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Legionella pneumophila cases in a community hospital: A 12-month retrospective review

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Abstract

Background: *Legionella* pneumonia has long been recognized as an important cause of community-acquired pneumonia associated with significant morbidity and mortality; however, the description of the incidence of this disease is restricted to sporadic cases in the literature. With the advent of an inexpensive and rapid urine antigen test, routine testing has become more common. We report findings of a retrospective review of 266 patients who were admitted with a clinical diagnosis of community-acquired pneumonia over a 12-month period and were tested for *Legionella pneumophila* serogroup 1, reporting the prevalence and determinants of *Legionella* infection.

Methods: Chart reviews of 266 patients admitted for community-acquired pneumonia and who underwent urine antigen testing for *Legionella pneumophila* during a 1-year time period were conducted, looking at demographic information as well as clinical and laboratory presentation, reporting on the prevalence and determinants of urine antigen positivity using multivariate logistic regression analysis.

Results: *Legionella pneumophila* serogroup 1 was found in 2.3% of cases of community-acquired pneumonia. We also found that altered mental status, diarrhea, history of lung disease, and alcohol intake were significantly associated with pneumonia associated with *Legionella*. The presence of these four factors had a low sensitivity in predicting *Legionella* infection (33%); however, they had a positive predictive value of 98%, with a specificity of 100. All the *Legionella*-infected patients in our study required admission to the intensive care unit, and one of them developed Guillain–Barré syndrome, which to our knowledge represents the only reported case of this syndrome related to *Legionella* infection in an adult in the English scientific literature.

Conclusion: *Legionella pneumophila* serogroup 1 is a common cause of sporadic cases of community-acquired pneumonia associated with a high morbidity and protean manifestations. Clinical features have a poor sensitivity in identifying cases, and routine urine antigen testing in patients with suggestive clinical symptoms appears to be a rational approach in the evaluation of community-acquired pneumonia.

Keywords

Legionella pneumophila serogroup 1, community-acquired pneumonia, hyponatremia, *Legionella* urinary antigen test

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Background

Legionella pneumophila is a common cause of community-acquired pneumonia (CAP) and a common cause of outbreaks of hospital-acquired pneumonia.[1–3] *Legionella* is considered an atypical pulmonary pathogen, along with mycoplasma and chlamydia species. Cases of community-acquired Legionnaires' disease are reportedly more severe; however, description of the true incidence of this disease is restricted to sporadic cases in the literature.[2] The clinical presentation of CAP due to *Legionella pneumophila* overlaps with those of other pathogens. Previous studies have described gastrointestinal and neurologic symptoms, as well as laboratory features such as hyponatremia and hepatic and renal dysfunction as more common in CAP due to *Legionella pneumophila*; however, these features are nonspecific.[4–6] Because delayed diagnosis and failure to institute appropriate antibiotic coverage have been

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associated with poor clinical outcomes,[7,8] rapid identification of a causative agent has been an attractive goal. Isolation of *Legionella* by culture is the ideal means of diagnosis; however, this approach is limited by several factors, including difficulty obtaining sputum samples in patients with non-productive or poorly productive cough, the effects of empiric antibiotic therapy on the yield of sputum samples, and delay in diagnosis as cultures take about 3–5 days to speciate.[9] Currently, diagnosis can be made by urine antigen testing targeting *Legionella pneumophila* serogroup 1, which has been implicated as the etiology in about 90% of cases.[7,10] This relatively inexpensive enzyme immunoassay has a reported sensitivity that ranges between 76% and 86% for sporadic cases of community-acquired Legionnaires' disease and a specificity that approaches 100%.[9,11] We report findings of a retrospective survey of 266 patients who were admitted with a clinical diagnosis of CAP over a 12-month period and were tested for *Legionella pneumophila* serogroup 1 as a routine laboratory test, reporting the prevalence and determinants of urine antigen positivity in the setting of a pneumonia.

Methods

Study population

This study was conducted at Milford Regional Medical Center (MRMC), a 121-bed community and regional teaching hospital. Retrospective chart reviews of 266 patients admitted from July 2012 to August 2013 with a clinical diagnosis of CAP and a clinical suspicion for *Legionella* pneumonia who underwent urine antigen testing were conducted. Information gathered included age, sex, reported history of underlying lung disease such as chronic obstructive lung disease (COPD) or asthma, as well as smoking history and a history of alcohol consumption (regardless of quantity). Information on reported symptoms such as diarrhea and confusion was retrieved from patient documentation in electronic medical records as documented in patient's charts by providers. Laboratory data at the time of admission for complete blood count and basic metabolic panel were also collected. All patients underwent testing for *Legionella pneumophila* serogroup 1 urine antigen using aqualitative rapid assay following manufacturer's instructions (Alere BinaxNOW®*Legionella* Urinary Antigen Card, Waltham, MA, USA). Other data collected included reports on sputum cultures and chest imaging such as radiographs and/or computed tomography. *Legionella* pneumonia was diagnosed in patients who had clinical features of pneumonia suggested by history and chest imaging; and had a positive urine antigen test.

Statisticalanalysis

All data were entered into an Epi Info™ 7.1.2 (Atlanta, GA, USA) data entry form and subsequently exported into STATA version 10 (StataCorp, College Station, TX, USA) for statistical analysis. Stepwise logistic regression was carried out using *Legionella pneumophila* serogroup 1 antigen positivity as a dependent variable. Independent variables included age, sex, smoking status, alcohol consumption, diarrhea (as documented in the medical records), altered mental status (AMS; defined as confusion, altered sensorium, or coma), presence of an elevated white blood cell (WBC) count greater than 11,000 or a low WBC (less than 4000), season of the year (Winter, Spring, Summer, or Fall), infiltrate on chest imaging (by chest radiograph or computed tomography), and positive sputum cultures for other pathogens. Variables with p value < 0.05 were deemed as significant predictors of *Legionella pneumophila* serogroup 1 antigen positivity and were retained in our final model.

Ethical statement

Chart review was done with adherence to our institutional Health Insurance Portability and Accountability Act (HIPAA) regulations. All personal identifiable information such as names, date of birth, medical record numbers, address, or social security numbers on patients included in the study was excluded in the data entry form before exporting to STATA for statistical analysis. Ethics approval was not required for this study as no contact or personal identifiable information was recorded, and all collected data were anonymized.

Results

Females accounted for 52.3% of participants, while males comprised 47.7%. Baseline characteristics (Table 1) of participants were similar, with a mean age of 71.1 years (95% confidence interval (CI): 69.0–71.2 years) and no statistically significant age difference between the sexes (mean age for females 73.0 years (95% CI: 70.1–75.9 years) vs mean age for males 69.0 years (95% CI: 66.0–71.9 years)). Smoking and the prevalence of reported underlying lung disease were also similar between the sexes. Alcohol use was reported for 12% in men compared to 7% in women, and this difference was statistically significant ($\chi^2 = 5.69$; $p = 0.02$).

Six of the 266 individuals in whom data were obtained during the retrospective review timeframe tested positive for *Legionella pneumophila* serogroup 1, resulting in a *Legionella* pneumonia prevalence of 2.3% (95% CI: 0.8%–4.8%). Five of the six individuals who were diagnosed with *Legionella* pneumonia were male, although this difference was not statistically significant ($\chi^2 = 3.12$; $p = 0.078$)

Five variables were found to be independent predictors of *Legionella pneumophila* serogroup 1 antigen positivity in our model (Table 2). They are the presence of underlying lung disease, alcohol use, presence of diarrhea, AMS, and age group. The strongest predictors were the presence of

Table 1. Baseline characteristics.

Age, years (95% CI)	71.1 (69.0–71.2)			
Legionella pneumophila serogroup 1 prevalence	Tested	*Legionella pneumophila* serogroup 1 antigen positive	95% CI	
	266	6 (2.3%)	0.8–4.8	
Prevalence by sex	Tested	*Legionella pneumophila* serogroup 1 antigen positive	χ^2	p value
Female	139	1 (0.7%)	3.12	0.078
Male	127	5 (3.9%)		
Age group (years)	Tested	*Legionella pneumophila* serogroup 1 antigen positive		
15–29	5	0 (0%)		
30–44	15	1 (6.7%)		
45–59	45	2 (4.4%)		
60–69	52	2 (3.9%)		
70–79	53	1 (1.9%)		
≥80	96	0 (0%)		
Smoking	Men	Women	χ^2	p value
Never smoked	55/127 (43.3%)	77/139 (55.4%)	4.65	0.098
Current smoker	26/127 (20.5%)	27/139 (19.4%)		
Former smoker	46/127 (36.2%)	35/139 (25.2%)		
Alcohol use	Men	Women	χ^2	p value
	32/127 (12%)	19/139 (7%)	5.69	0.02
Underlying lung disease*	Men	Women	χ^2	p value
	56/127 (44.1%)	49/139 (35.3%)	2.17	0.14

CI: confidence interval.

Table 2. Multivariate logistic regression analysis for *Legionella* pneumonia.

Explanatory variables	Odds ratio	β coefficient	95% CI	p value
Underlying lung disease (ULD)	8.00	2.08	1.47–43.51	0.016
Alcohol use (EtOH)	8.64	2.16	1.54–48.51	0.014
Reported diarrhea (Diarrhea)	9.63	2.27	1.49–62.39	0.017
Altered mental status (AMS)	9.64	2.27	1.10–84.57	0.041
Age group (Agegp)	0.58	−0.55	0.42–0.79	0.001

CI: confidence interval.

AMS (odds ratio (OR): 9.64; 95% CI: 1.10–84.57; p = 0.041) and diarrhea (OR: 9.63; 95% CI: 1.49–62.39; p = 0.017). Our model had a low sensitivity, identifying patients with *Legionella pneumophila* serogroup 1 with a sensitivity of 33.3%; however, it had a high specificity of 100%, the positive predictive value was 100%, and the negative predictive value was 98.5% (Table 3). Sex, smoking history, presence of hyponatremia (sodium less than 130 mmol), season of the year, or positive sputum cultures were not significant predictors of antigen positivity and were therefore excluded from the model.

Sputum cultures were positive in 18% of patients, and the common isolates from sputum cultures (in order of frequency) were *Staphylococcus aureus* (30%), *Streptococcus pneumoniae* (27.5%), *Pseudomonas aeruginosa* (12.5%), and *Klebsiella pneumoniae* (5%). *Corynebacterium* spp. was isolated in 25% of sputum cultures.

Table 3. Sensitivity analysis of multivariate logistic model.

Sensitivity	33.3%
Specificity	100%
Positive predictive value	100%
Negative predictive value	98.5%

Discussion

Our study shows that using routine urine antigen testing, *Legionella pneumophila* serogroup 1 accounted for a significant number of cases of CAP among hospitalized patients. Our reported prevalence of 2.3% appears to be low on the spectrum of reported prevalence of *Legionella* pneumonia in the literature.[1,7] The true prevalence could be higher because urine antigen testing has some limitations: first, it has a sensitivity that ranges from 76% to 86%, and, second, it does

not identify other serogroups or non-*Legionella pneumophila* species. Another potential factor inherent in our study design that may explain the relatively low prevalence of infections is that not all patients admitted with CAP were tested. A recent study by Murdoch et al.[12] found a fourfold increase in *Legionella* cases with the implementation of a routine polymerase chain reaction (PCR) testing strategy, suggesting that many cases will be missed when urine antigen testing is used alone. No cultures were performed on positive specimens, further limiting the ability to detect infected cases.

Our results also support the association of some clinical features with *Legionella pneumophila*, as the observation that the presence of underlying lung disease, alcohol consumption (regardless of quantity), presence of confusion or AMS, and diarrhea are strong predictors of infection (Table 2). When we stratified participants into different age groups (Table 1), there was a higher occurrence among middle-aged participants between 45 and 69 years of age compared to older participants. Furthermore, the odds of *Legionella* urine antigen positivity were inversely correlated with age group, suggesting a predilection for the younger age group (OR: 0.58; 95% CI: 0.42–0.79). This finding is at variance with reports of *Legionella* pneumonia among hospitalized patients occurring in older men with underlying diseases. We observed *Legionella* pneumonia in younger patients, with a trend toward a higher frequency among men, although this difference was not significant. Our observation is consistent with those of a large multicenter study in which Von Baum et al.[7] noted disease occurrence in younger patients, with an equal sex distribution and significantly fewer comorbidities among patients.

Some laboratory features such as hyponatremia have been reported to be associated with *Legionella pneumophila*; however, we failed to replicate this finding as hyponatremia was not associated with urine antigen positivity in multivariate analyses in our study. Indeed, hyponatremia is a nonspecific finding among patients with pneumonia, and it has not been consistently shown to have an association with *Legionella pneumophila* when compared to those who had pneumonia due to other causes.[13] Studies that found an association were among nosocomial cases and were reported to occur within 5 days of onset of pneumonia.[14] In our study, we only included sodium levels for each participant at the time of admission; hence, we may have found an association if other values in the hospitalization course were included in our analysis.

Our observation that alcohol consumption had a strong predictive effect on urine antigen positivity is intriguing because hepatic dysfunction (suggested by elevations in serum transaminases) is one of the reported laboratory derangements associated with *Legionella pneumophila*.[15,16] Although we did not quantify the amount of alcohol consumed or follow serum transaminases, establishing causality is difficult as we are unable to determine whether hepatic dysfunction is a direct consequence of *Legionella pneumophila* infection by way of hepatocellular injury or whether the observed elevations in hepatic transaminases are due to alcohol consumption, or both.

In sensitivity analysis, our multivariate logistic regression model had a low sensitivity in detecting cases (sensitivity 33%), probably attributed to the relative infrequency and sporadic occurrence of the disease. The multivariate model, however, had a good specificity and could virtually exclude the disease (specificity 100%, negative predictive value 98.5%). The sporadic occurrence of Legionnaires' disease as well as the nonspecific clinical and laboratory features demonstrated in studies makes clinical diagnosis a challenge. This is further compounded by the finding that CAP caused by *Legionella pneumophila* tends to be severe with a trend toward higher mortality. Although none of the six patients diagnosed with *Legionella pneumophila* in our study died, all of them required admission to the intensive care unit, and four of them (two-thirds) developed respiratory failure requiring intubation and mechanical ventilation. One patient developed Guillain–Barré Syndrome (GBS, diagnosed by electromyography) and had a protracted hospitalization.[17] To our knowledge, there have been only two reported cases of *Legionella pneumophila* causing GBS in the literature, both of which occurred in children.[1,18] One distinguishing feature of our study, as compared to other published studies, is that this was done at one community hospital, whereas other studies tend to be done in tertiary centers, or multicenter studies.

Our study has certain limitations: first, not all patients admitted with CAP were tested, and because of the retrospective design of our study, we could not ascertain what influenced physicians' decision to order the urine antigen test. The diagnostic test also has some limitations in that it does not detect other *Legionella* species as well as other serogroups of *Legionella pneumophila*. Selection bias is also another limitation as the patients who were tested may have been sicker and therefore not representative of all patients in the community.

Conclusion

Legionella pneumophila is a common cause of CAP among hospitalized patients; its occurrence tends to be sporadic and associated with a high morbidity. Clinical and laboratory features can neither reliably identify cases nor exclude them, and therefore, routine antigen testing among patients hospitalized for severe CAP should be used to promptly identify cases and guide clinicians to tailor antibiotic therapy early on in the hospitalization course. Formerly, when urine antigen testing was deemed expensive, clinical guidelines were in favor of using clinical syndromes to select patients for pathogen-specific diagnostic testing; however, given the availability of a simple and affordable urine antigen test (about US$35 per test), routine testing of severe cases of CAP,

especially among those who develop respiratory failure, appears to be a rational approach.

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Declaration of conflicting interests

We declare that we have no competing interests.

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