolized, i.e. very large numbers of infected patients are seen over a short period of time since all exposed individuals are at risk rather than selected compromised individuals prone to aspiration. Microbes that are spread by aerosolization include *Mycobacterium tuberculosis*, pneumonic plague (*Yersinia pestis*), *Coccidioides immitis*, respiratory tract viruses, etc.; these are highly contagious pneumonias and lead to epidemics. So, the scenario in many reports is that Legionella from a cooling tower that is located many kilometers away from the hospital, reaches the hospital by air currents, infects a few select patients yet spares virtually all of the other hospitalized patients and the intervening community populace. I find this scenario to be not credible from a pathogenic perspective. On the other hand, microbes (e.g. *Streptococcus pneumoniae* and *Klebsiella pneumoniae*) that cause pneumonia via the mechanism of aspiration have low attack rates since predilection for contracting pneumonia is dependent on host susceptibility. The fact that most of these patients in reports of cooling tower outbreaks have risk factors for aspiration especially cigarette smoking is an important clue to the real source.

Critical review of recent cooling tower outbreaks

Given the pathogenesis of pneumonia, it is worthwhile to review the details of reports in which cooling towers are the presumed source of hospital-acquired Legionnaires' disease. Medline lists 11 other publications dealing with cooling towers and legionellosis published in the past 4 years (García-Fulgueiras et al., 2003; Phares et al., 2007; Sabria et al., 2006; Nguyen et al., 2006; Rota et al., 2005; Hugosson et al., 2007; Isozumi et al., 2005; Greig et al., 2004; Gilmour et al., 2007; Sala et al., 2007; Kirrage et al., 2007). The number of confirmed cases of Legionnaires' disease in these 11 reports ranged from 2 to greater than 600.

With respect to epidemic presentation, three investigations involved large numbers of patients in short periods of time: Greig et al. (2004) (125 cases in 3 weeks), Sabria et al. (2006) (113 cases in 3 weeks) and García-Fulgueiras et al. (2003) (449–600 cases in 4 weeks). Of the studies in which smoking history was taken, all except one (García-Fulgueiras et al., 2003) found smoking to be a risk factor associated with Legionnaires' disease – the classic risk factor of aspiration. It is interesting that the patient so well-described by Engelhart et al. (2008) possessed the most common risk factors for aspiration; cigarette smoking and postoperative pneumonia. Postoperative pneumonia has been directly linked to Legionnaires' disease (Yu et al., 1982; Lowry et al., 1991).

Molecular subtyping with match between cooling tower isolate and patient isolate was found in 8 of 11 studies: clinical isolates were not available in three studies. The maximum distance from an infected patient to the putative cooling tower was 7 km (Nguyen et al., 2006). While Engelhart et al. used rigorous methodology with respect to discriminative ability for cooling tower isolates, it must be noted that molecular subtypes of Legionella within a cooling tower may be identical to that of a nearby hospital (Garbe et al., 1985).

Drinking water was sampled in six studies, but notably less intensely when compared to cooling tower sampling. In one study of cooling tower dissemination, 7% of cooling towers and 9% of patient homes yielded Legionella (Nguyen et al., 2006). In five studies, drinking water was not even considered as a possible source. This is a detection bias favoring implicating cooling towers as a source. It should be noted that Engelhart et al. cultured the drinking water of the hospital, but the cultures were negative.

Exposure history to cooling towers and/or time spent outdoors was sought in 9 of 11 studies. In contrast, history of drinking water and exposure to drinking water sources was only done in one study (Sabria et al., 2006), and a case-control analysis was not performed. It is now known that the drinking water of residences and workplace can be the source of Legionella infection. Before cooling towers can be definitively identified as the true source in either community- or hospital-acquired outbreaks of Legionnaires disease, it would be prudent to check sources of water to which the patient was recently exposed especially those of large buildings in which patients may have drunk water (restaurants, hotels, etc.).

Each of the 11 reports supported the cooling tower hypothesis by noting cases had disappeared following disinfection of the cooling tower. When disinfection is directed at the putative source, in this case cooling towers, disappearance of the disease may be mistakenly attributed to the disinfection procedure. Farr's Law states that in the natural course of epidemics, the incidence of cases tends to rise and then fall in the shape of a normal curve. Any intervention during the peak may mistakenly appear to be effective when the natural course is abatement of cases. So, caution must be exercised when attributing causation by a cooling tower when an epidemic of legionellosis subsides following disinfection of a cooling tower; this may only represent the natural course of an outbreak independent of the disinfection process. Thus, data from reports of cooling towers as sources can lead to pitfalls for investigators. Many of the reported cooling tower outbreaks in the literature probably emanated from the drinking water. To underscore this point, Engelhart et al. (2008), cited a number of studies as typical examples of legionella outbreaks in which the cooling tower was the putative source. And, some of them are now known to be hospital-acquired outbreaks (Muder et al., 1986). Investigators should now be aware that difficulty in having results replicated by different studies on infectious dose may well result from the fact that the cooling tower was not the actual source in some of the reports.

Disinfection of cooling towers

Uncertainties exist not only as to whether or not cooling towers are a major source, but also whether disinfection measures and maintenance of the cooling towers are effective. As Engelhart et al. point out, cleaning and disinfection of cooling towers is not an exact science and many recommended approaches have drawbacks. Nevertheless, virtually all of the investigators of the 11 cited-studies recommended that routine maintenance and microbiologic control measures be enacted. Although conscientious maintenance seems reasonable and many guidelines make such recommendations, no data exists to support the claim that maintenance minimizes colonization by Legionella, and that control measures are useful in preventing outbreaks of Legionnaires' disease from cooling towers. Keep in mind routine maintenance measures have also been recommended for hospital water despite the fact that several studies explicitly addressing the value of maintenance found that it had no impact on legionella colonization (Vickers et al., 1987; Liu et al., 1993).

Recommendations

I suggest a more rigorous approach be considered when cooling towers have been identified as a possible source. Adherence to these suggestions might resolve the uncertainties discussed and promote more effective epidemiologic surveillance.

Investigators must recognize that numerous sources of legionellosis exist and, before one source can be implicated as the source, rigor would demand that the other sources be considered as well. Specifically, in community outbreaks of Legionnaires' disease, drinking water sources should be considered and cultures of the homes and workplaces to which the patients were more intensely exposed should be performed. Large buildings are more likely to harbor Legionella because of temperature stratification (Flannery et al., 2006), so such buildings frequented by patients might be targeted for culture.

In the Engelhart et al. (2008) study, culture of hospital water was performed but such cultures have not been performed in most outbreaks of Legionnaires' disease attributed to cooling towers. To minimize bias, cultures of the water distribution system should be performed as frequently as cultures for cooling towers. A perfunctory approach with a few cultures for drinking water sources may overlook the true source. It is understandable that a cooling tower source may be implicated more often than the drinking water sources simply because of detection bias. Moreover in the community, homes, workplaces and other sites may logistically be more difficult to culture the water supply as opposed to focusing on one large accessible unit such as a cooling tower. Regardless, if one wants to identify the true source, cultures of other sources must be done.

Case-control studies of exposure investigation should focus not only on cooling towers and aerosols, but also on drinking water sources and degree of consumption. In the original 1976 American Legion outbreak in a Philadelphia hotel, it is not well-known that the only significant exposure finding by CDC investigators in a case-control study was that cases of Legionnaires' disease drank more water and consumed more ice than controls (Fraser et al., 1977)! This important finding was overlooked since culture methods for isolating Legionella from drinking water would not be developed until years later.

If a case of Legionnaires' disease is diagnosed, the index of suspicion may be raised with physicians ordering Legionella tests and a resultant increase in numbers of cases. What has occurred may not be a cluster of cases from an outbreak, but merely the discovery of endemic legionellosis.

Before attributing an outbreak to cooling towers because cases have declined following disinfection of cooling towers, it must be realized that Farr's law of epidemics may apply. So, surveillance must be conducted for years (not months) to document efficacy. Legionella is the fourth most common cause of community-acquired pneumonia admitted for hospitalization, but few cases are diagnosed because specialized Legionella tests are not used (Vergis and Yu, 1999; Fang et al., 1990; Marston et al., 1997). Investigators need to report long term (years) data on cooling tower counts and long-term surveillance for cases to assess the efficacy of the numerous approaches that they used and proposed. Engelhart et al. used a closed-circuit cooling tower and claimed success. In the CDC report cited by Engelhart (Garbe et al., 1985), the CDC investigators reported that hospital-acquired legionellosis disappeared 10 months after disinfection of the cooling tower. However, it was later revealed that cases recurred at 12 months and terminated when hospital drinking water was withheld from high-risk patients. Years later, a second outbreak of hospital-acquired Legionnaires' disease at this hospital was epidemiologically linked to the drinking water (Mermel et al., 1995).

In summary, Engelhart et al. (2008) concluded that prospective epidemiological studies are needed to better define the attributable risk for contracting legionellosis from cooling towers so as to develop rational and cost-effective guidelines for prevention. Reports of community-acquired Legionnaires' disease attributed to cooling towers should be carefully scrutinized to ensure that other likely sources are also cultured with the same frequency that cooling tower water is cultured. Rigorous evaluation with standardized microbiologic data may allow the formulation of a reproducible database. Over time, evidence-based recommendations will prevail given the fact that proposed recommendations can be evaluated scientifically. Hopefully, recommendations made in this commentary may pave the way to resolving the conundrums that Engelhart et al. (2008) have noted.

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