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Review Article

Mode of Transmission of *Legionella pneumophila*

A Critical Review

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Since the discovery of *Legionella pneumophila* as the cause of an outbreak of pneumonic illness at the American Legion Convention in Philadelphia in 1976,[1,2] it has become apparent that Legionnaires' disease is a relatively common form of pneumonia in both the community and nosocomial setting.[3,4] Despite admirable success in defining the illness and isolating the causative microorganism, investigators from the Centers for Disease Control (CDC), Atlanta, were not able to definitely identify the mode of transmission in the 1976 Philadelphia outbreak. Although the ensuing years have witnessed considerable advances in microbiologic technique as well as the accumulation of a substantial body of data regarding the microbial ecology and epidemiology of the Legionellaceae, the exact mode of transmission has eluded definition. In this article, we will critically examine various theories of transmission of Legionnaires' disease and attempt to place them in perspective in order to define future directions for epidemiologic research. We confine our discussion to disease due to *L pneumophila* since there is insufficient data regarding the transmission of other *Legionella* species.

AEROSOLIZATION AS A MODE OF TRANSMISSION

Airborne transmission of *L pneumophila*, with inhalation of contaminated aerosols as the presumed mechanism of infection, is the prevailing thesis. The evidence that supports this theory is discussed herein.

Pontiac Fever

Pontiac fever is a nonpneumonic form of legionellosis. It is characterized by an acute febrile illness with a high attack rate and short incubation period, averaging approximately 36 hours.[5,6] Pneumonia is not present nor has the organism ever been recovered from patients. Diagnosis is established by demonstration of seroconversion in the context of the characteristic clinical syndrome. Some workers have postulated that the syndrome is the result of a toxic or hypersensitivity reaction to the organism rather than an infection.[7,8]

In the original description of this syndrome in 1968, over 140 persons entering a public building in Pontiac, Mich, were stricken with a febrile "flulike" illness.[5] Tracer smoke studies indicated contamination of the air distribution system with effluent aerosol of an evaporative condenser. No new cases were noted after the air conditioning system was shut down, cleaned, and modified to preclude contamination of the duct system by aerosols. Subsequently, seroconversion to *L pneumophila*, serogroup 1, was demonstrated for 85% of the patients. More importantly, the organism was isolated from the lungs of guinea pigs exposed to air at the site of the outbreak.[7]

Given that Pontiac fever is contracted by aerosolization, it seems only logical to assume that Legionnaires' disease might have a similar, if not an identical, mode of transmission.

Cooling Towers and Evaporative Condensers

The first solid evidence supporting the aerosolization theory for Legionnaires' disease was presented by CDC investigators reporting an outbreak of Legionnaires' disease in Memphis.[9] In 1978, 39 persons in contact with a hospital contracted Legionnaires' disease. Four cases had contact limited to the street outside of the building. The operation of an auxiliary air conditioning tower was temporally associated with the outbreak. Tracer studies demonstrated that aerosols from the tower could have reached air intake supplying patient rooms. *Legionella pneumophila* was isolated from the implicated tower as well as from a tower not implicated in disease transmission.

The authors reported that the attack rate for patients was significantly higher in those rooms supplied by air intakes receiving potentially contaminated aerosols than in the rest of the hospital. However, they were not able to demonstrate a significantly higher attack rate for patients occupying rooms supplied with contaminated air than for patients occupying rooms in the same wing receiving air from other sources. Thus, patient location on the particular wing might have been the major risk factor independent of air source. More importantly, cases occurred in wings of the hospital having no relationship to the implicated tower. Therefore, other reservoirs of the organism cannot be excluded especially since the potable water system was not sampled. Although the authors conducted a retrospective review to locate cases in all areas of the hospital, the methods used in case finding are not reported in detail. For example, the proportion of cases of nosocomial pneumonias in which sera were collected for detection of legionella antibodies was not

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reported. These points are relevant because intensive prospective serologic studies have demonstrated that many cases of legionella infection may be unrecognized.[3,10,11] Thus, the possibility of diagnostic bias cannot be excluded from this report.

In a retrospective analysis of a nosocomial outbreak in Burlington, Vt, Joly and Winn[12] typed clinical and environmental isolates with monoclonal antibody methods. They found that in cases associated with an outbreak the antigenic subtypes of clinical isolates were identical to those of cooling tower isolates whereas, in cases designated as "sporadic," the clinical isolates matched those from the water distribution system. As the authors point out, the analysis was not optimal. Only seven environmental isolates were tested for an epidemiologic analysis that spanned six years, and environmental isolates from the cooling tower and water distribution system were not taken at the same time. Furthermore, a link of cases to the hospital water distribution system was not prospectively studied.

In another study using plasmid analysis of legionella isolates recovered concurrently from a cooling tower, hot water tanks, and patients with legionellosis at a Rochester, NY, hospital, Nolte et al[13] found the patient and hot water isolates to have identical plasmid profiles. The cooling tower isolates were a different profile. Nolte et al concluded that the water distribution system was the source of the infection.

In a well-publicized outbreak at Wadsworth Veterans Administration Medical Center in Los Angeles, it was originally reported that disease was associated with cooling towers or with excavation around the new hospital.[14] Subsequent investigation showed that control of disease was not achieved until the organism was eradicated from the potable water distribution system of the hospital.[15] A link to the cooling tower was initially suggested because decontamination of the cooling tower was followed by a decrease in disease incidence; accumulation of several years of surveillance data uncovered the actual source of infection.

A report by CDC investigators[16] of an outbreak of nosocomial Legionnaires' disease in a Rhode Island hospital illustrates the difficulty in interpreting those studies which have implicated cooling towers as the disseminator of *L pneumophila*. In this outbreak, a cluster of 15 cases of nosocomial legionellosis was identified within a ten-week period. The monoclonal antigenic subtype of the patients matched the subtype isolated from a nearby cooling tower. Following decontamination of the cooling tower, no new cases were identified in a ten-month follow-up period.

Although the authors claimed to have demonstrated a causal role for the cooling tower in the transmission of disease, there are serious concerns about the validity of their conclusion. The absence of nosocomial legionellosis prior to the index cases was surmised on the basis of retrospective chart review, a method that could easily overlook a significant number of cases.[3] Second, the monoclonal antigenic subtype isolated from patients was also recovered from the potable water system as well as from the cooling tower! Third, the major point put forward in support of the cooling tower as a means of transmission was the disappearance of cases after decontamination. There was, however, no documentation of the nature of intensity of continuing surveillance during the follow-up period. For example, in what percent of cases of nosocomial pneumonias, both predecontamination and postdecontamination, were acute and convalescent sera obtained? Fourth, surprisingly, the authors provided no data concerning the status of *L pneumophila* in the potable water system following the end of the apparent outbreak. Finally, given the known cyclical nature of nosocomial legionellosis, the duration of follow-up was disappointingly brief (ten months) and failed to include those months in which the original cluster first occurred.

Airborne transmission from an evaporative condenser or cooling towers has been implicated in a number of studies.[17-20] Although we will not probe these studies in detail, a critical perusal reveals there is insufficient data to assign causation. These studies all suffered from a number of methodological flaws including potential bias in discovering cases and failure to consider the possibility that other environmental sources, especially potable water, might be involved. Although the report of Girod et al[21] suggests that transmission from cooling towers might occur in certain circumstances, it is also well-documented that numerous outbreak-associated cases have occurred while nearby cooling towers were culture-negative.[22-24] The widespread acceptance of cooling towers as an established disseminator for *L pneumophila* appears unwarranted.

Showers

Contaminated showers have been suggested as a vehicle for transmission of *L pneumophila* presumably by the generation of infectious aerosols based on reports of isolation of *L pneumophila* from showers.[25,26] Tobin et al[25] found two cases of Legionnaires' disease in renal transplant patients occupying the same cubicle. (The shower in the cubicle was colonized with the same serogroup of *L pneumophila*.) Cordes et al[26] reported findings from three hospitals in Chicago, Pittsburgh, and Los Angeles, respectively. In all three, *L pneumophila* of the same serogroup as that causing disease in patients was isolated from showerheads. *Legionella pneumophila* was also isolated from showers in two other hospitals without reported cases of disease. No epidemiological link between disease and showering could be found in either report.

In a series of demonstration experiments using air aspirator and culture plate-settling methods, contaminated showers were capable of aerosolizing only minimal amounts of *L pneumophila*.[27-29] On the other hand, Bollin et al[29] noted the aerosol size may be sufficiently small so as to penetrate the lower respiratory tract. Woo et al[27] noted that when showerheads are cultured, stagnant water and sediment constituted the bulk of the cultured sample. Once a shower was in full operation with flowing water, the more contaminated water was rapidly expelled; subsequent water samples taken revealed no *L pneumophila*. Thus, culture methodology would overestimate the amount of *L pneumophila* actually available for aerosolization during showering.

Given the ubiquitousness of *L pneumophila* in water distribution systems, it is obvious that mere isolation of the organism from showers should not necessarily be linked to causation. Increased exposure to showers has never been rigorously demonstrated for cases as opposed to controls,[15,29-32] and, in our experience, many patients acquiring the disease were never exposed to showers.

Humidifiers and Respiratory Therapy Devices

Zuravleff et al[33] demonstrated that a hospital humidifier with water supplied from a contaminated potable water system could cause subclinical infection in guinea pigs, and that *L pneumophila* could be recovered from culture plates exposed to aerosols generated by the device. Woo et al[27] showed that portable humidifiers filled with tap water aerosolized *L pneumophila* throughout a two-patient room. Arnow et al[34] linked inhalation of aerosolized tap water from jet nebulizers and a portable humidifier to nosocomial Legionnaires' disease in five patients.

Other Issues Relevant to Airborne Transmission

One feature of the 1976 Philadelphia outbreak that bears directly on the issue of airborne transmission is the occurrence of "Broad Street pneumonia."[1] Thirty-nine persons contracted a clinical illness fitting the case definition of Legionnaires' disease without having entered the hotel implicated as the source of the outbreak. All, however, had been within one block of the hotel. In only seven of the 39 persons was Legionnaires' disease confirmed by a positive serologic test.

Although these findings have been interpreted to support an airborne route of transmission, an uncritical acceptance of this theory may not be warranted. Could "Broad Street pneumonia" have been acquired through contact with sources of *L pneumophila* other than the outbreak-implicated hotel (for example, another hotel in the area)? Unfortunately, details concerning exposure to other environmental water sources was not provided. It is interesting to note, however, that a retrospective serologic survey of patients acquiring pneumonia in Philadelphia in the summer of 1976 found additional cases of Legionnaires' disease in patients with no exposure to the outbreak-associated hotel, indicating that other potential reservoirs in the area existed.[35] Since environmental surveys for *L pneumophila* were not feasible in 1976, the issue remains unresolved.

Similarly, in the Memphis hospital outbreak discussed previously, four cases of Legionnaires' disease were reported to occur in individuals walking outside the hospital.[9] As in the Philadelphia outbreak, it would seem plausible to postulate an airborne route of transmission. However, one cannot exclude contact with other nearby sources of the organism, especially since *L pneumophila* was recovered from another site three miles away and, thus, was likely to be widespread in the area. Finally, it is possible that persons living or working near the implicated hospital were likely to seek care at that institution when ill, and were more likely to have been correctly diagnosed as having Legionnaires' disease due to heightened awareness of hospital personnel. If other, unrecognized, cases of Legionnaires' disease were occurring elsewhere in the community, sporadic cases may have been erroneously linked to a simultaneously occurring outbreak.

DIRECT INSTILLATION VIA RESPIRATORY DEVICES

A number of respiratory therapy devices have the potential to disseminate pathogenic microorganisms. These devices may deliver gases at high pressures and volumes and may generate rather intensive aerosols; thus, they may be capable of overwhelming or bypassing the normal defense mechanisms of the respiratory tree. As mentioned previously, nosocomial Legionnaires' disease has been linked to the use of jet nebulizers filled with contaminated water.[34]

Health care personnel frequently rinse respiratory apparatus and tubing with tap water. In a series of in vivo experiments, Woo et al[27] demonstrated that this practice could lead to deposition of *L pneumophila* in the lung if the water was contaminated. Two studies provide clinical support for such a mode of transmission. Muder et al[3] found in a prospective study that patients with Legionnaires' disease were significantly more likely than patients with other pneumonias to have undergone endotracheal intubation prior to onset of illness. During the period of study, rinsing of ventilator tubing with tap water was a frequent practice at the hospital, and the potable water was demonstrated to be contaminated with *L pneumophila*. Workers from the CDC showed in a retrospective chart review study at Stanford (Calif) University Hospital that heart transplant patients with Legionnaires' disease had significantly longer intubation times postoperatively.[36]

ASPIRATION AS A MODE OF TRANSMISSION

Development of pneumonia in the human host occurs, via at least two mechanisms, as follows: (1) aerosolization, or (2) aspiration, generally of organisms colonizing the oropharynx. Pneumonias associated with aerosolization, eg, varicella and tuberculosis, typically have a high attack rate. On the other hand, pneumonias occurring in the context of aspiration typically have a low attack rate because acquisition depends primarily on the susceptibility of the individual patient.

We point out that Legionnaires' disease is not a pneumonia with a high attack rate but, instead, a pneumonia with a strikingly low attack rate. Despite the large numbers of people exposed to the organism (for example, via contaminated water supplies), only a small group of individuals acquire the disease while individuals with compromised host defenses, especially those with underlying pulmonary disease, become the principal victims. On the other hand, Pontiac fever, which is convincingly spread by airborne route, is characterized by an attack rate of 90% to 100%.[5,6] It is also interesting to note that simultaneous occurrence of pneumonic and nonpneumonic legionellosis in the setting of common-source transmission has been reported only once[21]; this seems surprising if airborne spread with aerosolization is a predominant mode of transmission of Legionnaires' disease.

Bacteria associated with aspiration pneumonia tend to be normal flora capable of colonizing the oropharynx in the situation of prolonged hospitalization. Many such bacteria are endowed with organelles such as pili that mediate adherence to pharyngeal epithelial cells; of note is that legionella also possesses pili.[37] Stout et al[38] has also shown symbiosis between selected oropharyngeal flora and legionella.

Thus, the setting for aspiration as a potential portal of entry might be anticipated given the clinical context. However, this mode of transmission has been largely overlooked because of the popularity of the aerosolization theory originally advanced in the 1976 Philadelphia outbreak. A reexamination of previously reported outbreaks from this new perspective is worth considering. In the original 1976 Philadelphia outbreak, the attack rate of American Legion delegates was 6.8% and hotel employees was less than 0.25%. The only parameter that could be linked statistically to acquisition of the disease was ingestion of water[1]—an association that has been widely overlooked. Affected individuals had a high incidence of conditions that could predispose to subclinical aspiration, such as alcohol ingestion, or impede pulmonary clearance of aspirated microorganisms, such as cigarette smoking.[1] Given the new information that water distribution systems of large buildings may be decontaminated, it now seems plausible that acquisition of the organism occurred not via an air conditioning system as is currently believed, but via the water distribution system with aspiration of contaminated water as the mode of entry into the lungs.

In a prospective pneumonia study at the Pittsburgh Veterans Administration Hospital, we reported that risk factors for acquisition of Legionnaires' disease were similar to risk factors for acquisition of other bacterial pneumonias.[39] Of note was the observation that preceding surgical procedures were more common in the Legionnaires' disease group than in the control group, a difference that approached statistical significance. General anesthesia with endotracheal intubation may have been predisposing

factors for aspiration. The water system of the hospital was contaminated with *L pneumophila*,[40] and the frequency of isolation of the organism from the system was shown to be highly correlated with incidence of infection.[41] Aspiration of *L pneumophila* acquired from the hospital water system as the mechanism of spread is consistent with these observations.[42] Stout et al[43] has shown that ice machines can be contaminated with *L pneumophila*—a potentially important finding since this may be the primary source of the patient's drinking water.

In an ongoing prospective pneumonia study, we have noted a high rate of documented aspiration or of instrumentation of the respiratory tract preceding the development of nosocomial legionellosis. The incidence of such occurrences is similar in patients acquiring other pneumonia who are matched for age and underlying disease (R. R. Muder, MD, unpublished data, 1983).

In a prospective pneumonia study performed by Johnson et al,[44] a population of oncologic head and neck surgical patients was surveyed for the presence of occult nosocomial legionellosis.[44] This patient group was selected for study because of these patients' almost universal propensity for aspiration since the site of tumor and resective surgery is the oropharynx. In addition, most of these patients have a history of heavy cigarette smoking—a risk factor not only for head and neck cancer, but also for Legionnaires' disease. This two-year study revealed that 30% of nosocomial pneumonias could be attributed to legionella, one of the highest incidences ever recorded for endemic legionellosis. The serogroup of the infecting *L pneumophila* was found to match the serogroup of the *L pneumophila* in the hospital water distribution system.

The major weakness of the aspiration theory is that oropharyngeal colonization by *L pneumophila* has not been convincingly demonstrated. We have failed to isolate the organism from asymptomatic patients known to have consumed water from contaminated hospital supplies (J. E. Stout, unpublished data, 1982). Although positive direct fluorescent antibody staining of pharyngeal specimens from hospitalized patients has been observed, simultaneous cultures have been uniformly negative.[45,46] Zanen-Lim et al[47] isolated *L pneumophila* from a throat swab, but clinical details were not given. As *L pneumophila* is fastidious and easily overgrown by resident pharyngeal flora, it is conceivable that the organism may be present in the pharynx but remain undetectable with current culture techniques.

INGESTION AS A MODE OF TRANSMISSION

As previously noted in the 1976 Philadelphia outbreak, consumption of water at the implicated hotel was significantly associated with acquisition of Legionnaires' disease. A potential mechanism by which legionella might be transmitted via ingestion is that of bacteremic spread after penetration of the gastrointestinal tract. *Legionella pneumophila* can disseminate to extrathoracic organs[48,49] and is recoverable from blood in up to 38% of infected patients.[50]

Diarrhea may be a prominent symptom in Legionnaires' disease.[51,52] Although comparative studies have failed to confirm a predilection for gastrointestinal symptoms in *L pneumophila* as compared with pneumonias of other etiology,[39,53] these early clinical observations are compatible with the possibility that the gastrointestinal tract was the portal of entry. Interestingly, both Katz and Matus[54] and Plouffe et al[55] were able to produce illness in guinea pigs by oral inoculation with legionella-containing water. The organism was recoverable from lungs, spleens, and blood of infected animals.

Evidence to support ingestion in humans as a mode of transmission is scanty. Dournan et al[56] reported the case of a 70-year-old man who presented with fever, pneumonia, diarrhea, and vomiting. Despite treatment with penicillin, the patient developed worsening pulmonary disease followed by acute abdominal pain, septic shock, and death. At autopsy, *L pneumophila* was demonstrated in multiple organs by culture and direct fluorescent antibody staining. "Innumerable" organisms were demonstrated by direct fluorescent antibody staining in peritoneal fluid, intestinal wall, and intestinal mucus.

OTHER NONPULMONARY PORTALS OF ENTRY

Because pneumonia is the presenting clinical manifestation in more than 95% of cases of Legionnaires' disease, nonpulmonary portals have not been considered likely. Legionella infection developing at sites other than lung are generally thought to be the result of bacteremic spread with lung as the portal of entry. Thus, infections from nonpulmonary sites *in the absence of pneumonia* warrant scrutiny.

There have been two reports of pericarditis followed by a seroconversion to *L pneumophila* in the absence of pneumonia.[57,58] In addition, there is a report of culture-documented *L pneumophila* prosthetic valve endocarditis in the absence of pneumonia.[59]

More convincing evidence of nonpulmonic portal of entry comes from a report of *L pneumophila* wound infections occurring in a postoperative patient who had undergone daily immersions in a Hubbard tank.[60] Both the wound and the water supply of the tank yielded *L pneumophila*, serogroup 4; no clinical evidence of pulmonary infection developed. Thus, contact with contaminated water may, on rare occasions, lead to soft-tissue infection with *L pneumophila*.

COMMENT

In this article, we have reviewed possible modes of transmission for *L pneumophila* that include aerosolization, direct instillation into the respiratory tract, aspiration, ingestion, and other nonpulmonary portals of entry. It is apparent from this article, as well as somewhat surprising, that so little is known about this important link in disease causation while so much is known about the microbiology of the organism and the clinical presentation of the disease.

This situation has occurred for a number of reasons. Early investigations were hampered by lack of availability of adequate culture methodology preventing a systematic search for the vehicle of transmission. The habitat and ecology of the organism was not elucidated until after a considerable number of epidemiologic and clinical studies had been completed. As a result, unavoidable bias was present in the early epidemiologic investigations. For example, the designation of cooling towers as the reservoir and transmission via aerosolization by showers are two plausible theories that were generated from insufficient data, but which have become unduly emphasized. Both of these well-publicized theories are now proving inadequate in accounting for most cases of Legionnaires' disease.

The most serious pitfall in the earlier epidemiologic studies was the assignment of causation to a specific reservoir or mode of transmission based on decline of disease following eradication measures that were directed at a putative source. We now know there exists a natural variation in the incidence of Legionnaires' disease over time; outbreaks can terminate spontaneously without intervention.[40,41] This may be followed by a period of relaxed vigilance with a resultant decline in the ordering of specialized laboratory tests for legionella. Subsequent cases,

especially if sporadic, may, therefore, go unrecognized. In this situation, incorrect conclusions may be inferred by investigators under pressure to find immediate solutions.

What constructive points can be devised from our analysis? First, in future studies an attempt must be made to identify all cases within the study population in order to avoid unintentional biases. This will require intensive prospective surveillance with the routine application of specialized laboratory tests including direct fluorescent antibody stains, culture on selective media, and most importantly, convalescent serology after resolution of pneumonia.

Second, vigorous surveillance of legionella infections must be continued for extended periods (years) after a putative reservoir is identified and eliminated; this longer period is necessary in order to rule out the possibility of a natural decline in the incidence of disease independent of interventional measures.

Third, we suggest Evans' interpretation[61] of Koch's postulates be considered before causation is assigned. Although individual postulates may be difficult to fulfill, nevertheless, this overall approach demands a rigor that has been absent from most epidemiologic studies of Legionnaires' disease. We find it interesting that since the recognition of the importance of a hospital water distribution system as a reservoir for Legionnaires' disease,[40] virtually all outbreaks occurring from 1982 onward now cite the water distribution system as a culprit, usually with no stronger evidence than pre-1982 studies citing cooling towers as the culprit.

Finally, because of the possibility that multiple reservoirs as well as multiple modes of transmission may be concurrently operative, multi-institutional case-control studies of nosocomial legionellosis may be the only practical means for answering the remaining questions.

Certainly, with the advent of improved culture methodology and increasing awarenes among physicians of the frequency of this disease, more outbreaks are being discovered and the opportunities for determining the precise mode of transmission will increase. Our hope is that, given our review, the methodology for future investigations can be improved such that more definitive answers will be forthcoming.

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