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Original Article

# Community-acquired Legionnaires' disease at a medical center in northern Taiwan



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## KEYWORDS

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Community-acquired pneumonia

**Abstract** *Background/purpose:* *Legionella pneumophila* had been recognized as an important pathogen for community-acquired pneumonia. We aimed to investigate clinical features and outcomes of patients with Legionnaires' disease at a tertiary medical center in northern Taiwan. *Methods:* From June 2012 to February 2017, a retrospective review of adult community-acquired Legionnaires' disease at a medical center was conducted. All *Legionella* infections were confirmed by positive urinary *Legionella* antigen assay, sera indirect immunofluorescence assay, or sputum culture for *Legionella*. Literature review of Legionnaires' disease from Medline and PubMed websites was performed.

*Results:* A total of 32 cases of Legionnaires' disease were identified. Their mean age was 64.3 years, with male predominance (27 cases, 84.3%). The underlying diseases were varied and most were attributed to chronic disorders, such as diabetes mellitus (31%) and cigarette smoking (40.6%). The most common symptoms were cough (68%) and fever (59.3%). More than half of patients (18, 56.2%) with Legionnaires' disease could initially present with extrapulmonary manifestations. Sixteen (50%) patients had delay in initiation of appropriate antibiotic therapy. Patients without adequately initiation of appropriate antibiotic therapy had higher proportion (11 of 16, 68.7%) of intensive care unit admission than patients with adequate initiation (5 of 16, 31.2%). Our results inferred that a delay in treatment might result in worsening of disease severity and the need for more intensive management. Overall mortality rate was 21.8%. Development of vasopressor requirement is an independent risk factor associated with mortality.

*Conclusion:* Legionnaires' disease in Taiwan frequently present with extrapulmonary manifestations. Patients with hemodynamic instability that need vasopressor therapy associated with mortality.

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## Introduction

*Legionella* is a pathogenic group of Gram-negative bacteria, including the species *Legionella pneumophila*, causing Legionellosis (all illnesses caused by *Legionella*) including a pneumonia-type illness called Legionnaires' disease and a mild flu-like illness called Pontiac fever.<sup>1–4</sup> Among 48 species and 70 serogroups that had already been identified, more than 20 species were confirmed to be associated with human diseases.<sup>3–5</sup> The study of Su et al. showed that the most commonly isolated *Legionella* from pneumonia patients from 2001 to 2003 in Taiwan was *L. pneumophila* serogroup 1, followed by *Legionella dumoffii*.<sup>6</sup> In Taiwan, the study of Pan et al. showed that the proportion of pneumonia due to *L. pneumophila* infection was about 8.6%.<sup>7</sup>

Pneumonia is the predominant clinical manifestation of *Legionella* infection. The first clinical descriptions of Legionnaires' disease were of toxic patients with high fever and gastrointestinal symptoms accompanying pneumonia.<sup>1</sup> As specialized laboratory diagnostic tests became more widely available, it became clear that the clinical presentation was more varied and nonspecific. The incubation period for Legionnaires' disease ranges from 2 to 10 days.<sup>1</sup> Respiratory symptoms are not prominent initially, that is, the cough at first is mild and only slightly productive. The sputum may be blood streaked, but gross hemoptysis is rare. Chest pain can occur in some patients and, if accompanied by hemoptysis, may lead to an erroneous diagnosis of pulmonary embolism. Gastrointestinal symptoms are often prominent with diarrhea, nausea, vomiting, and abdominal pain. Patients are commonly lethargic with headache and occasionally stupor.

Laboratory abnormalities are common but nonspecific and include renal and hepatic dysfunction, thrombocytopenia, leukocytosis, and hypophosphatemia. Hyponatremia (serum sodium <130 mEq/L) occurs significantly more frequently in Legionnaires' disease than in pneumonias of other etiologies.<sup>5,8–10</sup> Hematuria and proteinuria are also common findings of urinary analysis.<sup>11,12</sup> Serum ferritin levels have also been noted to be elevated in Legionnaires' disease.<sup>13</sup> Elevated procalcitonin levels are a marker for severity of illness.<sup>14,15</sup>

There is no characteristic chest radiograph finding for Legionnaires' disease. The most common pattern is a patchy unilobar infiltrate that progresses to consolidation. However, all types of infiltrates have been reported including diffuse, interstitial infiltrates.<sup>14</sup> Pleural effusions are also commonplace. Due to the strict growth requirement of *Legionella* species, clinical diagnosis relying on sample culture was difficult.<sup>15</sup> Identification of this disease needs other tests such as enzyme immunoassay and urinary antigen test.<sup>16</sup> Therefore, awareness and understanding of the clinical characteristics of Legionnaires' disease are important for clinicians to better recognize the disease and optimize clinical management.

In Taiwan, several reports of Legionnaires' disease had been presented since 1983.<sup>6,7,17–21</sup>

In recent years, the annual number of confirmed Legionnaires' disease cases is about 40–110 in Taiwan. Legionnaires' disease epidemic also occurred in hospitals,

resorts, hotels and gyms. Regarding the age distribution of Legionnaires' disease cases, Taiwan has the same trend with other countries, with the incidence increasing with age. The elders are at a higher risk of Legionnaires' disease, and this will be a main target of disease prevention.

However, most studies were case reports or epidemiology studies carried out by the notification system from southern Taiwan. The clinical presentations, types of antimicrobial therapy and outcomes of Legionnaires' disease were limited. Therefore, the present study aims to assess the epidemiology, clinical features, chest radiographic findings, and outcomes of Legionnaires' disease at a university hospital in northern Taiwan over a 4-year period.

## Methods

### Study design

We conducted a single-center retrospective, observational study of all patients with hospitalized community-acquired Legionnaires' disease at National Taiwan University Hospital (NTUH), a 2800-bed medical center in northern Taiwan, between June 2012 and February 2017.

### Case definitions

Community-acquired infection is defined as infection acquired outside a hospital or long-term care facility. It occurs within 48 h of hospital admission or in a patient presenting with infection who does not have any of the characteristics of healthcare-associated pneumonia, i.e., hospitalized in an acute care hospital for 2 or more days within 90 days of infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attend a hospital or hemodialysis clinic.

Legionnaires' disease was defined as the presence of symptoms and signs of respiratory tract infections such as fever, sepsis, cough, and sputum production, pulmonary infiltrates consistent with pneumonia on a chest radiograph, and a positive result of urinary *Legionella* antigen assay in the central laboratory of NTUH, or seroconversion by paired acute and convalescent phase sera analysis using indirect immunofluorescence assay (IFA), or a positive sputum culture result for *Legionella* performed in Taiwan Center for Disease Control (CDC). The urinary *Legionella* antigen assay was performed using a commercial Binax Immunochromatographic Test Kits (Alere, Orlando, FL, USA). The Binax test has >70% sensitivity and >99% specificity for *L. pneumophila* serogroup 1 only.<sup>22</sup> Shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.<sup>23</sup> Elevated blood leukocyte count was defined as white blood count more than 10,000/uL. Antibiotics with anti-*Legionella* activity is defined as prescribing macrolides, quinolones, ketolides, tetracyclines or Trimethoprim/sulfamethoxazole. Delayed administration of appropriate antibiotic treatment was

defined as not commencing antibiotics with anti-*Legionella* activity within 24 h after the patient presented to the emergency department. Acute kidney injury (AKI) is defined as increase in serum creatinine to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days. Cigarette smoking is defined as smoking more than ten cigarettes per day. Hyponatremia was defined as serum sodium  $< 130$  mEq/L. Medical records were reviewed for demographic information, comorbidities, clinical presentations, laboratory data, clinical course, and outcomes. If a patient had more than one pneumonic episode, only the first episode would be included for further analysis. Literature review of Legionnaires' disease in Taiwan searched from Medline and PubMed websites from year 1980–2016 was performed.

### Statistical analysis

Statistical analysis was performed by the SAS statistical software (Version 9.4; SAS Institute Inc., Cary NC, USA). Continuous variables were expressed as means  $\pm$  standard deviations, and compared using Student's t test or One-way analysis of variance (ANOVA). Categorical variables were expressed as numbers (percentages) and compared using chi-square test. The primary endpoint was all-cause in-hospital mortality. For the risk factors of mortality, variables with a p value of  $< 0.2$  identified by the univariate logistic regression analysis would be further analyzed by means of multivariate logistic regression method. A two-tailed p value of  $< 0.05$  was regarded to be statistically significant.

## Results

### Demographics and characteristics

From June 2012 to February 2016, there were a total of 32 hospitalized community-acquired Legionnaires' disease cases identified at NTUH. Thirty (93.7%) of them were confirmed by the urinary *Legionella* antigen assay, one (3.1%) was confirmed by sputum culture growing *Legionella longbeachae*, and one (3.1%) was confirmed via seroconversion. The mean age of the patients was 64.2 years, and 27 (84.4%) of them were male. Demographics, medical comorbidities and risk factors are presented in Table 1. The majority (20 patients, 62.5%) of patients had various comorbidities, including hypertension, dyslipidemia, and diabetes mellitus. In addition to the presence of comorbidities, the other common associated factors for Legionnaires' disease in this patient population included cigarette smoking (13, 40%).

### Clinical features and laboratory results

Upon presentation to the emergency department (Table 1), twenty-two patients (68.7%) reported cough, with 36.3% of the patients reporting sputum production. Besides, more than half of patients (18, 56.2%) presented with extrapulmonary manifestations. Among extrapulmonary manifestations, gastrointestinal symptoms are prominent (14,

43.7%), followed by musculoskeletal symptom (10, 31.2%) and neurologic abnormalities (2, 6.2%).

Laboratory results were recorded for patients upon presentation to the emergency department and are provided in Table 1. The most common laboratory abnormalities included an elevated leukocyte count (53.1%), and hyponatremia (65.6%). The chest radiographic findings of patients at the time of admission are summarized in Table 1. Twenty-two patients (68.7%) had bilateral infiltrates visualized by chest X-ray, and half of patient (16, 50%) had pleural effusion.

### Treatment, complications and outcomes

The clinical complications, and outcomes of the 32 patients with Legionnaires' disease are summarized in Table 1. Delayed administration of appropriate antibiotic treatment with anti-*Legionella* activity occurred in sixteen patients. The mortality rate in patients with delay in initiation of appropriate antibiotic therapy was 18.7% (3/16), compared with the mortality rate in patients without delay in initiation of appropriate antibiotic therapy was 25% (4/16). There was no statistically significant difference between two groups. However, patients without adequately initiation of appropriate antibiotic therapy had higher proportion (11/16, [68.7%]) of ICU admission than patients with adequate initiation (5/16, [31.2%]). Overall, Sixteen patients (50%) required admission to an intensive care unit (ICU). Sixteen patients (50%) required mechanical ventilation, ten patients (31.2%) required vasopressor support, and ten patients (31.2%) required renal replacement therapy. Clinical improvement was protracted, with average ICU stay and hospital lengths of stay of 18 and 20 days, respectively. The hospital mortality rate was 21.8% in this cohort. Patients developed vasopressor requirement reached a statistically significant association with death (see Table 2).

## Discussion

Legionellosis is an important community-acquired disease in Taiwan. In this study, we found the mortality was 21.8%. The development of vasopressor requirement during the clinical course was independently associated with mortality. In previous Legionnaires' disease studies in Taiwan,<sup>6,7,17–21</sup> the influences of delayed administration of appropriate antibiotic therapy were rarely discussed, delay in initiating appropriate antibiotic therapy is known to be a poor prognostic factor in patients infected by *Legionella*.<sup>24</sup> From this study, sixteen (50%) patients had not adequately in initiation of appropriate empirical antibiotic therapy. However, there is no the significant differences in mortality revealed by univariate analysis, this could be attributed to our small group of subjects. But, patients without adequately initiation of appropriate antibiotic therapy had higher proportion (11/16, [68.7%]) of ICU admission and mechanical ventilation than patients with adequate initiation (5/16, [31.2%]), Therefore, it might be inferred that a delay in treatment might result in worsening of disease severity and the need for more intensive management.

**Table 1** Demographic characteristics, comorbidities, initial presentations of Legionnaires' disease in Taiwan.

Variable	This study	Lin SF et al.	Lay CJ et al.	Yeh KM et al.	Hung TL et al.
reference		18	19	20	21
Case number	n = 32	n = 21	n = 38	n = 29	n = 61
Age, years, median	64.2	60.3	—	55.7	61.1
Male sex, n (%)	27 (84.3)	15 (76.1)	30 (78.9)	20 (68.9)	43 (70.5)
Comorbidities					
Diabetes	11 (34.3)	6 (28.5)	9 (23.7)	(17.0)	22 (36.0)
Hypertension	17 (53.1)	—	—	—	—
Dyslipidemia	4 (12.5)	—	—	—	—
Cirrhosis	3 (9.3)	2 (9.5)	1 (2.6)	(7.0)	6 (9.8)
COPD	6 (18.7)	3 (14.2)	11 (28.9)	(21.0)	2 (3.2)
CAD	7 (21.8)	—	—	—	—
CKD	8 (25.0)	—	—	—	14 (22.9)
Malignancy	5 (15.6)	4 (19.0)	3 (7.89)	(10.0)	15 (24.5)
Solid organ transplant	2 (6.2)	—	—	—	3 (4.9)
Cigarette smoking	13 (40.6)	6 (28.5)	17 (44.7)	(21.0)	—
Initial presentation					
Fever	19 (59.3)	19 (90.4)	28 (73.7)	(97.0)	61 (100)
Cough	22 (68.7)	16 (76.1)	24 (63.2)	—	(67.2)
Purulent sputum	8 (25.0)	6 (28.5)	21 (55.3)	—	(50.8)
Initial presentation (extrapulmonary)	18 (56.2)	—	—	—	—
GI symptom	14 (43.7)	9 (42.8)	14 (36.8)	7 (24.1)	—
Diarrhea	6 (18.7)	—	—	—	(19.7)
Nausea/vomiting	8 (25.0)	—	—	—	(19.7)
Myalgia/arthralgia	10 (31.2)	3 (14.2)	4 (10.5)	—	(8.2)
Laboratory					
Leukocytosis	17 (53.1)	14 (63.2)	24 (63.2)	—	—
Elevated hepatic transaminases	6 (18.7)	11 (52.3)	18 (47.4)	7 (24.1)	—
AKI	14 (43.7)	11 (52.3)	18 (47.4)	7 (24.1)	—
Hyponatremia	21 (65.6)	11 (52.3)	17 (44.7)	10 (34.4)	—
Chest radiograph findings					
Parenchymal pattern					
consolidation	21	12	—	4	—
Infiltrate other than consolidation	11	9	—	25	—
Pleural effusion	16	—	—	7	—
Unilateral distribution	10	10	—	8	—
bilateral distribution	22	2	—	21	—
Outcomes					
Ventilator use	16 (50.0)	9 (42.8)	7 (18.4)	14 (48.2)	19 (31.1)
Shock	10 (31.2)	10 (47.6)	10 (26.3)	—	—
Dialysis	10 (31.2)	—	—	1 (3.4)	—
Mortality	7 (21.8)	3/21 (14.2)	7 (18.4)	7 (24.1)	6 (9.8)

COPD = chronic obstructive pulmonary disease; CAD = Coronary Artery Disease; CKD = Chronic kidney disease; GI = Gastrointestinal; AKI = acute kidney injury; "—" = not available.

The clinical presentation of Legionnaires' disease was varied and nonspecific. Our study shown the most common presentations were fever and cough. Extrapulmonary manifestations were rarely discussed in Taiwan. In our study, more than half of patient (56.2%) presented extrapulmonary symptoms upon presentation to the emergency department. Among extrapulmonary manifestations, gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain) were predominant, followed by musculoskeletal symptom and neurologic abnormalities with altered mental status and limb weakness.

Only a minority of reports (2 of 6) of Legionnaires' disease in Taiwan had mentioned chest radiograph findings. As

shown in our study, there is no characteristic chest radiographic finding of Legionnaires' disease. In our cohort, we have higher proportion of lobar consolidation, which was different from the observation of the study of Yeh et al., that showed the most common pattern were pulmonary infiltrations.<sup>20</sup> Besides, our study found that neither the distribution pattern (bilateral or unilateral) of chest X-ray at the time of admission, nor the presence of extrapulmonary manifestations upon presentation to the emergency department was not associated with mortality.

Several classes of antimicrobial agents have been shown to be effective against *Legionella* species, including macrolides, tetracyclines, ketolides, Trimethoprim/

**Table 2** Univariate and multivariate analysis for risk factors associated with in-hospital mortality of 32 patients with Legionnaires' disease.

Variable	Univariate analysis				Multivariate analysis			
	OR	CI_LOWER	CI_HIGHER	p-value	OR	CI_LOWER	CI_HIGHER	p-value
Age	1.00	0.94	1.06	0.9246	0.10	0.01	1.29	0.0770
Sex	0.12	0.01	0.93	0.0424				
Hypertension	1.23	0.23	6.67	0.8097				
Dyslipidemia	1.22	0.11	13.97	0.8718				
Diabetes	0.71	0.11	4.44	0.7153				
Cigarette smoking	0.18	0.02	1.73	0.1373	0.17	0.01	3.09	0.2306
Cough	0.24	0.04	1.37	0.1079	0.44	0.04	4.59	0.4932
Diarrhea	9.60	0.72	127.53	0.0866	10.94	0.17	702.73	0.2600
HR > 90bpm	0.52	0.04	6.77	0.6188				
Respiratory rate > 20Bpm	1.13	0.21	6.14	0.8918				
Temperature < 36 °C or > 38 °C	0.42	0.08	2.32	0.3212				
Leukocyte (3.54–9.06) × 10 <sup>9</sup> /L	0.91	0.78	1.05	0.2003	0.91	0.77	1.07	0.2436
Sodium (135–145) mmol/L	1.02	0.87	1.19	0.8458				
Delay in appropriate antibiotic therapy	0.69	0.13	3.75	0.6698				
Appropriate antibiotic therapy								
2 <sup>a</sup> vs 1 <sup>b</sup>	5.00	0.77	32.57	0.0923				
3 <sup>c</sup> vs 1 <sup>b</sup>	—	—	—	—				
CXR at ER	4.00	0.42	38.43	0.23				
Clinical complication								
ICU admission	—	—	—	—				
Vasopressor requirement	31.50	2.94	337.47	0.0044	28.97	1.18	711.60	0.0393
Mechanical ventilation	—	—	—	—				
Renal replacement therapy	31.50	2.94	337.47	0.0044	28.97	1.18	711.60	0.0393

<sup>a</sup> Quinolones-based regimen.

<sup>b</sup> Macrolide-based regimen.

<sup>c</sup> Quinolones–Macrolide combination regimen.

CXR (using unilateral consolidation as reference).

sulfamethoxazole (TMP/SMX) and quinolones<sup>22,23</sup>. Previous studies of Legionnaires' disease in Taiwan rarely discussed the effectiveness of different antibiotic regimen on outcome. In our study, 16 of 32 patients (50%) received empirically macrolide-based regimen, and two (12.5%) died. Totally 12 of 32 patients received empirically fluoroquinolone-based regimen, and 5 (41.6%) died, compared with 4 of 32 patients received fluoroquinolone-macrolide combination therapy and no fatality was noted. Overall the mortality rate was 21.8% (7/32). Our study showed that patients received fluoroquinolone-based treatment had higher proportion of mortality (5/12, [41.6%]) than macrolide-based group (2/16, [12.5%]). This finding is inconsistent with the result of Gershengorn et al.,<sup>25</sup> which showed that azithromycin alone or a quinolone alone for the treatment of *Legionella* pneumonia was associated with similar mortality, hospital stay, and total hospital cost. Reviewing medical records, patients tended to receive empirically fluoroquinolone-based regimen had more severe symptom clinically. The higher mortality might reflect the more severity in quinolone-based group.

In our study, the development of vasopressor requirement during the clinical course was statistically significantly associated with death. The study of Hung et al. found that fatality was associated with cancer and a high Charlson comorbidity score indicated that those with immunocompromised or complicated comorbidities will herald a grave prognosis,<sup>21</sup> if acquired Legionnaires'

disease. Lin et al. showed a few factors could be used to predict clinical outcome, such as old age, the development of respiratory failure or shock during the clinical course. However the statistical difference was only borderline.<sup>18</sup> Yeh et al. showed that the mortality rate was higher in patients with hyponatremia, respiratory failure and in those older than 70 years.<sup>20</sup>

Our study was limited by small case numbers and by the fact that our retrospective data collection by chart review was dependent on the reporting and diagnostic tests ordered by other healthcare professionals. As a result, full patient histories and laboratory values could not be obtained for each patient. A prospective study would overcome this limitation. Last, we do not have a control group with non-*Legionella* community-acquired pneumonia to assess specific risk factors for Legionnaires' disease.

## Conclusions

More than half of patients with Legionnaires' disease in Taiwan could initially present with extrapulmonary manifestations, included gastrointestinal, musculoskeletal and neurological symptoms. The delay in initiating appropriate antibiotic therapy might worsen disease severity and result in a need for more intensive management. Patients with hemodynamic unstable need vasopressor therapy associated with mortality.

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