Sporadic and Epidemic Community Legionellosis: Two Faces of the Same Illness

N. Sopena*, L. Force[#], M.L. Pedro-Botet*, P. Barrufet[#], G. Sauca[π], M. García-Núñez*, G. Tolchinsky*, J.A. Capdevila[#], M. Sabrià*.

*Infectious Diseases Unit of the University Hospital Germans Trias i Pujol in Badalona, Barcelona, Spain; [#]Internal Medicine Department and [π]Microbiology Laboratory of Hospital de Mataró, in Mataró, Barcelona, Spain.

Request for reprints or correspondence: Dra. Nieves Sopena, Unitat de Malalties Infeccioses. Hospital Universitari Germans Trias i Pujol. C/ Canyet, s/n. CP 08916 Badalona, Barcelona, Spain.

E-mail: nsopena.germanstrias@gencat.net

Phone number: 0034 93 4978826

Fax number: 0034 93 4978843

Short title: Sporadic vs. Epidemic Community Legionellosis

1

ABSTRACT: The presented study compares the risk factors, presentation and outcome of community-acquired *Legionella pneumophila* pneumonia for 138 sporadic-case patients (1994 to 2004) and 113 outbreak-case patients (2002) attended in two hospitals in Catalonia (Spain) since urinary antigen assays were adopted.

Univariate and multivariate analysis was performed to compare epidemiological and clinical features, blood chemistry values, radiological findings and outcome of sporadic and epidemic Legionnaires' disease.

Univariate analysis showed that male gender, chronic lung disease, human immunodeficiency virus infection and immunosuppressive therapy prevailed in sporadic cases. Presentation with respiratory symptoms, confusion and blood chemistry alterations such as hyponatremia, aspartate aminotransferase and blood urea nitrogen elevation, and pO$_2$ <60 mm Hg was more frequent in sporadic cases, while headache prevailed in outbreak cases. Sporadic cases had a greater delay in treatment, were more severe and had a worse outcome than epidemic cases. Multivariate analysis showed significant differences in gender, chronic lung disease, human immunodeficiency virus infection and headache.

The clinical and outcome differences between the two groups may be explained by the detection of milder forms of Legionnaires' disease, the earlier treatment and the lower severity of underlying disease in the outbreak cases.

Introduction

The incidence of Legionnaires' disease has increased in the last decade since the introduction of urinary antigen immunoassays [1,2]. This test accounts for most of the diagnostics due to its high sensitivity and to be easy to perform [3]. *Legionella pneumophila* has become one of the leading causes of community-acquired pneumonia in adults, accounting for 6-14% of cases requiring hospitalization in recent studies [4,5]. Legionnaires' disease occurs sporadically and in outbreaks, with the sporadic form representing 65-82% of the cases [1,2,6]. Nevertheless, the number of confirmed community outbreaks, including several with more than 100 cases, has increased in recent years due to the use of *Legionella* antigenuria [2,6]. Routine testing for *Legionella* urinary antigen has increased the number of diagnostics of Legionnaires' disease, has allowed earlier diagnosis and treatment, greatly improving the prognosis of Legionnaires' disease [7]. This has been particularly true for milder cases, mainly in the outbreak setting [8]. However, most of knowledge on risk factors, clinical presentation and outcome of community-acquired Legionnaires' disease are based in studies performed before the routine urinary antigen testing [9,10]. Moreover, recent community outbreaks had contributed to the better understanding of Legionnaires' disease in this setting [11-13].

There are no comparative studies of the characteristics of sporadic and outbreak-related Legionnaires' disease. In theory, the risk factors and the clinical presentation of epidemic Legionellosis may differ from those of sporadic forms because of the higher attack rate and the diagnosis of a proportion of milder cases that may go undetected in a non-outbreak setting. During an outbreak, physicians' greater awareness of the range of clinical presentations may promote earlier diagnosis and treatment and modify the outcome of Legionellosis [8,9]. Thus, the objective of our

study was to compare the risk factors, the clinical presentation and the outcome of community-acquired Legionnaires' disease, with respect to sporadic and outbreak context in the years since we were able to implement antigenuria immunoassays.

Patients and methods

Setting

From 1994 to the present we have prospectively studied the cases of community-acquired Legionnaires' disease admitted to the Hospital Germans Trias i Pujol, a 650-bed tertiary center located in Badalona (north Barcelona), that serves an urban area of 700,000 inhabitants with 22,000 admissions annually. The Legionella urinary antigen assay has been used in the diagnosis of community-acquired pneumonia in our hospital since 1994. Some aspects of this study have been published [6,14].

Between July and August 23, 2002, an explosive outbreak of community-acquired Legionnaires' disease developed in Mataró, a manufacturing center and seaport northeast of Barcelona. This incident involved at least 154 persons, 113 with definitive (confirmed) Legionnaires' disease [15].

Patients

This study included 138 persons in whom sporadically community-acquired Legionnaires' disease was prospectively diagnosed from 1994 to 2004 in Hospital Germans Trias i Pujol, and all 113 persons in whom *Legionella pneumophila* pneumonia was conclusively diagnosed with in the Mataró outbreak.

A confirmed case of Legionnaires' disease was defined as a case of pneumonia with laboratory evidence of acute infection with Legionella including isolation from respiratory samples, a fourfold o higher rise in antibody titters from

1:128 against *Legionella pneumophila* sg. 1-6 by immunofluorescence (IF) in paired acute and convalescent phase serum specimens or detection of *L. pneumophila* sg. 1 in urine by enzyme-linked immunoabsorbent assay (ELISA) or immunochromatographic test (ICT).

Microbiological diagnosis

Urinary antigen detection of *Legionella pneumophila* serogroup 1 by ELISA or ICT was positive in 117 of the 138 sporadic cases and in 110 of the 113 outbreak cases. *L. pneumophila* was isolated from sputum of 10 sporadic cases and 10 outbreak cases. Seroconversion was detected in 43 (31.1%) sporadic cases and in 24 (21.2%) outbreak cases. Some cases were diagnosed by more than one of the mentioned tests.

Variables studied

We studied the following variables: 1) demographic (age and gender); 2) individual risk factors (including cigarette smoking and alcohol abuse), 3) underlying diseases such as chronic lung disease, chronic heart disease, diabetes mellitus, liver cirrhosis, neoplasm, chronic renal failure and human immunodeficiency virus (HIV) infection, 4) pharmacological immunosuppressive therapy (corticosteroids or chemotherapy), 5) clinical features, laboratory data and radiological findings on presentation, 6) Fine score risk category, need for hospital and intensive care unit admission, and delay in treatment, 7) type, duration and efficacy of antibiotic treatment, and 8) outcome (time to apyrexia, and/or complications, cure, recurrence or death related to pneumonia).

Patients in Fine score risk classes I and II are defined as having sufficiently low risk for death and other adverse medical outcomes that physician can consider outpatient treatment [16]. Delay in treatment was defined as the number of days from the onset of illness (fever, if present) to administration of appropriate antibiotic therapy. Time to apyrexia was defined as hours of fever following the initiation of appropriate antibiotic treatment. Antibiotic treatment was considered adequate if it included a quinolone or a macrolide. Death was considered to be related to pneumonia when it was directly caused by pneumonia or its complications.

Statistical methods

Univariate analysis was performed using the Student t test comparing quantitative variables and the Chi-square test for qualitative variables, using SPSS 11.5 for Windows. In all cases, significance was defined as a p value ≤ 0.05. All variables found to be significant on univariate analysis, and all clinically important variables, were included in the multivariate logistic regression analysis.

Results

Demographic data and risk factors

Male gender, some underlying diseases (including chronic lung diseases and HIV infection), and a history of immunosuppressive therapy (mainly with corticosteroids), were significantly more frequent in sporadic cases than in outbreak cases. A history of alcohol abuse was also more frequent in sporadic cases, although this variable did not achieve statistical significance on univariate analysis. On the other hand, 113 (81.9%) of the sporadic cases and 92 (81.4%) of the outbreak cases

had known individual risk factors for Legionnaires' disease, including cigarette smoking, alcohol abuse and/or underlying diseases (Table 1).

Clinical presentation, analytical data and radiological findings

Clinical presentation with respiratory symptoms such as cough, expectoration, thoracic pain and dyspnea as well as confusion prevailed in sporadic cases. Headache was significantly more frequently observed in outbreak cases (Table 2). Blood chemistry alterations on presentation such as hyponatremia (Na <130 mmol/L), aspartate aminotransferase (AST) elevation, an increase in blood urea nitrogen (BUN) ≥13 mmol/L and a pO2 <60 mm Hg were significantly more frequent in sporadic cases. Presentation with X-ray evidence of bi-lobar or multi-lobar infiltrates on chest radiograph was also significantly more frequent in sporadic cases than in outbreak cases: 19.1% *vs*. 9.3%, respectively (Table 2).

Treatment and outcome

Placement in Fine score risk class III, IV or V was significantly more frequent for patient in sporadic cases than in outbreak cases. Hospital admission was needed for 138 sporadic cases (96.4%), compared with 68 outbreak cases (60%) and intensive care unit (ICU) admission was required 16.1% of the sporadic cases vs. 4.4% of the cases related to the outbreak (Table 3).

The delay before receiving adequate treatment was significantly longer in sporadic cases than in outbreak cases. Although significantly more patients were treated with macrolides than with quinolones, we did not find a significant difference between the percentages of sporadic and outbreak patients who received a course of appropriate

treatment. However, the mean duration of treatment was longer for outbreak patients (Table 3).

Regarding outcome, the incidence of complications such as respiratory failure, need of mechanical ventilation, acute renal failure and septic shock was significantly higher in sporadic cases compared with outbreak cases. Recurrences occurred in 2 sporadic cases. Decline to death occurred in 5.8% of sporadic cases compared with 1.8% in the outbreak cases (Table 3).

On multivariate analysis only the variables gender, chronic lung disease, HIV infection and headache remained significant (Table 4).

Discussion

To our knowledge, this is the first study of *Legionella* pneumonia to compare sporadic and outbreak presentation since the advent of antigenuria testing. The results of this study show that patients with sporadic community-acquired LD were more frequently males and had a higher prevalence of chronic lung disease, HIV infection and corticosteroid therapy compared with outbreak-associated cases. Presentation with respiratory symptoms, confusion and blood chemistry alterations such as hyponatremia <130 mmol/L, AST elevation, BUN increase ≥13 mmol/L and pO_2 <60 mm Hg was more frequent in sporadic cases, while headache prevailed in outbreak cases. Finally, sporadic Legionnaires' disease was more severe and had a worse outcome than epidemic disease.

Several risk factors for acquisition of Legionnaires' disease have been identified in observational and case-control studies and include advanced age, male sex, cigarette smoking, alcohol abuse and underlying diseases such as chronic lung disease, neoplasm, diabetes, HIV infection and immunosuppressive therapy,

especially with corticosteroids [9,10,12,13,17]. Similar to other studies, most of the sporadic and epidemic cases in this study had one or more of the known risk factors for Legionellosis, including cigarette smoking, alcohol abuse and underlying diseases [11,13,18-22]. This fact underlines the importance of the susceptibility of the population even with the higher degree of exposure to the source of *Legionella* that occurs in an outbreak setting. In particular, nearly half of the patients in the two groups were smokers, a fact that emphasizes the increased susceptibility to Legionnaires' disease in persons with compromised mucociliar clearance in the tracheobroncheal tree [12,17]. However, it is of note that only half of the patients in the two groups had underlying diseases and were older than 60 years. This fact is in contrast with the high prevalence of advanced age or underlying diseases observed in *S. pneumoniae* pneumonia, thereby emphasizing the importance of general immunity in pneumococcal infection [23,24].

The higher frequency of males in sporadic cases observed in our study may be explained by the higher prevalence of some underlying risk factors. It has been argued that the greater prevalence of cigarette smoking and its complications in men may predispose *Legionella* infection by deterioration of the respiratory mucosa [17]. On the other hand, the higher frequency of chronic pulmonary disease, HIV infection and immunosuppressive therapy observed in sporadic cases may at least partly account for the greater susceptibility of these patients to *Legionella* infection, even with exposure to a small inoculum [18,25]. Moreover, one might expect that patients with severe underlying diseases will be referred more frequently to the hospital for diagnosis of sporadic community-acquired pneumonia.

In this study, we observed a more atypical presentation of Legionnaires' disease in the outbreak cases, with lower incidence of respiratory symptoms and

higher reporting of headache. The classical differential clinical manifestations (extrarespiratory symptoms) and analytical data (hyponatremia and increased AST and creatin kinase) for suspected Legionellosis are of questionable value considering their low sensitivity and specificity [4,26,27]. However, some authors maintain that these data may increase the level of suspicion for Legionnaires' disease, particularly for persons who go to the physician late in the course of the disease [27]. The higher frequency of respiratory symptoms, confusion, hyponatremia, hipoxemia and BUN increase in sporadic cases may be explained by a higher incidence of underlying pulmonary disease and the greater severity of Legionnaires' disease [28]. As observed in other studies, the high frequency of AST elevation in both groups (48.8% of the sporadic cases, and 31.3% of the outbreak cases) is noteworthy because the occurrence is lower in community-acquired pneumonia caused by other microorganisms [26,27].

The mortality of sporadic and epidemic community-acquired Legionellosis has decreased in the last decade, due partly to urinary antigen testing, which allows early diagnosis and the detection of milder forms and partly to the use of more active antibiotics [7,8,14,20,29]. Sporadic Legionnaires' disease was more severe, according to the higher Fine score, the more extensive radiographic abnormalities on presentation, and the higher frequencies of complications and hospital or ICU admission. These differences may be explained by the higher frequency of severe underlying diseases, the underdiagnosis of sporadic cases with only the more severely ill patients being detected, and maybe the greater delay in treatment of sporadic cases compared with outbreak-associated cases. The frequency of adequate treatment was similar in the two groups, although the cases of sporadic Legionellosis were more often treated with quinolones which have been reported to

be produce a faster clinical response than the older macrolides [14,19]. The low mortality observed in the sporadic cases in this study compared with the previous literature may be explained by the early diagnosis and adequate treatment of these cases [7]. The lower mortality of the outbreak cases compared with sporadic cases in this study (1.8 *vs.* 5.9%), agrees with other reports of sporadic Legionellosis and community outbreaks [19]. The diagnosis of milder forms of Legionnaires' disease and the early treatment in the outbreak setting may justify these differences [14]. The lack of statistical significant differences may be due to the lower number of cases.

Our study has some limitations. The fact that the sporadic and the outbreak cases were studied in two different centers and by two different investigators at different times may represent a bias, especially in regard to risk factors and clinical presentation. However, the investigators followed the same diagnostic protocol, evaluated the same clinical data and used the same definitions of risk factors. Moreover, less severe cases of community-acquired Legionellosis not requiring hospital care may have been under-reported in the sporadic case series. Consequently, the characteristics observed in this study can not be completely extrapolated to other settings. Different degrees of virulence have been reported among *L. pneumophila* strains [30], but this aspect was not analyzed in our study.

Several conclusions may be made. Firstly, recognized risk factors for Legionellosis are usually necessary for the appearance of the disease, even in an outbreak setting. Secondly, differences found between sporadic and epidemic community-acquired Legionnaires' disease regarding risk factors, clinical presentation and outcome may be explained by some characteristics of the cases related to the outbreak: the detection of milder forms of Legionellosis, the lower severity of underlying disease and the earlier treatment. Finally, the uncharacteristic

presentation of both sporadic and outbreak Legionnaires' disease makes it necessary to take this disease into account and thereby perform adequate diagnostic tests.

References

1. Joseph CA on behalf of the European Working Group for Legionella Infections. Legionnaires' disease in Europe 2000-2002. *Epidemiol Infect* 2004;132:417-424.

2. Alvarez J, Oyaga N, Escofet N, Codony F, Orcau A, Oliva JM. Community-acquired legionellosis in the Barcelona region between 1992 and 1999: epidemiological characteristics and diagnostic methods. *Med Clin (Barc)* 2001;117:485-496.

3. Den Boer JW, Yzerman EPF. Diagnosis of *Legionella* infection in Legionaires' disease. *Eur J Clin Microbiol Infect Dis* 2004;23:871-878.

4. Gupta SK, Sarosi GA. The role of atypical pathogens in community-acquired pneumonia. *Med Clin North Am* 2001;85:1349-1365.

5. Sopena N, Sabrià M, Pedro-Botet ML, Manterota JM, Matas L, Domínguez J, Modol JM, Tudela P, Auxina V, Foz M. Prospective study of community-acquired pneumonia of bacterial etiology in adults. *Eur J Clin Microbiol Infect Dis* 1999;18:852-58.

6. Alvarez J, Domínguez A, Sabrià M, Ruiz L, Torner N, Caylà J, Barrabeig I, Sala MR, Godoy P, Camps N, Minguell S and the Working group of communicable diseases of the RCESP. Community outbreaks of legionellosis in Catalonia, 1990-2003 [abstract 1324]. In: Abstracts of the 15th European Congress of Clinical Microbiology and Infectious Diseases (Copenhaguen,

Denmark). European Society of Clinical Microbiology and Infectious Diseases 2005:424.

7. Benin AL, Benson RF, Bessser RE. Trends in Legionnaires' disease, 1980-1998. Declining mortality and new patterns of diagnosis. *Clin Infect Dis* 2002;35:1039-1046.

8. Formica N, Yales M, Beers M, Carnie J, Hogg G, Ryan N, Tallis G. The impact of diagnosis by *Legionella* urinary antigen test on the epidemiology and outcomes of Legionnaires' disease. *Epidemiol Infect* 2001;127:275-280.

9. Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease: risk factors for morbidity and mortality. *Arch Intern Med* 1994;154:2417-2422.

10. Straus WL, Plouffe JF, File TM Jr, Lipman HB, Hackman BH, Salstrom SJ, Benson RF, Breiman RF. Risk factors for domestic acquisition of legionnaires disease. Ohio Legionnaires Disease Group. *Arch Intern Med* 1996;156:1685-1692.

11. García-Fulgueiras A, Navarro C, Fenoll D, García J, González-Diego P, Jiménez-Buñuales T, Rodríguez M, Lopez R, Pacheco F, Ruiz J, Segovia M, Baladrón B and Carmen Pelaz. Legionnaires' disease outbreak in Murcia, Spain. *Emerg Infect Dis* 2003;9:915-921.

12. Greig JE, Carnie JA, Tallis GF, Ryan NJ, Tan AG, Gordon IR, Zwolak B, Leydon JA, Guest CS, Hart WG. An outbreak of Legionnaires' disease at the Melbourne Aquarium, April 2000: investigation and case-control studies. *MAJ* 2004;180:566-572.

13. Den Boer JW, Yzerman EP, Schellekens J, Lettinga KD, Boshuizen HC, Van Steenbergen JE, Bosman A, Van den Hof S, Van Vliet HA, Peeters MF, Van Ketel RJ, Speelman P, Kool JL, Conyn-Van Spaendonck MA. A large outbreak

of Legionnaires' disease at a flower show, the Netherlands, 1999. *Emerg Infet Dis* 2003;53:77-80.

14. Sabrià M, Pedro-Botet ML, Gomez J, Sabria M, Pedro-Botet ML, Gomez J, Roig J, Vilaseca B, Sopena N, Banos V and the Legionnaires Disease Therapy Group. Fluoroquinolones versus macrolides in the treatment of legionnaires's disease. *Chest* 2005; 128:1401-5.

15. Barrufet-Barqué MP, Sauca-Subias G, Force-Sanmartí L, Barrufet-Barque MP, Sauca-Subias G, Force-Sanmartin L, Felip-Benach A, Martinez-Perez E, Capdevila-Morell JA. An outbreak of Legionnaires' disease in Mataró (Spain). *Med Clin (Barc)* 2006;126:178-182.

16. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243-250.

17. Edelstein PH, Cianciotto NP. Legionella. *In:* Mandell GL, Benett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 16th Ed. Elsevier Churchill Livingstone, New York, 2005; pp. 2711-2724.

18. Lieberman D, Porath A, Schlaeffer F, Liebermana D, Boldur I. Legionella species community-acquired pneumonia. A review of 56 hospitalised adult patients. *Chest* 1996;109:1243-49.

19. Mykietiuk A, Carratalà J, Fernandez-Sabe N, Dorca J, Verdaguer R, Manresa F, Gudiol F. Clinical outcomes for hospitalized patients with Legionella pneumonia in the antigenuria era: the influenza of levofloxacin therapy. *Clin Infect Dis* 2005;40:794-99.

20. Fernandez JA, López P, Orozco D, Merino J. Clinical study of an outbreak of Legionnaires' disease in Alcoy, Southeastern Spain. *Eur J Clin Microbiol Infect Dis* 2002;21:729-35.

21. Jericó C, Nogués X, Santos MJ, Félez M, Garcés JM, Mariñosa M, Sanz X. *Legionella pneumophila* pneumonia community epidemic outbreak in Barcelona: "The Barceloneta outbreak" Effect on early diagnosis and treatment. *Rev Clin Esp* 2004;204:70-74.

22. Monforte R, Estruch R, Vidal J, Mensa J, Marco F, Cervera R, Tarrero I, Jiménez de Anta MT, Urbano A. A community outbreak of Legionnaires' disease in Barcelona: clinical and microbiological study. *Med Clin (Barc)* 1989;93:521-25.

23. Sopena N, Pedro-Botet ML, Sabrià M, García-Parés D, Reynaga E, García-Nuñez M. Comparative study of community-acquired pneumonia caused by *Streptococcus pneumoniae, Legionella pneumophila or Chlamydia* pneumoniae. *Scand J Infect Dis* 2004;36:330-34.

24. Watanakunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital, 1992-1996. A detailed analyisis of 108 cases. *Arch Intern Med* 1997;157:1965-71.

25. Pedro-Botet ML, Sabrià M, Sopena N, et al. Legionnaires' disease and HIV infection. *Chest* 2003;124:543-47.

26. Sopena N, M Sabrià-Leal, ML Pedro-Botet, Padilla E, Domínguez J, Morera J, Tudela P. Comparative study of the clinical presentation of *Legionella* pneumonia and other community-acquired pneumonias. *Chest* 1998;113:1195-200.

27. Mulazimoglu L and Yu VL. Can Legionnaires Disease be diagnosed by clinical criteria?. A critical review. *Chest* 2001;120:1049-53.

28. Vergis EN, Akbas E, Yu VL. Legionella as a cause of severe pneumonia. *Sem Resp Crit Care Med* 2000;21:295-304.

29. Health CH, Grove DI, Looke DFM. Delaying appropriate therapy of Legionella pneumonia associated with increased mortality. *Eur J Clin Microbiol Infect Dis* 1996;15:286-90.

30. Swanson MS, Hammer BK. *Legionella pneumophila* pathogenesis: a fateful journey from amoebae to macrophages. *Annu Rev Microbiol* 2000;54:567-613.

TABLES

Table 1. Demographic data and risk factors.

VARIABLE	Sporadic cases No. (%) N=138	Outbreak cases Nº (%) N=113	P value
Age (yr) (mean, SD)	56.6 ±15.5	59.5 ±16.6	0.1
Age >60 yr	60 (43.5)	59 (52.2)	0.2
Sex (male)	113 (81.9)	73 (64.6)	0.002*
Individual risk factors	113 (81.9)	92 (81.4)	1
Cigarette smoking	67 (48.6)	51 (48.1)	1
Alcohol abuse	37 (26.8)	17 (16.5)	0.08
Underlying diseases	76 (55.1)	56 (49.6)	0.4
Chronic lung disease	27 (19.6)	11 (9.7)	0.04*
Chronic heart disease	17 (12.4)	13 (11.5)	0.9
Diabetes	21 (15.2)	27 (23.9)	0.1
Liver cirrhosis	8 (5.9)	10 (8.8)	0.5
Neoplasm	10 (7.3)	10 (8.8)	0.8
HIV infection	16 (11.6)	2 (1.8)	0.003*
Chronic renal failure	3 (2.2)	2 (1.8)	0.8
Corticoids treatment	8 (5.8)	0	0.009*

*Statistical significance in univariate analysis

Table 2. Clinical, analytical and radiological presentation.

VARIABLE	Sporadic cases No. (%) N=138	Outbreak cases No. (%) N=113	P value
Fever	134 (97.1)	112 (99.1)	0.4
Days of fever (mean, SD)	4.3±2.6	4.04±1.9	0.4
Cough	97 (70.3)	58 (51.8)	0.004*
Expectoration	54 (39.1)	15 (14)	<0.001*
Thoracic pain	32 (23.2)	14 (12.6)	0.04*
Dyspnea	62 (44.9)	24 (28.6)	0.02*
Headache	35 (25.5)	61 (56.5)	<0.001*
Confusion	23 (16.7)	8 (7.5)	0.04*
Diarrhea	29 (21)	21 (18.9)	0.8
WBC/mm^3 >12000	64 (48.1)	48 (43.6)	0.6
Na <130 mmol/L	27 (21.3)	7 (6.7)	0.003*
CK >232 U/L[#]	30 (27.5)	5 (13.5)	0.1
GOT >37 U/L	62 (48.8)	30 (31.3)	0.01*
BUN ≥13 mmol/L	18 (14.6)	2 (2)	0.001*
PO2 <60 mm Hg	60 (45.8)	35 (31)	0.02*
≥2 lobes x-ray extension	26 (19.1)	10 (9.3)	0.04*

[*] Statistical significance in univariate analysis
[#] CK: creatinin kinase

Table 3. Treatment and outcome.

VARIABLE	Sporadic cases No. (%) N=138	Outbreak cases No. (%) N=113	P value
Fine score classes III-V	48 (57.8)	34 (41)	0.04*
Hospital admission	138 (96.4)	68 (60)	0.003*
ICU admission	22 (16.1)	5 (4.4)	0.004*
Delay in treatment (d) (mean, SD)	5± 2.8	4.2±2.4	0.02*
Adequate antibiotic treatment	124 (97.6)	113 (100)	0.2
Days of treatment (d) (mean, SD)	16.9±6.1	14.76±2.5	0.001*
Treatment with macrolides vs	77 (68.1)	109 (97.3)	0.001*
Quinolones	47 (31.9)	4 (2.7)	
Time to apyrexia (hr) (mean, SD)	59.7± 67.4	57.8± 30.8	0.80
Complications	75 (54.3)	37 (32.7)	0.001*
-Respiratory failure	70 (50.7)	37 (32.7)	0.006*
-Mechanical ventilation	15 (10.9)	4 (3.5)	0.03*
-Acute renal failure	10 (7.4)	0	0.002*
-Septic shock	11 (8)	2 (1.8)	0.04*
Evolution			
Cure	128 (92.6)	111 (98.2)	
Death related to pneumonia	8 (5.9)	2 (1.8)	0.1
Recurrence	2 (1.5)	-	

*Statistical significance in univariate analysis

Table 4. Multivariate analysis.

Variable	P value	OR	CI 95%
Sex (male)*	0.05	2.56	1.32-4.94
Chronic lung disease*	0.01	2.67	1.20-5.94
HIV infection*	0.004	9.75	2.09-45.48
Headache#	0.006	2.79	1.34-5.80

OR: odds ratio, CI: confidence interval

*Independent risk factors for sporadic Legionnaires' disease

#Independent risk factor for epidemic Legionnaires' disease