

Legionnaires' Disease: Clinicoradiological Comparison of Sporadic Versus Outbreak Cases

Hafiz Rizwan Talib Hashmi¹, Lakshmi Saladi¹, Frances Petersen², Misbahuddin Khaja^{1,3} and Gilda Diaz-Fuentes^{1,3}

¹Division of Pulmonary and Critical Care Medicine, Bronx-Lebanon Hospital Center, Bronx, NY, USA. ²Department of Infection Control, Bronx-Lebanon Hospital Center, Bronx, NY, USA.

³Icahn School of Medicine at Mount Sinai, New York, NY, USA.

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ABSTRACT

BACKGROUND: In 2015, New York City experienced the worst outbreak of Legionnaires' disease in the history of the city. We compare patients seen during the 2015 outbreak with sporadic cases of *Legionella* during the past 5 years.

METHODS: We conducted a retrospective chart review of 90 patients with Legionnaires' disease, including sporadic cases of *Legionella* infection admitted from 2010 to 2015 (n=55) and cases admitted during the 2015 outbreak (n=35).

RESULTS: We saw no significant differences between the 2 groups regarding demographics, smoking habits, alcohol intake, underlying medical disease, or residence type. Univariate and multivariate analyses showed that patients with sporadic case of *Legionella* had a longer stay in the hospital and intensive care unit as well as an increased stay in mechanical ventilation. Short-term mortality, discharge disposition, and most clinical parameters did not differ significantly between the 2 groups.

CONCLUSIONS: We found no specific clinicoradiological characteristics that could differentiate sporadic from epidemic cases of *Legionella*. Early recognition and high suspicion for Legionnaires' disease are critical to provide appropriate treatment. Cluster of cases should increase suspicion for an outbreak.

KEYWORDS: Legionnaires' disease, *Legionella*, atypical pneumonia, epidemic, outbreak

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CORRESPONDING AUTHOR: Gilda Diaz-Fuentes, Division of Pulmonary and Critical Care Medicine, Bronx-Lebanon Hospital Center, Bronx, NY 10457, USA.
Email: gdfuentes@bronxleb.org

Background

Legionnaires' disease was initially recognized during an outbreak of respiratory illness in Philadelphia, PA, at an American Legion convention in 1976.¹ The disease causes significant morbidity and mortality in immunosuppressed patients or those with certain comorbid conditions. During July to early August 2015, an increased number of patients with Legionnaires' disease were identified in New York City; 12 patients died and more than 120 were affected. The source of the outbreak was traced to contaminated cooling towers in the South Bronx. This was defined as the worst outbreak of Legionnaires' disease in the city's history. A team of environmental health experts from New York and Centers for Disease Control and Prevention (CDC) collected and tested samples from every cooling tower in that area. The DNA "fingerprint" from the bacteria found in each of the patients was identical to that of the bacteria found in one of the cooling towers, confirming that it was the specific *Legionella* bacteria from that cooling tower that infected each of those patients. The suspected cooling tower and those in the surrounding area were cleaned and treated, achieving control of the outbreak.²

Pontiac fever is an acute, benign, nonpneumonic, febrile upper respiratory tract infection caused by *Legionella* that often goes unrecognized and results in spontaneous recovery.³ The term *Legionnaires' disease* refers to more severe and atypical

pneumonia caused by *Legionella pneumophila*.⁴ *Legionella* bacteria commonly cause community-acquired pneumonia and, rarely, hospital-acquired pneumonia, although many cases of Legionnaires' disease remain undiagnosed.⁵ Hotels, apartment buildings, long-term residential facilities, hospitals, and other buildings with complex water and ventilation systems are common origin sites for outbreak of Legionnaires' disease.

The exact incidence of legionellosis is unknown due to lack of awareness and inconsistencies in diagnostic testing, although the number of cases in the United States has steadily increased since the first known outbreak 1976. In most cases, water cooling or air-conditioning systems directly contributed to transmission of the disease,⁶ whereas fountain water and portable water systems in hotels have also been implicated in a few cases.^{7,8} Incidence of Legionnaires' disease in New York City increased by 230% from 2002 to 2009, and the outbreak in summer of 2015 involved 120 patients, resulted in 12 deaths, and carried a 10.6% fatality rate.⁶ The outbreak was centered in the South Bronx, the poorest urban country in United States, which is already struggling with a very high prevalence of asthma and diabetes mellitus.

Although understanding of the disease itself has increased dramatically since its discovery,^{9,10} only scarce literature comparing the clinical and radiological features of sporadic and



Table 1. Demographic characteristics.

	SPORADIC CASES, 2010–2015 N=55 (%)	EPIDEMIC CASES, SUMMER 2015 N=35 (%)	P VALUE
Age (mean±SD)	57.48±12.66	55.14±13.05	T=0.845; P=.400
Sex			
Male	31 (56.4)	16 (45.7)	.39
Female	24 (43.6)	19 (54.3)	
Home			
Home	52 (94.6)	31 (88.6)	.67
Nursing home	1 (1.8)	2 (5.7)	.56
Assisted living/Shelter	2 (3.6)	2 (5.7)	.64
Race			
African American	24 (43.6)	21 (60)	.19
Hispanic	21 (38.2)	13 (37.1)	1.00
Other	10 (18.2)	1 (2.9)	.045

outbreak or epidemic cases of *Legionella* infection is available. Thus, we aimed to compare the clinical characteristics of sporadic and epidemic Legionnaires' disease cases, admitted to our hospital. Potentially, this could aid in early detection of outbreak patients and limit spread of the disease among at-risk populations.

Methods

Bronx-Lebanon Hospital Center is a 415-bed hospital whose emergency department responds to approximately 141 000 visits annually, one of the busiest in New York. The first case of Legionnaires' disease in New York was diagnosed at our hospital in September 1977.¹¹ The hospital system maintains a uniform electronic medical record system from which we searched inpatient and outpatient cases of *Legionella* infection from 2010 to 2015. We retrieved 90 records through the MedMined portal and hospital medical records based on *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis.

We conducted a retrospective chart review of the medical records. In total, 55 cases of legionellosis were treated from January 2010 to June 2015, which we classified as sporadic Legionnaires' disease (SLD; group 1). Thirty-five cases, in July and August 2015 during the outbreak, were classified as epidemic Legionnaires' disease (ELD; group 2). All patients with the diagnosis of *Legionella* infection were admitted, but there was 1 patient in the ELD group. We obtained data regarding demographic information, co-morbid conditions, and clinical, laboratory, and radiological features from the patients. Three of the authors reviewed each radiograph themselves and reached an agreement regarding findings. Patient outcomes, such as occurrence of respiratory failure and shock, hospital mortality, duration of mechanical ventilation, and length of stay (LOS) in the intensive care unit (ICU) and hospital, were evaluated.

Statistics

Group differences for continuous variables and proportions were tested with unpaired Student *t* test and Fisher exact test, respectively.

Five regression models were constructed to understand the predictive power of independent variables. Model 1 tested the predictive power of epidemiology (epidemic/sporadic), presence of pleural effusion, and age and sex of the subjects on hospital stay duration. Model 2 tested the predictive power of disease epidemiology (epidemic/sporadic), albumin level, and patient age and sex on ICU stay length. Model 3 tested the predictive power of disease epidemiology (epidemic/sporadic) and patient age and sex on number of days in mechanical ventilation. Model 4 tested the predictive power of disease epidemiology (epidemic/sporadic) and patient age on odds of pleural effusion. Model 5 tested the predictive power of epidemiology (epidemic/sporadic) and patient age on odds of unilateral infiltration. Models 1 to 3 were linear multiple regressions, whereas models 4 and 5 were binomial logistic regressions.

The significance of the association was measured with 2-tailed *P* value. All the tests were performed with Statistical Package for Social Sciences (SPSS version 17), with a 2-tailed $P \leq .05$ considered significant.

Results

The average age of the group was 57 years in sporadic cases and 55 years in epidemic cases. The majority of patients in our cohort were African American (Table 1). We found no significant differences in age, sex, and race or residence type between the groups.

There were higher number of non-African Americans and non-Hispanics in the sporadic group, mainly from Asia. Comorbid conditions were present in 89% of participants; half

Table 2. Comorbid conditions present on admission.

CONDITION	SPORADIC CASES, 2010–2015 N=55 (%)	EPIDEMIC CASES, SUMMER 2015 N=35 (%)	P VALUE
Hypertension	36 (65.5)	21 (60)	.66
Diabetes mellitus	28 (50.9)	11 (31.4)	.08
Asthma	7 (12.7)	10 (28.6)	.09
COPD	2 (3.6)	2 (5.7)	.64
Congestive heart failure	5 (9.1)	2 (5.7)	.70
Substance abuse: opioid/cocaine	12 (21.8)	11 (31.4)	.33
Cancer	5 (9.1)	1 (2.9)	.39
HIV	12 (21.8)	7 (20)	1.00
Steroid use	2 (3.6)	3 (8.5)	.37
Alcohol	23 (41.8)	13 (37.1)	1.00
Smoking	31 (56.4)	22 (62.9)	.66
No of co-morbidities			
1	14 (25.5)	7 (20)	.62
2	9 (16.4)	5 (14.3)	1.00
3 or more	28 (50.9)	17 (48.6)	1.00

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

of these patients exhibited 3 or more co-morbid conditions. We found no significant differences regarding comorbid conditions, such as diabetes mellitus, chronic lung diseases, or AIDS, between the 2 groups. Use of tobacco, alcohol, and recreational drugs was common (Table 2).

The most common clinical presentation of patients with legionellosis included fever (84% of cases) and respiratory symptoms, which were seen more often in ELD cases than in SLD cases ($P=.04$). Only 9% of patients reported gastrointestinal symptoms (Table 3).

All patients had chest radiographs (CXR) available for review, and chest computed tomography (CT) was performed in 52% of patients. Eleven patients had a normal admission CXR, but chest CT in all tested patients revealed some abnormalities. Their radiological findings ranged from unilateral to bilateral multilobar infiltrates (Table 3). Other radiological findings included nodules, emphysema, fibrosis, pleural effusion, and lymphadenopathy. Comparisons of pertinent laboratory data from the 2 groups are shown in Table 4. Patients with ELD had lower serum albumin levels than patients with SLD ($P=.002$), but we saw no other significant differences in laboratory features between the 2 groups. All patients tested positive for the urine *Legionella* antigen.

In our cohort, 37 (42%) of the 89 patients admitted required ICU care. Fifteen patients (17%) developed acute

respiratory failure requiring mechanic ventilation, and 8 patients (8.9%) developed shock and acute kidney injury requiring hemodialysis. Patients with SLD experienced more days in mechanical ventilation and longer LOS in the ICU and hospital than patients with ELD. We found no significant differences in discharge disposition or hospital mortality between groups, although 4 patients (4.4%) died, of whom 3 were in the ELD group. Outcome data for all patients are summarized in Table 5.

Legionella cases were dichotomized into a binary variable indicating either sporadic or epidemic case status. *Legionella* case type was significantly associated with hospital length of stay in both bivariate and multivariate analyses.

Multivariate analysis revealed that (1) epidemic cases had 7 days less of hospital stay than sporadic cases ($P=.008$). Pleural effusion increased hospital stay by 10.76 days ($P=.002$). Age and sex were not significant predictors of hospital LOS. (2) Albumin level, age, and sex were not significant predictors of ICU LOS. (3) There was a 24.3% variability in days in mechanical ventilation (adjusted $R^2=0.243$). Epidemic cases were 13.2 days less in mechanical ventilation than sporadic cases ($P=.001$). (4) Probability of pleural effusion is higher in epidemic cases and increases with age, although it remained on the verge of becoming statistically significant ($P=.052$). (5) Probability of unilobar infiltrates is lower but not significant in epidemic cases (Table 6).

Table 3. Clinical and radiological manifestations on admission.

	SPORADIC CASES, 2010–2015 N=55 (%)	EPIDEMIC CASES, SUMMER 2015 N=35 (%)	P VALUE
Symptom			
Fever	46 (83.6)	30 (85.7)	1.00
Respiratory	17 (30.9)	19 (54.3)	.046
Gastrointestinal	3 (5.5)	5 (14.3)	.25
Central nervous system	5 (9.1)	2 (5.7)	.70
Multisystemic	30 (54.5)	16 (45.7)	.52
Radiological findings			
CXR available	55 (100)	35 (100)	1.00
Normal	8 (14.5)	3 (8.6)	.52
Unilobar infiltrates	37 (67.3)	22 (62.9)	.82
Multilobar infiltrates	10 (18.2)	8 (22.9)	.59
Bilateral involvement	8 (14.5)	6 (17.1)	.77
Pleural effusion	6 (10.9)	9 (25.7)	.08
Chest CT available	28 (50.9)	19 (54.3)	.83
Normal CT	0	0	1.00
Unilobar infiltrates	8 (28.6)	8 (42.1)	.39
Multilobar infiltrates	15 (53.6)	10 (52.6)	1.00
Bilateral involvement	12 (42.9)	9 (47.4)	.79
Pleural effusion	6 (21.4)	8 (42.1)	.15
Other findings	10 (18.2)	3 (15.8)	.24

Abbreviations: CT, computed tomography; CXR, chest radiographs.

Table 4. Comparison of laboratory parameters.

PARAMETERS	SPORADIC CASES, 2010–2015 N=55 (%)	EPIDEMIC CASES, SUMMER 2015 N=35 (%)	P VALUE
Urine <i>Legionella</i> antigen	55 (100)	35 (100)	1.00
<i>Legionella</i> culture/DFA	2 (3.6), DFA	1 (2.9)	1.00
Other respiratory cultures	1 (1.8)	2 (5.7)	.56
Sodium (mean±SD)	131±11	132±7	$T=0.45$; $P=.63$
Platelets (mean±SD)	214±102	206±70	$T=0.41$; $P=.67$
Serum creatinine (mean±SD)	1.63±1.29	1.64±1.79	$T=0.03$; $P=.97$
ProBNP >400	18 (32.7)	8 (22.9)	.35
Abnormal liver function test	23 (41.8)	8 (22.9)	.07
Serum creatinine phosphokinase (mean±SD)	8344±19228	2644±7292	$T=1.676$; $P=.09$
Rhabdomyolysis	20 (36.4)	15 (42.9)	.66
Albumin (mean±SD)	3.59±0.53	3.22±0.56	$T=3.158$; $P=.002$

Abbreviations: BNP, brain natriuretic peptide; DFA, direct fluorescent antibody

Table 5. Comparison of patient outcomes.

OUTCOMES	SPORADIC CASES, 2010–2015 N=55 (%)	EPIDEMIC CASES, SUMMER 2015 N=35 (%)	P VALUE
Acute respiratory failure on ventilator	9 (16.4)	6 (17.1)	1.00
No. of inpatients	55 (100)	34 (97.1)	.34
No. of outpatients	0	1 (2.9)	.39
Intensive care unit admission	23 (41.8)	14/34 (42)	1.00
APACHE IV (mean±SD)	67.6±20.11	63.7±20.79	T=0.89; 0.38
Days in mechanical ventilation (mean±SD)	22±21.26	5.66±2.16	T=4.53; P=.0001
ICU length of stay (mean±SD)	9.56±11.44	5.15±3.41	T=2.22; P=.029
Hospital length of stay (mean±SD)	11.8±14.28	6.06±3.92	T=2.319; P=.02
Septic shock	3 (5.5)	5 (14.3)	.25
Hemodialysis requirement	5 (9.1)	3 (8.6)	1.00
Discharge to skill nursing facility	8 (14.5)	2 (5.7)	.31
Discharge home	46 (83.6)	26 (74.3)	.29
Transfer to acute care hospital	0	2 (5.7)	.15
Hospital mortality	1 (1.8)	3 (8.6)	.29

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ICU, intensive care unit.

Review of seasonal distribution of patients with legionellosis admitted over the past 5 years showed a mid-year clustering during summer (Figure 1), likely due to increased air-conditioning and cooling tower use, which promotes transmission of the disease. We also found that the overall number of patients with *Legionella*-associated pneumonia at our hospital has increased in the past 5 years (Figure 2), which corroborates a CDC report describing a significant increase in disease occurrence in the past 15 years.⁶

We performed a subgroup analysis of human immunodeficiency virus (HIV)-infected patients (n=12 SLD and n=7 ELD) in our cohort. We wanted to evaluate whether outcomes were different due to immunosuppressive state. Ten patients (53%) had a CD4⁺ count of less than 300 cells, and 6 patients (32%) had an undetectable viral load. The clinicoradiological presentation and outcomes were not different from the other non-HIV-infected patients.

Discussion

Few studies have compared different forms of *Legionella*-associated pneumonia. One comprehensive review discussing clinical comparative analyses of nosocomial and community-acquired pneumonias caused by *Legionella* concluded that demographic, clinical, laboratory, radiological, and outcome data in patients with different forms of the disease are similar.¹² Thus, identifying parameters unique to each type of *Legionella*-associated pneumonia is important for differentiating between sporadic and outbreak cases of the disease. To this end, we

reviewed records from all patients with legionellosis admitted to our hospital during the 2015 epidemic and compared them with the sporadic cases admitted over the past 5 years. The demographic features of our patients were similar in both groups.

Chronic lung disease, immunosuppression, smoking, and advanced age are known risk factors of *Legionella*-associated pneumonia. In our study population, low albumin on admission occurred more often in outbreak patients than in sporadic cases, supporting the idea that both immunosuppression and poor nutritional status predispose individuals to legionellosis. However, other patient habits and comorbidities, including diabetes mellitus, smoking, substance abuse, AIDS, and chronic lung diseases, were not uniquely associated with either form of the disease, which is in concordance with findings from prior studies.^{12,13}

Clinically speaking, the absence of classic respiratory symptoms on initial presentation in more than 50% of cases makes a specific diagnosis challenging to identify.¹⁴ We observed more patients presenting with only respiratory symptoms among the epidemic cases. Gastrointestinal system involvement, especially diarrhea, was the most common nonpulmonary condition in both groups, as similarly seen in previous reports.^{13,15,16} However, gastrointestinal symptoms were only present in 9% of patients in our study. Severe neurological complications may be associated with Legionnaires' disease,¹⁷ but none of our patients had focal neurological symptoms. The most common central nervous system symptom reported by our patients was

Table 6. Significant multivariate models of *Legionella* case type on several outcome variables.

	BETA	P _{2-TAILED}
Model 1: Hospital length of stay		
Adjusted R²=0.12; F=3.89; P=.006		
Epidemic cases	Decreased 7.00 days	.01
Pleural effusion	Increased 10.76 days	.00
Age	0.02	.82
Sex	-2.26	.37
Model 2: ICU length of stay		
Adjusted R²=0.17; F=2.53; P=.05		
Epidemic cases	Decreased 6.88 days	.01
Albumin level	0.23	.86
Age	0.00	.96
Sex	-2.28	.35
Model 3: Days in mechanical ventilation		
Adjusted R²=0.24; F=5.82; P=.00		
Epidemic cases	Decreased 13.16 days	.00
Age	0.09	.48
Sex	-2.65	.44
Model 4: Pleural effusion		
Nagelkerke R²=0.11; χ^2=6.33; P=.04		
Epidemic cases	1.17 (3.21)*	.05
Age	0.04 (1.04)*	.09

Abbreviation: ICU, intensive care unit.

*Values in parenthesis are Exp(B).

headache, followed by transient altered sensorium. The frequencies of other laboratory abnormalities in our patients were similar to those in other published studies.^{13,18} For example, hyponatremia and mild transaminitis occurred in more than 50% and 30% of patients, respectively, with no significant difference observed between patients with ELD and SLD.

Legionnaires' disease can be diagnosed by antigen detection or culture methods. A positive urine antigen is associated with more severe form of the disease. Although it is often the first diagnostic test performed, the test only detects *L pneumophila*.¹⁹ Currently, the urine antigen test is performed if suspected in parallel with respiratory cultures. In 2008, a multicenter study employed thorough testing for legionellosis in both outpatient and inpatient cases of community-acquired pneumonia. They identified *Legionella* as the causative agent in 3.8% of the cases and found an unacceptably high discordance rate with respect to initial antimicrobial treatment.²⁰ Sole screening with the urine antigen test may contribute to under-recognition of Legionnaires'

disease cases. The American Thoracic Society and the Infectious Disease Society of America recommend urine antigen testing in patients with community-acquired pneumonia who are not responding to treatment, those with severe forms of community-acquired pneumonia, patients with history of alcoholism, those aged more than 50 years, or patients admitted with pneumonia during an outbreak of Legionnaire' disease.²¹ All cases of nosocomial pneumonia are also recommended for urine antigen testing. In our study, all patients exhibited positive urine antigen tests, whereas only 2 bronchoalveolar lavage cultures and direct fluorescent antibody test among the patients were positive.

Chest radiological findings in patients with Legionnaires' disease are usually nonspecific. Most common findings are unilobar and multilobar infiltrates. Tan et al²² concluded that CXR in these patients is useful only for monitoring disease progression, not for diagnostic purposes. In our study, 11 patients had normal CXR on admission. Unilobar infiltrates, as described in previous reviews,^{23,24} were present in 59 (66%) patients.

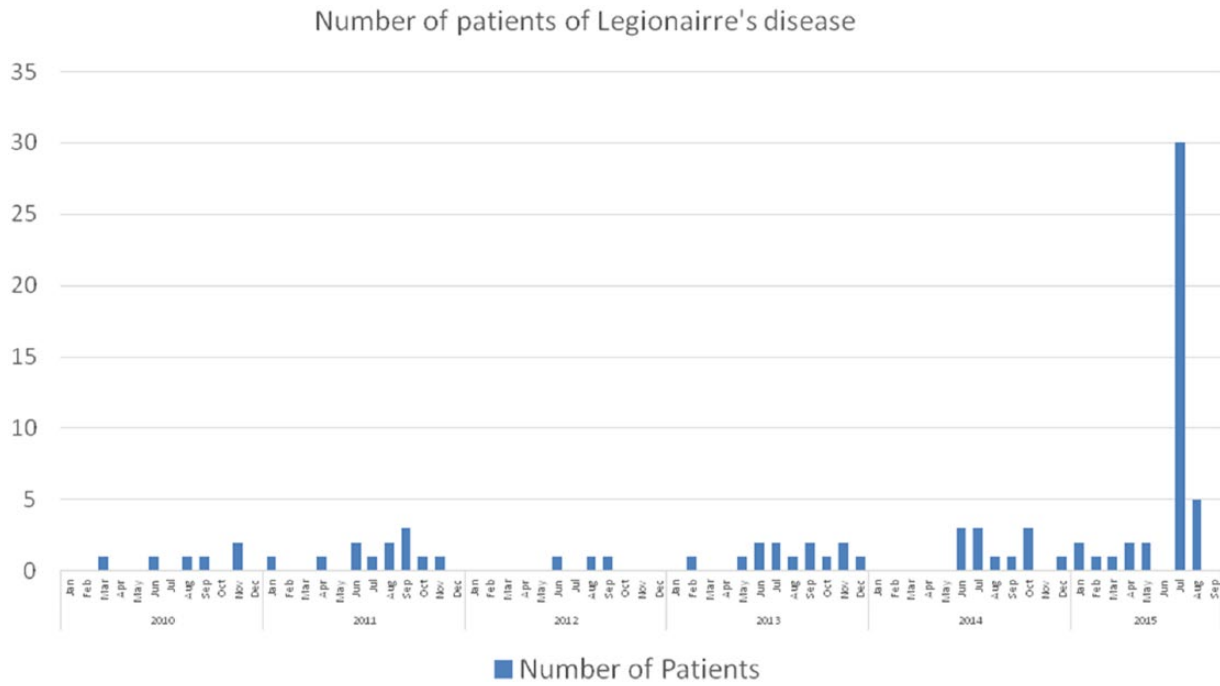


Figure 1. Seasonal distribution of Legionnaires' disease cases from 2010 to 2015.

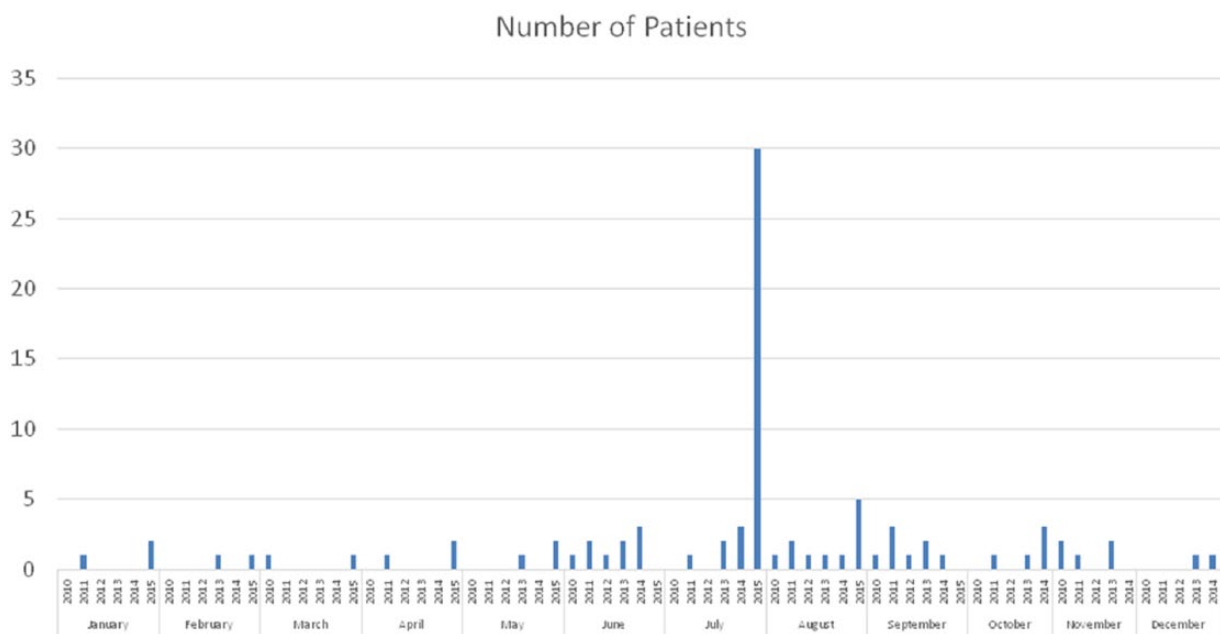


Figure 2. Annual occurrence of Legionnaires' disease cases from 2010 to 2015.

Respiratory failure and progression of CXR abnormalities are the most common complications in patients with Legionnaires' disease.²⁵ Fifteen patients in our cohort required endotracheal intubation and mechanical ventilation (n=9 SLD; n=6 ELD). Interestingly, patients with SLD required significantly longer time in mechanical ventilation and longer ICU and hospital LOS than patients with ELD. Severity of illness as evaluated by Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score was comparable between

groups, so it is difficult to assume that patients in the sporadic group waited longer to seek medical care leading to different outcomes. Other outcome measures, including discharge disposition and hospital mortality, were not significantly different between the 2 groups, possibly due to the small sample size of our study population.

Host cellular immunity plays a major role in eradicating and containing *Legionella*. Immunosuppression, as seen in transplant recipients, and certain chronic underlying diseases

are important risk factors for acquiring *Legionella* infection. Interestingly, although HIV infection is associated with impaired cellular immunity, few clinical reports have explored the effects of an individual's HIV infection on development of Legionnaires' disease. In described cases, the disease's severity varies independently from the patients' CD4⁺ counts.²⁶ In our study, we saw no differences in patients with and without HIV infection with respect to demographic features, clinical risk factors, presentation, and outcomes. Considering the nonspecific presentation and poor prognosis of Legionnaires' disease, a prompt diagnosis is very important. Coexisting opportunistic infections in immunosuppressed patients may also pose a diagnostic challenge.

There are some limitations in our study. First, this was a single-center study in an area where the characteristic of the population could differ from others; second, the diagnosis of *Legionella* infection was based mainly on urinary antigen test, so differentiation between sporadic and epidemic is not absolutely conclusive and "outbreak" group could have been contaminated with sporadic cases. However, our hospital is located in the epicenter of the outbreak, so it is likely that patients seen during July to August 2015 were part of the outbreak.

Conclusions

In conclusion, demographic and radiological features of sporadic and epidemic cases of Legionnaires' disease do not differ significantly, nor do certain comorbidities or chronic lung conditions predispose an individual to either form of the disease. A normal CXR does not preclude diagnosis of Legionnaires' disease. The index of suspicion should remain high for earlier recognition of legionellosis cases, and annual screening of health care and residential facilities should be promoted to avoid outbreaks of Legionnaires' disease.

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Author Contributions

All authors contributed substantially to the manuscript. HIRTH and LS made substantial contributions to conception and design, acquisition of data, and analysis of data. MK, FP, and GD-F made substantial contributions to conception and design of the study and revised the manuscript critically for important intellectual content. In addition, HIRTH, MK, and GD-F reviewed all the chest radiographs and gave final approval of the version to be published and agreed to be accountable for all aspects of the work regarding accuracy and integrity of the work.

Ethics Approval

The study was approved by the Institutional Review Board (IRB) at Bronx-Lebanon Hospital Center (IRB number: 09-10-15-06); patients' consents were waived.

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