Clinical Presentation of Community-Acquired Legionella Pneumonia Identified by Universal Testing in an Endemic Area

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Abstract: The rapid identification of Legionella pneumonia is essential to optimize patient treatment and outcomes, and to identify potential public health risks. Previous studies have identified clinical factors which are more common in Legionella than non-Legionella pneumonia, and scores have been developed to assist in diagnosing cases. Since a Legionella pneumonia outbreak at VA Pittsburgh in 2012, nearly all patients with pneumonia have been tested for Legionella. The purpose of this study was to evaluate distinguishing characteristics between Legionella and non-Legionella pneumonia with the application of universal testing for Legionella in all cases of community-acquired pneumonia. We performed a retrospective case-control study matching Legionella and non-Legionella pneumonia cases occurring in the same month. Between January 2013 and February 2016, 17 Legionella and 54 non-Legionella cases were identified and reviewed. No tested characteristics were significantly associated with Legionella cases after Bonferroni correction. Outcomes of Legionella and non-Legionella pneumonia were comparable. Therefore, in veterans who underwent routine Legionella testing in an endemic area, factors typically associated with Legionella pneumonia were non-discriminatory.

Keywords: Legionella; Legionnaires’ disease; Legionella pneumonia

1. Introduction

Legionnaires’ disease is a pneumonia caused by Legionella bacteria associated with case fatality rates of 10–25% [1]. Legionella can account for up to 15% of cases of community-acquired pneumonia and has been associated worldwide specifically with human-made water systems [1,2]. These water systems can include, but are not limited to, cooling towers, hot tubs, decorative fountains, shower heads, and medical equipment [1]. Various studies have identified clinical and laboratory factors that are associated with Legionella pneumonia [2–10]. These prediction models were derived from pneumonia cases diagnosed without mandatory testing for Legionella. Indeed, current guidelines do not recommend routine testing for Legionella [11]. Rather, targeted testing of healthcare and severe community-acquired pneumonias is recommended—an approach that misses a significant percentage of Legionella cases [12]. Therefore, studies of Legionella pneumonia have artifactual biases toward more severe cases and presentations with conventionally attributed symptoms.

Following a Legionnaires’ disease outbreak at the Veterans Affairs Pittsburgh Healthcare System (VAPHS) [13], we instituted mandatory Legionella testing for all patients with pneumonia [14]. Legionella was subsequently identified in 1% of patients with pneumonia; almost half of these cases would...
have been unrecognized if we followed current testing guidelines. Our systematic protocol afforded an opportunity to identify characteristics of Legionella pneumonia in an endemic area, without biases introduced by selective testing. The purpose of this study was to identify the differentiating characteristics between Legionella and non-Legionella pneumonia in patients with pneumonia.

2. Materials and Methods

After Institutional Review Board approval was obtained (IRB Pro00001725), a retrospective, case-control comparison of patients with community-acquired Legionella pneumonia or non-Legionella pneumonia at VAPHS was performed. Legionella pneumonia was identified from January 2013 through February 2016—a period in which >97% of pneumonia cases were tested for Legionella [14]. No outbreak cases have been identified at VAPHS since 2012. Inclusion criteria for community-acquired pneumonia were clinical features of pneumonia along with radiographic findings on chest radiography or another imaging modality. These criteria were based on Centers for Disease Control, (Atlanta, Georgia) surveillance definitions [11,15]. One control patient was excluded as Legionella testing was not performed. Patients with pneumonia were tested by Legionella urinary antigen (BinaxNOW® Legionella Urinary Antigen Card, Alere, Waltham, MA, USA) and/or sputum culture for Legionella, as previously described [14]. Patients were diagnosed with Legionella pneumonia if any of urinary antigen, sputum culture, or autopsy lung culture were positive for Legionella. For each month when there was at least one Legionella pneumonia case diagnosed, all the non-Legionella pneumonia cases from that month were randomized into a list and the first five were then chosen. Demographic and clinical factors, disease severity, and outcomes were compared. Chi-square and Fisher exact tests were used as appropriate to determine statistical significance. After Bonferroni correction [16] for 44 variables, a calculated value of $p < 0.001$ was considered significant.

3. Results

Overall, 1691 pneumonia cases were diagnosed. Seventeen cases of Legionella pneumonia (1%) occurred in 11 of 38 months; none of these cases were hospital-acquired. Fifty-five patients with non-Legionella pneumonia were randomly identified and 54 were included in the analysis (representing 3.2% and 11% of pneumonias overall and in reviewed months, respectively).

Twelve and nine patients with Legionella pneumonia had positive urinary antigens and sputum cultures, respectively. One patient was negative by urinary antigen and sputum culture, but an autopsy lung biopsy culture grew Legionella pneumophila. Fifteen and two patients were infected with L. pneumophila serogroups 1 and (2–14), respectively. Fifty-one (93%) and 37 (67%) non-Legionella pneumonia patients had negative Legionella urinary antigens and sputum cultures, respectively. One patient in the non-Legionella pneumonia group had neither urinary antigen nor sputum sent for Legionella testing.

Demographic information and clinical data are shown in Tables 1 and 2, respectively.

Table 1. Demographic characteristics of pneumonia cases. N: Number, w/in: Within, HIV: Human Immunodeficiency Virus, COPD: Chronic Obstructive Pulmonary Disease. $p$-Values obtained by Fisher exact or Chi-square testing as appropriate.

|                | Non-Legionella N = 54 (%) | Legionella N = 17 (%) | p-Value |
|----------------|---------------------------|-----------------------|---------|
| Male           | 51 (94)                   | 17 (100)              | 1       |
| Age > 75       | 17 (31)                   | 1 (6)                 |         |
| Age 50–75      | 35 (65)                   | 15 (88)               | 0.11    |
| Age < 50       | 2 (4)                     | 1 (6)                 |         |
| Steroid therapy| 2 (4)                     | 2 (13)                | 0.24    |
| Nursing home resident within last 30 days | 39 (72) | 2 (13) | 0.031 |
| Hospitalization w/in last 90 days | 23 (43) | 4 (24) | 0.16  |
Table 1. Cont.

| Clinical Characteristics                              | Non-Legionella N = 54 (%) | Legionella N = 17 (%) | p-Value |
|-------------------------------------------------------|---------------------------|-----------------------|---------|
| Enrolled in Wound Care                                | 2 (4)                     | 0                     | 1       |
| HIV                                                   | 0                         | 0                     |         |
| Cancer or hematologic malignancy                      | 17 (31)                   | 4 (24)                | 0.76    |
| Chemotherapy in last 6 months                        | 3 (5)                     | 1 (6)                 | 1       |
| Immunomodulator/biologic therapy                      | 2 (4)                     | 3 (18)                | 0.085   |
| Current tobacco use                                   | 16 (29)                   | 10 (59)               | 0.082   |
| Any tobacco use                                       | 37 (69)                   | 14 (82)               | 0.57    |
| Active alcohol abuse                                  | 3 (6)                     | 0                     | 1       |
| Diabetes mellitus                                     | 17 (31)                   | 5 (29)                | 1       |
| COPD                                                  | 33 (61)                   | 6 (35)                | 0.093   |
| Heart failure                                         | 15 (28)                   | 5 (29)                | 1       |
| Kidney disease                                        | 13 (24)                   | 4 (24)                | 1       |
| Cirrhosis                                             | 1 (2)                     | 2 (13)                | 0.14    |
| Cerebrovascular disease                               | 10 (19)                   | 1 (6)                 | 0.28    |

Table 2. Characteristics of Legionella and pneumonia cases. AMS: Altered Mental Status, PSI: Pneumonia Severity Index, RR: Respiratory Rate, SBP: Systolic Blood Pressure, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, O2: oxygen. P-values obtained by Fisher exact testing.

| Clinical Characteristics                              | Non-Legionella N = 54 (%) | Legionella N = 17 (%) | p-Value |
|-------------------------------------------------------|---------------------------|-----------------------|---------|
| Cough                                                 | 34 (63)                   | 12 (71)               | 0.77    |
| Shortness of breath                                   | 30 (56)                   | 7 (41)                | 0.41    |
| AMS/Confusion                                         | 18 (33)                   | 6 (35)                | 1       |
| Sputum production                                     | 27 (50)                   | 5 (29)                | 0.17    |
| Complaint of diarrhea                                 | 7 (13)                    | 2 (12)                | 1       |
| Myalgia/arthritisalga                                 | 11 (20)                   | 5 (29)                | 0.75    |
| PSI Class 1–3                                         | 16 (30)                   | 7 (41)                | 0.38    |
| PSI Class 4–5                                         | 39 (72)                   | 10 (59)               |         |
| Infiltrate                                            | 54 (100)                  | 17 (100)              |         |
| Uni-lobar infiltrate                                  | 33 (61)                   | 14 (82)               | 0.15    |
| Multi-lobar infiltrate                                | 21 (39)                   | 3 (18)                | 0.15    |
| Pleural effusion                                      | 17 (31)                   | 5 (29)                | 1       |
| Vital signs on admission                              |                           |                       |         |
| RR > 29                                               | 3 (6)                     | 3 (18)                | 0.14    |
| SBP < 90                                              | 7 (13)                    | 1 (6)                 | 0.67    |
| Temp > 39.0 Celsius                                   | 5 (9)                     | 7 (41)                | 0.0055  |
| Pulse > 124                                          | 2 (4)                     | 3 (18)                | 0.085   |
| Laboratory characteristics                            |                           |                       |         |
| pH < 7.35                                             | 4 (7)                     | 2 (12)                | 1       |
| Serum phosphorus < 2.5 mg/dL                          | 5 (9)                     | 5 (29)                | 0.25    |
| Serum sodium < 133 mEq/L                              | 7 (13)                    | 8 (47)                | 0.0055  |
| Urine protein > 30                                    | 7 (13)                    | 8 (47)                | 0.0094  |
| AST > 42 IU/L                                         | 13 (24)                   | 5 (29)                | 1       |
| ALT > 60 IU/L                                         | 8 (15)                    | 2 (12)                | 0.71    |
| Glucose > 249 mg/dL                                   | 5 (9)                     | 3 (18)                | 0.39    |
| Hematocrit < 30%                                      | 7 (13)                    | 2 (12)                | 1       |
| Lactate dehydrogenase > 180 IU/L                      | 0                         | 1 (6)                 | 0.11    |
| Creatine kinase > 200 U/L                             | 4 (7)                     | 4 (24)                | 0.63    |
| C-reactive protein > 1.0 mg/dL                        | 2 (4)                     | 1 (6)                 | 1       |
| Partial pressure O2 < 60                              | 6 (11)                    | 5 (29)                | 0.42    |
| Platelet count < 171 × 10⁹/L                          | 15 (28)                   | 7 (41)                | 0.28    |

No variables were significant after Bonferroni correction. Mortality was low in our cohort and not significantly different between groups at 30 days, 90 days, or after hospital discharge (Table 3). All patients received Legionella-active treatment on presentation with pneumonia.
Table 3. Patient outcomes by group. ICU: Intensive Care Unit. Successful treatment refers to resolution of pneumonia clinical symptoms. p-Values obtained by Fisher exact testing.

|                      | Non-Legionella | Legionella | p-Value |
|----------------------|----------------|------------|---------|
| ICU admission        | N = 55 (%)     | N = 17 (%) | 0.088   |
| Successful treatment | 18 (33)        | 10 (59)    | 0.59    |
| Survival to discharge| 51 (94)        | 15 (88)    | 0.72    |
| 30-day survival      | 43 (80)        | 15 (88)    | 0.21    |
| 90-day survival      | 39 (72)        | 15 (88)    |         |

4. Discussion

To our knowledge, this is the first study assessing factors associated with *Legionella* pneumonia in a clinical setting that employed universal testing. Immunomodulatory therapy, fever, tachycardia, hyponatremia and proteinuria trended toward association with *Legionella* pneumonia by univariate analysis. Nursing home residency and sputum production trended toward an association with non-*Legionella* pneumonia. However, none of these factors were present in a majority of patients with either type of pneumonia, nor were the factors significant after Bonferroni correction. In the end, clinical and laboratory factors previously found to be predictive of *Legionella* pneumonia either were not significantly different in the two groups or they were not tested consistently (e.g., C-reactive protein, lactase dehydrogenase, Creatine phosphokinase (CPK)).

None of the prior studies of *Legionella* pneumonia risk factors or prediction models utilized a Bonferroni correction, which likely would have reduced or eliminated the significance of findings. We did not retrospectively apply the Winthrop University weighted score or the Ito-Ishida score, as none of our patients had majority of the components included in each. In order to utilize these tools accurately, clinicians must perform tests that are not typically performed for community-acquired pneumonia. Rather than conducting these additional tests and applying a score, we found it simpler in veterans from an endemic area to send *Legionella* testing.

In our population, the percentage of patients with a class IV or V pneumonia severity index was higher among patients with non-*Legionella* pneumonia than those with *Legionella* pneumonia (72% and 59%, respectively), and patients’ outcomes were comparable. The data demonstrate that *Legionella* pneumonia presents across a spectrum of severity. Studies identifying factors that predicted *Legionella* pneumonia or reporting increased mortality and morbidity compared to other community-acquired pneumonias may have been biased by a failure to test all patients for *Legionella* and the inclusion of only more severe cases or patients with previously identified risk factors.

Current guidelines do not recommend routine *Legionella* testing since empirical treatment regimens for pneumonia generally include antibiotics with anti-*Legionella* activity, and testing in low-risk settings may not be cost-effective. In regions that are endemic for *Legionella*, however, systematic testing identifies cases that would otherwise remain undetected, facilitates targeted antibiotic therapy, and serves a public health function as surveillance for potential outbreaks. Rapid, accessible microbiologic methods are more sensitive and specific than any scoring algorithm and may be easier to use as a screening method than a complex score requiring multiple tests not typically sent on non-critically ill pneumonia patients. In the aftermath of an outbreak, such as occurred in our hospital, routine *Legionella* testing afforded confidence that cases were not missed, and that water management and infection prevention protocols remained effective.

There are limitations to this study. Our study population was ≥95% male. Results in our patients may not be relevant to other cohorts, since veterans are typically older and have more health conditions than the general population. Veterans may also be hospitalized sooner as they have a higher use of medical resources compared to the general population. *Legionella* is known to be more prevalent in the northeastern part of the country, and in Pittsburgh in particular, than in other regions. In addition to differences in clinical findings or characteristics, patients with *Legionella* pneumonia in
other parts of the country may be detected at later, more severe stages of the disease. The relatively small number of patients we encountered and our single center study design may bias our findings due to low statistical power. Finally, since this was a retrospective study, we were limited to laboratory or clinical data that were collected clinically. Although some factors were considered significant by univariate analysis before the Bonferroni calculation, we felt it was important to use the correction to avoid the promotion of weak associations of limited practical utility or potentially erroneous associations unique to our patient population.

5. Conclusions

*Legionella* pneumonia in our experience was indistinguishable from other causes of community-associated pneumonia. Our experience suggests that testing all pneumonia cases for *Legionella* in endemic areas is more practical than attempting to derive prediction models to identify high-risk patients for testing. The broad application of testing in an endemic area allows for better-targeted antibiotic therapy and may increase public health awareness and help prevent outbreaks with heightened infection control practices as a result of the testing. In non-endemic regions, testing should be considered on a case-by-case basis while bearing in mind the indistinguishable characteristics between *Legionella* and other causes of community-associated pneumonia.

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