New Insights in Hospital Acquired Legionnaires Disease: A Retrospective Multicentre Cohort Study

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Abstract

Background: Legionnaires' disease is a recognised cause of community acquired pneumonia, however legionella is an overlooked pathogen in hospital-acquired pneumonia. Death rate seems to be greater whenever hospital-acquired legionnaires' disease occurs, however factors related to the poor outcome and preferred treatment strategy are poorly known.

Aim: Investigate mortality in patients admitted for legionnaires' disease and its associated factors. Additionally, determinant factors of onset of hospital-acquired Legionnaires' disease were analysed.

Methods: Medical records of the last three years were retrospectively reviewed at three university hospitals (UZ Brussel, CHU Brugmann and CHU Saint Pierre). Hospital-acquired legionnaires' disease was defined as symptoms onset at ten days or more after admission. Univariate and propensity score adjusted multivariate logistic regressions analyses were performed.

Results: Fifty patients were included in the study, among them 13 (26%) were diagnosed with hospital acquired legionnaires' disease. Mortality was 22%, mainly driven by patients affected by hospital acquired legionnaires' disease, with a death rate of 61.54% in this group. Multivariate analysis for prediction of all cause mortality showed significant differences in Sepsis related Organ Failure Assessment (SOFA) score and treatment with respiratory fluoroquinolones based regimen. Complementary adjusted regression analyses for prediction of hospital acquired Legionnaires' disease pointed out significant differences in chronic respiratory disease and bilateral pulmonary involvement.

Conclusion: In the current cohort, hospital acquired legionnaires' disease represents a considerable burden as its mortality seems to be elevated. It may affect particularly chronic respiratory disease patients with bilateral lung injuries. SOFA score at diagnosis was associated with higher risk of mortality while use of respiratory fluoroquinolones based treatment was associated with lower mortality.

Keywords: Legionnaires' disease; Legionella; Hospital acquired pneumonia; SOFA score; Fluoroquinolones

Introduction

Materials and Methods

A retrospective search of the medical records was conducted from 1st January 2016 up to 31th January 2019. Medical records of CHU Brugmann, CHU Saint Pierre and UZ Brussel were explored. The study protocol was approved by the institutional review boards of all three institutions. Due to the retrospective design of the study, waiver of informed consent was obtained. Clinicaltrial.gov was used as repository for registration (trial number: NCT04106037). All confirmed cases of LD, admitted in one of the three previously cited hospitals, were enrolled in the current study [4,5]. Identification of LD cases was made through microbiology laboratory database. The definition of LD diagnosis was met whenever positive respiratory samples cultures or Polymerase Chain Reaction (PCR) were detected, or positive LUA was observed. Duration of Legionella incubation is between two and ten days, mainly six or seven day. Therefore, nosocomial acquisition of LD was defined as symptoms onset at ten or more days from admission, as defined by the Centres for Disease Control and prevention (CDC). Epidemiological, clinical, biological, radiological data were collected from the medical records of enrolled patients at diagnosis. The variable “chronic respiratory disease” was defined as presence of asthma or Chronic Obstructive Pulmonary Disease (COPD).

Study characteristics considering hospital acquired LD as primary endpoint			
Parameters	**Hospital acquired LD (n=13)**	**Community acquired LD (n=37)**	**P-value**
Age, year	71(59-78)	63 (73-48)	0.141
CCI, index	7 (6-9)	4 (1-6)	0.003
CRP, mg/L	289 (160-367)	313 (251-403)	0.269
WBC, (103/µL)	15.0 (5.5-19.0)	14.0 (9.5-19.0)	0.485
Creatinine, mg/dL	2.0 (1.0-3.5)	1.0 (1.0-2.0)	0.669
SOFA, index	6 (4-8)	2 (1-4)	<0.001
Days of antibiotics	14 (10-21)	12 (10-19)	0.839
Gender (%)	10 (76.9%)	26 (70.3%)	0.734
Active smoker, yes (%)	3 (23.1%)	21 (56.8%)	0.054
Neoplasms, yes (%)	4 (30.8%)	6 (16.2%)	0.42
Chronic respiratory disease, yes (%)	8 (61.5%)	7 (18.9%)	0.011
Severe respiratory insufficiency, yes (%)	8 (61.5%)	11 (29.7%)	0.054
Lactate elevation, yes (%)	5 (38.5%)	7 (18.9%)	0.256
Bilateral lung consolidations, yes (%)	5 (38.5%)	4 (10.8%)	0.04
ICU Admission, yes (%)	11 (84.6%)	9 (24.3%)	<0.001
Non-respiratory fluoroquinolones, antibiotic, yes (%)	3 (23.1%)	7 (18.9%)	0.707
Negative LUA, yes (%)	2 (15.4%)	1 (2.7%)	0.162
All-cause mortality, yes (%)	8 (61.5%)	3 (8.1%)	<0.001

Note: Baseline Characteristics for primary endpoint hospital acquired Legionnaires' disease; CCI: Charlson comorbidity Index; CRP: C Reactive Protein; WBC: White Blood Cells; SOFA: Sepsis Related Organ Failure Assessment; ICU: Intensive Care Unit; LUA: Legionella Urinary Antigen test; '-' is used for 'no observation' or 'not applicable'; Data are expressed as median and interquartile range for continuous variable and numbers and proportions for categorical Variables.

Initial exploration of independent predictors of mortality and onset of LD in hospital setting was done using univariate logistic regression analyses. This was further assessed using two multivariate propensity score adjusted regression models encompassing different composite adjustment factors [9]. In the first model, the propensity score was derived from age and gender and the second one, previously defined adjustment factors were complemented by the comorbidities, expressed as CCI (Table 3).

Independent variables	**Univariate regression analysis**		**Propensity score adjusted regression analysis**			
			Model 1		**Model 2**	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Age	1.02 (0.98-1.07)	0.287	-	-	-	-

Neoplasm	5.67 (1.25-25-73)	0.025	5.96 (1.23-28.85)	0.026	2.01 (0.32-12.75)	0.457
Active smoker	0.17 (0.03-0.90)	0.037	0.21 (0.04-1.20)	0.079	0.27 (0.04-1.63)	0.154
CRP	1.00 (0.99-1.01)	0.745	1.00 (0.99-1.01)	0.395	1.00 (0.99-1.01)	0.708
WBC	1.00 (0.99-1.00)	0.633	1.00 (1.00-1.00)	0.571	1.00 (1.00-1.00)	0.631
Creatinine	1.07 (0.80-1.45)	0.634	1.03 (0.76-1.41)	0.83	0.81 (0.47-1.37)	0.422
SRI	6.79 (1.52-30.39)	0.012	5.79 (1.26-26.66)	0.024	4.49 (0.88-23.04)	0.071
Lactate elevation	3.81 (0.90-16.10)	0.069	3.83 (0.86-17.13)	0.079	3.15 (0.63-15.81)	0.163
Bilateral lung consolidations	3.89 (0.83-18.24)	0.085	3.70 (0.73-18.61)	0.113	8.75 (1.22-62.53)	0.031
SOFA score	2.70 (1.48-4.91)	0.001	2.61 (1.40-4.85)	0.002	2.35 (1.24-4.44)	0.008
Negative LUA	1.85 (0.15-22.54)	0.63	1.18 (0.09-15.25)	0.9	0.15 (0.01-4.51)	0.276
ICU admission	29.00 (3.29-255.94)	0.002	31.22 (3.30-295.42)	0.003	22.05 (2.24-217.07)	0.008
Non respiratory fluoroquinolones antibiotic regimen	10.50 (2.17-50.69)	0.003	9.49 (1.91-47.21)	0.006	7.51 (1.32-42.60)	0.023
Days of antibiotics	0.96 (0.86-1.09)	0.552	0.98 (0.87-1.10)	0.706	0.99 (0.87-1.12)	0.875
Hospital acquired LD	18.13 (3.57-92.13)	>0.001	15.96 (3.07-82.98)	0.001	11.46 (2.04-64.44)	0.006

Note:

WBC	1.00 (0.99-1.01)	0.859	1.00 (0.99-1.01)	0.866	1.00 (0.99-1.00)	0.783
Creatinine	0.98 (0.72-1.34)	0.904	0.95 (0.68-1.32)	0.767	0.70 (0.39-1.26)	0.237
SRI	3.78 (1.01-14.17)	0.048	3.13 (0.80-12.21)	0.101	2.28 (0.53-9.80)	0.267
Lactate elevation	2.68 (0.67-10.73)	0.164	2.58 (0.62-10.78)	0.192	2.04 (0.45-9.22)	0.354
Bilateral lung consolidations	5.16 (1.12-23.69)	0.035	4.69 (1.13-22.59)	0.044	9.37 (1.51-58.33)	0.016
Negative LUA	6.54 (0.54-79.23)	0.14	4.79 (0.38-60.34)	0.226	1.91 (0.10-34.92)	0.664

Note: [illegible]

HA LD died without receiving effective antibiotics, as the correct diagnosis was significantly delayed and empirical treatment did not cover Legionella. SOFA score seems to be an appropriate tool to estimate the mortality at diagnosis. As observed in the current study a high SOFA score, major or equal to five, had similar good specificity and sensitivity to predict mortality. In HA LD, SOFA score had better sensitivity but insufficient specificity [12].

A previous large retrospective cohort suggested a possible improvement in mortality whenever standard dose Levofloxacin, 500 mg daily, is chosen for community acquired LD treatment in comparison with Azithromycine. As culture of Legionella is technically demanding and standard disc diffusion susceptibility is considered to be not appropriate, microbial sensitivity tests are hence rarely performed. It is theoretically assumed that both first line antibiotic classes, fluoroquinolones and macrolides, are always susceptible. However, some resistance mechanisms, as macrolides efflux pumps, may reduce sensitivity for first line antibiotics. Furthermore, a patient diagnosed with a ciprofloxacin resistant LD pneumonia was previously reported. Additional investigations suggested lower alveolar macrophages and bronchial secretions concentration of ciprofloxacin compared with respiratory fluoroquinolones and less favourable minimal inhibitory capacity/ minimal bactericidal capacity rapport. In the current cohort patients treated with high dose Levofloxacine (750 mg up to 1000 mg daily) and Moxifloxacine (400 mg daily) had significant lower mortality in comparison with patients who received other antibiotic regimens. In case of oxygen dependent LD patients or HA LD previous cited antibiotic regimen should be considered. Hospital acquired LD patients represents a non negligible part of the current cohort. The major disease predictor was medical history of asthma or COPD. Controversially, active smoking status resulted as a negative predictor. Longstanding respiratory disease patients receive profound smoking counselling and the rate of active smoker in advanced respiratory disease are lower. Moreover, this significant difference disappears after Gender and age adjustment and a previous article reported the same issue. Furthermore, although it is estimated that the main imaging finding is patchy unilobar infiltrate, bilateral consolidation, independently of pleural effusion presence, was a predictor of HA LD diagnosis in the current cohort.

Conclusion

The strengths of this study are the multicentre design and the rigorous structure. Strict definition of the variants was applied, particularly of HA LD which followed CDC definition. Furthermore, the current cohort accounts one of higher described number of hospital acquired LD patients. To the best of our knowledge, this study is the first that found predictors for HA LD. Finally, the current study enforces the evidence based antibiotic treatment in hospitalized patients affected by LD and HA LD. A potential limitation of this study is the retrospective design, which may not exclude confounding factors. Moreover, a relative low number of patients were included in the current study, which may undermine the power of this study. A randomized clinical trial should address the same questions. However, it seems not feasible considering the relative rarity of this condition. In summary, even though underreported and overlooked LD represents a considerable burden and its investigation should be systematic. Outcomes are particularly poor in HA LD and SOFA score at diagnosis may be good prognostic tool. Moxifloxacine or high dose Levofloxacine based treatment may increase