

Community-Acquired *Legionella* Pneumonia in HIV-Infected Adult Patients: A Matched Case-Control Study

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Abstract

We investigated whether the clinical presentations and outcomes (length of hospital stay [LOS], intensive care unit[ICU] admission, 30-day mortality) of *Legionella* pneumonia in HIV-infected patients were comparable to those without HIV infection.

Clinical presentation and outcomes in HIV-infected patients with *Legionella* pneumonia did not differ from patients without HIV infection.

Keywords: *Legionella* pneumonia; HIV-infected patients; community-acquired pneumonia

Background

Community-acquired pneumonia (CAP) remains a major complication in HIV- infected patients, even in the era of combined antiretroviral therapy (ART)[1,2]. Legionnaires' disease (LD) is often present as a severe form of pneumonia and is caused by the intracellular pathogen *Legionella pneumophila*, which has an atypical presentation with nonspecific radiographic patterns and clinical presentation [3]. The presence of extra-pulmonary complications that could affect the central nervous system, heart, liver, gastrointestinal tract, and kidney are the main differences from the typical presentation of bacterial pneumonia [4].

Although pneumonia caused by *Legionella* is more common in patients with immunosuppressive conditions, it has rarely been described in HIV-infected patients [5]. *Legionella pneumophila* accounts for approximately 20% of all adult HIV-associated pneumonias, compared with 10% to 15% in the general population [6]. Most information on this population is based on case reports published between 1994 and 2001 [7-9]. However, in some studies performed between 1983 and 2001 [6,9,11], it has been observed to occur up to 40 times more frequently in patients who develop *acquired immune deficiency syndrome* (AIDS) than in the general population [10]. Furthermore, some of these studies suggest that pneumonia caused by *L. pneumophila* tends to present with more severe clinical features in HIV-infected patients and requires special attention [6,9,11]. Given the conflicting information on clinical outcomes of *Legionella* pneumonia in HIV-infected patients, the aim of this study was to investigate whether the clinical presentations and outcomes (length of hospital stay [LOS], intensive care unit [ICU] admission, and 30-day mortality) of *Legionella* pneumonia in HIV-infected patients were comparable to those seen in non-HIV-infected patients, using a case-control design.

Methods:

We performed a multicenter observational case-control study in three Spanish hospitals; two in Barcelona and one in Badalona. Case patients were defined as HIV-infected adults (age, ≥ 18 years) with a diagnosis of community-acquired *Legionella* pneumonia between 1994 and 2016. Three control cases of *Legionella* pneumonia patients without HIV infection were selected for each case patient. Matched criteria were: similar age (± 10 years) and same center, sex, baseline pneumonia severity index (PSI) score of I-III or IV-V, and pneumonia diagnosis in the same calendar period ± 1 year. Study outcomes were: ICU admission, LOS, and 30-day mortality.

The study was approved by the ethics committee of our institution (no. 2009/5451). The need for written informed consent was waived due to the non-interventional design.

Results:

CAP caused by *Legionella pneumophila* was diagnosed in 32 consecutive cases (HIV infection) and 96 controls (non-HIV infection) (Figure 1). It thus accounted for 128 (4%) of all episodes of CAP diagnosed in the three hospitals and 32 (6%) of the 565 HIV-infected patients with CAP. Of the 32 cases included, 25 (78%) were males, with a median (IQR) age of 40.0 (38; 50) years. Data on the probable route of exposure were available in 53% of cases. HIV infection was acquired by homosexual, intravenous drug use and heterosexual transmission in 4 (24%), 6 (35%), and 7 (41%) cases, respectively. Twenty-three cases (74%) were on ART at the time of diagnosis. ART regimens were based on non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and other regimens in 3 (19%), 3 (19%), 9 (56%), and 8 (34%) cases, respectively. Thirteen of these 23 patients (54%) had an undetectable HIV RNA viral load in plasma (< 200 copies/mL). The median (IQR) CD4+ T cell count before diagnosis

was 335 (215; 500)/mm³, two cases received PCP prophylaxis (22%) and an AIDS-defining disease was diagnosed in 1 case (3%). Most patients (84%) were classified as low risk (PSI risk class I-III). Ten patients (31%) presented co-infection with HCV, and 1 patient (3%) had HBV co-infection. Three patients (9%) were admitted to the ICU and two of these (6%) required mechanical ventilation. The median LOS was 7.0 (4.0; 11.0) days. The overall 30-day mortality was 3%.

Baseline characteristics comparing cases and controls are given in Table 1 and did not differ significantly between groups. Case patients were younger than controls and had a higher rate of HCV co-infection and neurological disease. One hundred and twenty-four patients (98%) were diagnosed by urinary antigen test and 8 patients (16%) were diagnosed with sputum culture.

The most frequent empirical antibiotic treatment were β -lactam plus macrolide (13 cases [41%] vs. 33 controls [34%]; $p=0.52$), macrolide monotherapy (8 cases [25%] vs. 26 controls [27%]; $p>0.99$), fluoroquinolone monotherapy (9 cases [28%] vs. 19 controls [20%]; $p=0.32$), β -lactam plus fluoroquinolones (0 cases [0%] vs. 8 controls [8%]; $p=0.20$), and macrolide plus fluoroquinolone (2 cases [6%] vs. 5 controls [5%]; $p>0.99$), without differences between cases and control patients. Patients in the macrolide monotherapy group received erythromycin (7 cases [22%] vs. 20 controls [21%]; $p=0.90$), azithromycin (1 case [3%] vs. 3 controls [3%]; $p>0.99$) or clarithromycin (0 cases [0%] vs. 3 controls [3%]; $p=0.57$).

ICU admission (3 cases [9%] vs. 15 controls [16%]; $p=0.56$), the need for mechanical ventilation (2 cases [6%] vs. 6 controls [6%]; $p>0.99$), LOS (7 [4; 11] days in the case group vs. 6 [4; 9] days in the control group; $p=0.39$), and 30-day mortality (1 case [3%] vs. 3 controls [3%]; $p>0.99$) were similar between cases and controls.

In a multivariate logistic regression analysis, previous antibiotic treatment, PSI risk class IV-V, PaO₂/FiO₂ <250, the presence of pleural effusion, and the presence of multilobar involvement were associated with ICU admission (area under the receiver operating characteristic [ROC] curve of the predictive model was 0.89 [95% CI, 0.81 to 0.97]). In a multivariate analysis, multilobar involvement and a white blood cell count <10 x10⁹ cell/L were associated with prolonged LOS (>6 days; cut-off value the median value of LOS) (area under the ROC curve of the predictive model was 0.68 [95% CI, 0.57 to 0.80]). HIV infection was not associated with ICU admission or increased LOS in the univariate analyses, even after adjustments for case patient and potential confounding factors in the multivariate analyses. In a univariate analysis of HIV-infected patients, we did not observe a relationship between ICU admission or LOS and to be on ART, to have a plasma HIV RNA viral load <200 copies/mL or a CD4+ cell count <200 cells/μl (data not shown).

Discussion:

To the best of our knowledge, this is the first case-control study performed on HIV-infected patients with community-acquired *Legionella* pneumonia, and our main conclusion is that HIV-infected individuals presented neither a more severe disease nor a worse clinical outcome than matched HIV-negative control patients. An interesting observation in our study is that we did not find differences in antimicrobial treatment between cases and controls. The similarities that we observed between HIV-infected and uninfected patients as regards clinical outcomes of *Legionella* pneumonia indicate that *Legionella* infection affected patients with correct immunological status more frequently.

Information on *Legionella* infection and prognosis in HIV-infected patients is controversial. Some studies prior to the advent of ART therapy reported a worse prognosis in HIV patients with *Legionella* pneumonia, with a higher number of complications; however, other studies,

especially in the post-ART era, showed few significant differences. In our study, HIV infection was well controlled in most cases. However in an study of *Legionella* disease in HIV-infected patients carried out in the pre-ART era (1983-2003), the immunological characteristics were similar to those recorded in our population [1]. In all likelihood, HIV-infected patients with poor immune status do not develop *Legionella* infections due to the cotrimoxazole prophylaxis that they receive.

The main limitation of our study was that it was conducted over a long period of time. However, protocols and microbiological procedures have not substantially changed in this time. A second limitation is that although we found no differences in outcomes for case patients *versus* control patients, we were only able to analyze 32 cases, and this sample size may have led to a large type II error. Nonetheless, our sample size was larger than that of many previous studies of *Legionella* pneumonia in HIV-infected patients reported in the literature. Third, we did not have data about time from onset of symptoms to *Legionella* pneumonia diagnosis and the start of target antibiotic therapy. However, all cases in our study received an adequate empiric antibiotic therapy. Fourth, even though we included consecutive cases, 54% had virological suppression, and because of the small number of cases included our results cannot be extrapolated to non-suppressed HIV-infected patients. Five, despite that *L. pneumophila* serotype 1 has been associated with 90 % of cases reported in Europe and Catalonia the region where our study was carry out was related to several outbreaks of *Legionella*, it is possible to misdiagnosis other species or serotypes of *Legionella* since urinary antigen test is insensitive for the detection of non-Pontiac monoclonal subtypes of *L. pneumophila* serogroup 1, and extremely insensitive for the detection of other *L. pneumophila* serogroups and *Legionella* species.

In conclusion, this case-control study describes a subpopulation of HIV-infected patients with *Legionella* pneumonia in whom clinical presentation and outcomes did not differ from those

for patients with similar clinical characteristics but without HIV infection. The management of these HIV-infected patients should be the same as for HIV-uninfected individuals and should be included in CAP management guidelines.

Acknowledgments

We are indebted to all medical and nursing colleagues for their assistance and cooperation in this study. We thanks to Michael Maudsley by his assistance in language review.

Financial support: This study was supported by Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028), and 2009 Support to Research Groups of Catalonia 911; IDIBAPS. Dr Cilloniz is the recipient of a Postdoctoral Grant (Strategic plan for research and innovation in health-PERIS 2016-2020). JMM received a personal 80:20 research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain during 2017–19.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Appendix:

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Table 1. Baseline characteristics of the entire population

Variables	Case patients	Control patients	P value
	(HIV infection)	(non-HIV infection)	
	(n = 32)	(n = 96)	
Male, n (%)	25 (78)	77 (80)	0.80
Current smoker, n (%)	23 (72)	71 (74)	0.82
Current alcohol abuse, n (%)	12 (38)	25 (26)	0.22
Length of symptoms, median (IQR), days	3.5 (2.0; 4.0)	4.0 (3.0; 6.0)	0.23
Comorbidities*, n (%)	9 (28)	27 (28)	>0.99
Co-infection with HCV, n (%)	10 (31)	1 (10)	<0.001
Co-infection with HBV, n (%)	1 (3)	2 (2)	>0.99
Symptoms, n (%)			
Fever	32 (100)	87 (91)	0.11
Cough	23 (72)	70 (73)	0.91
Purulent sputum	11 (34)	35 (37)	0.83
Pleuritic pain	8 (25)	26 (27)	0.82
Dyspnea	9 (28)	42 (44)	0.12
Pneumonia Severity Index risk class, n (%)			0.32
I-III	27 (84)	73 (76)	
IV-V	5 (16)	23 (24)	
Multilobar involvement, n (%)	13 (41)	39 (41)	>0.99

Variables	Case patients	Control patients	P value
	(HIV infection)	(non-HIV infection)	
	(n = 32)	(n = 96)	
Pleural effusion, n (%)	4 (13)	5 (5)	0.23
Respiratory distress	1 (3)	5 (5)	>0.99
Septic shock, n (%)	3 (9)	7 (7)	0.71
ICU admission, n (%)	3 (9)	15 (16)	0.56
Invasive mechanical ventilation, n (%)	2 (6)	6 (6)	>0.99
Length of hospital stay, median (IQR), days	7.0 (4.0; 11.0)	6.0 (4.0; 9.0)	0.39
30-day mortality, n (%)	1 (3)	3 (3)	>0.99

* Chronic respiratory disease, chronic cardiovascular disease, diabetes mellitus, neurological disease, chronic renal disease, chronic liver disease.

Figure 1. Temporal distribution of cases and controls throughout the study period

