Legionella pneumophila pneumonia: A 5-year retrospective clinical evaluation and commentary

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Abstract. Although legionellosis represents a widely underestimated disease for various reasons, the rate of *Legionella pneumophila* infections has increased steadily over the past 30 years. The present study describes the characteristics of patients hospitalized due to legionellosis. The present study retrospectively reviewed 10 cases of legionellosis during the defined period and documented the epidemiological and clinical characteristics of the patients, as well as the methods used for diagnosis and therapeutic management. The majority of the patients were male (80%) with a mean age of 55.8 years. The most common comorbidities were hypertension (40%) and tumors (20%). Fever was present in all the cases (100%) and the most frequent imaging finding was lung consolidation. Half of the cases exhibited hyponatremia, 40% of them had leukocytosis, and 50% of the patients presented elevated procalcitonin levels, as well as elevated levels of transaminases. In total, 2 patients (20%) required non-invasive oxygen support. All the cases presented a positive urinary antigen test for *Legionella pneumophila* serogroup 1. A total of 9 patients (90%) received levofloxacin-based therapy for a mean duration of 17.7 days. All the cases described herein were successfully discharged without any complications. On the whole, the present study demonstrates that a prompt clinical diagnosis along with early testing and treatment represent the cornerstone for positive outcomes in patients affected by Legionnaire's disease.

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Introduction

Legionella pneumophila is a Gram-negative bacterium, ubiquitous in water and soil, facultative intracellular pathogen, recognized as the leading cause of legionellosis, named after an outbreak of this disease at an American Legion convention held in Philadelphia in 1976 (1). This disease can be present in its acute, rarely transmissible, pneumonic form [Legionnaire's disease (LD)] with a mortality rate of 5-30% in hospitalized patients and up to 50% in intensive care units (ICUs) (2), or in a milder non-pneumonic form that usually improves without medical care (Pontiac fever) (3). Due to the influenza-like symptoms (4), Pontiac fever is often misdiagnosed (5). In the USA and the European Union (EU), legionellosis notification is mandatory. The overall number of legionellosis cases is markedly increasing in the USA, rising from 1,000 cases in the year 2000 to 10,000 cases in 2018 (6). Conversely, according to the European Centre for Disease Prevention and Control (ECDC), the legionellosis trend among the EU countries has exhibited a decreasing trend, with a rate of 1.9 cases per 100,000 inhabitants in 2020 vs. 2.2 cases for 100,000 inhabitants recorded in 2019 (7). However, in Italy, an upward trend has been observed over the past 25 years, with cases of legionellosis increasing from <100 in 1997, possibly due to the lack of correct diagnosis, to >3,000 cases recorded in 2019. The prevention measures employed to contain the spread of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) also affected other infectious diseases; thus the number of cases of legionellosis in Italy decreased to 2,074 in 2020 (8-10).

Due to the demanding growth conditions requiring charcoal in the media and particular humidity levels (11), the diagnosis of legionellosis is usually performed through urinary *Legionella* antigen tests targeting one of the 15 serogroups (SGs), i.e., the most common SG1, in which *Legionella pneumophila* (*L. pneumophila*) is further classified (12). Although the method is rapid and reliable, it may lead to the misdiagnosis of *L. pneumophila* infection caused by strains belonging to other SGs (13). In fact, there are some reports of cases with negative urinary antigen tests (UATs) that yielded positive results by PCR of bronchoalveolar lavage, suggesting the possibility of using molecular analysis if legionellosis is suspected (14).

The fastidious nature of *L. pneumophila* is responsible for the difficulty in performing antimicrobial susceptibility testing (AST), and the association between AST *in vitro* and clinical outcomes is often uncertain; however, acquired antimicrobial resistance appears to be an extremely rare event in this species. Furthermore, the selection of the appropriate therapy should take into account the possible intracellular nature of *L. pneumophila*, preferring antibiotics able to enter cells. For these reasons, the elective therapy for *L. pneumophila* pneumonia is represented by macrolides, fluoroquinolones and rifampicin rather than β-lactams and aminoglycosides. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the minimum inhibitory concentration (MIC) distributions for wild-type SG1 and SG2 *L. pneumophila* range from 0.016 to 2 mg/l for azithromycin, clarithromycin, erythromycin, ciprofloxacin and levofloxacin, and from 0.125 to 4 mg/l for moxifloxacin. The range is slightly lower for rifampicin (≤0.008 to 0.032 mg/l, with the exception of two SG2 isolates) and is higher for doxycycline and tigecycline, ranging from 0.25 to 8l and 16 mg/l, respectively (15). These values indicate that the physician may set an empiric therapy in the presence of pneumonia in order to limit the possible worsening of the clinical image due to a misdiagnosis of legionellosis.

Patients and methods

In the present study, all the patients with legionellosis admitted to the Infectious Diseases Unit of the ARNAS Garibaldi Hospital (Catania, Italy), between January, 2017 and September, 2022, were retrospectively identified and evaluated. All patients signed an informed consent form to allow the collection and anonymous analyses of their data. Legionellosis was defined as a new or progressive pulmonary infiltrate on a chest radiography, along with the presence of symptoms and signs of pneumonia, and a positive result for the urinary *Legionella* antigen test, which detects *L. pneumophila* SG1 soluble antigen. The medical records of the patients were evaluated for demographic and clinical data, including comorbidities, symptoms, clinical course, laboratory data, oxygen use, treatment and outcomes. Written informed consent was obtained from all the patients whose data are presented herein. Ethic approval was waived due to the retrospective nature of the study.

Results

From January, 2017 to September, 2022, 10 patients with legionellosis were admitted to Infectious Diseases Unit of the ARNAS Garibaldi Hospital. The characteristics and clinical data of all the patients are presented in Table I. In total, 8 patients were male (80%), and the mean age of the patients was 55.8 years (ranging from 36 to 78 years). The most common comorbidities were hypertension (40%) and tumors (20%). In addition, 2 patients revealed smoking habits.

Upon admission, fever was present in all the cases (100%) and the other two most common symptoms were cough (40%) and asthenia (30%). The number of days from symptom onset to the hospital visit ranged from 2 to 10 days, with a mean of 5 days.

The imaging results revealed that 4 patients (40%) had bilateral pneumonia and 5 patients (50%) had pleural effusion. The mean levels of C-reactive protein were 21.5 mg/dl, ranging from 5.32 to 38 mg/dl (normal range, <0.5 mg/dl).

Other abnormal laboratory data included hyponatremia (sodium levels in blood <135 mEq/l). in half of the cases and leukocytosis (>10,500/mm^3) in 4 cases. In addition, 5 patients exhibited elevated procalcitonin levels (>0.5 ng/ml), as well as elevated levels of transaminases (glutamic-oxaloacetic transaminase, >40 IU/l; glutamic pyruvic transaminase, >40 IU/l).

In total, 2 patients (20%) required non-invasive oxygen support (Venturi mask and high-flow nasal cannula). The days from hospitalization to the time of diagnosis ranged from 1 to 2 days. All the cases presented a positive UAT for *L. pneumophila* SG1. Of the 10 patients, 9 patients were treated with levofloxacin (750 mg daily). Due to an allergy to fluoroquinolones, 1 patient received clarithromycin for 21 days. The mean duration of antibiotic therapy was 17.7 days, ranging from 15 to 21 days of therapy. The mean hospital duration was 17.1 days, ranging from 2 to 26 days. All patients were discharged with the resolution of pneumonia and without clinical complications or recurrence following 6 months follow-up. Each patient hospitalized during the COVID-19 pandemic tested negative for SARS-CoV-2. None of the patients revealed other cases of pneumonia among their community (Table I).

Discussion

The number of cases of legionellosis in Italy has steadily increased over the past 30 years, although it remains a widely underestimated disease for various reasons, including misdiagnoses and notification bias (16). In 2020, 2,021 cases of legionellosis were reported in Italy, with an incidence of 34.8/1,000,000 inhabitants and mostly involving males, with a mean age of ≥60 years (8).

Another issue is related to the diagnostic method which, in almost all cases and according to the 2019 ECDC report (7,17), is carried out by the detection of urinary soluble antigen of *Legionella* spp. The majority of commercially available tests for the detection of urinary antigen are specific to *L. pneumophila* SG1; thus, some cases are not correctly diagnosed due to infection with other species or SGs. These biases have led to a marked variability in incidence rates between different geographical areas in Italy (8). In Europe, ~80% of human cases of legionellosis are caused by *L. pneumophila* SG1, with other SGs accounting for 16% and other species for 3% of infections, resulting in the proper diagnosis of the majority of cases (7,17).

The *Legionella* antigen is detectable by the UAT from the first day of the onset of symptoms (ranging from 1 to 3 days), demonstrating a high positive predictive value, although it may persist for weeks or months, thus being ineffective for follow-up or for recent infections (18,19).

Although the culture of respiratory samples continues to represent the gold standard for the diagnosis of legionellosis, allowing species and SG detection along with antibiotic susceptibility testing, it is a challenging test necessitating significant expertise and several days to grow the bacterium on

Table I. The clinical and epidemiological characteristics of the patients in the present study.

Case no.	Age, years	Sex	Underlying diseases	Symptoms	Time form onset to hospitalization (days)	Imaging findings	Other abnormal laboratory findings	Oxygen use	Hospitalization to diagnosis (days)	Diagnostic methods	Antibiotic regimen	Treatment duration (Days)	Days of hospitalization	Outcome	6-Month follow-up status
1	68	M	Hypertension, history of heart attack, heart diabetes mellitus, stroke, melanoma	Fever	2	LUL consolidation	Sodium, 132 mEq/l; CRP, 38 mg/dl; PCT, 1.7 mcg/l; WBC, 14,800 cells/mm^3	VM	1	UAT	Levofloxacin	17	17	DISCH	NEG
2	52	M	Hypertension, smoking	Fever with chills, general malaise	5	LUL, LLL, RUL consolidation, mild left pleural effusion	Sodium, 131 mEq/l; CRP, 28 mg/dl; WBC, 14,700 cells/mm^3; γ-GT, 890 UI/l; GOT, 100 UI/l; CPT, 400 UI/l	None	1	UAT	Levofloxacin	16	18	DISCH	NEG
3	53	M	Idiopathic myelitis, cerebrovascular disease, occult HBV infection	Fever, altered mental status	10	LUL, RLL consolidation, mild right pleural effusion	Sodium, 134 mEq/l; CRP, 8.89 mg/dl; PCT, 1,24 mcg/l; WBC, 8,300 cells/mm^3; PLT, 585,000 cells/mm^3; GOT, 242 UI/l; GPT, 77 UI/l; γ-GT, 89 UI/l; AMI, 229 UI/l	None	1	UAT	Levofloxacin	18	19	DISCH	NEG
4	36	M	Hepatic steatosis, occult HBV infection	Fever, cough, arthralgias, headache	3	LUL consolidation, mild left pleural effusion	Sodium, 134 mEq/l; CRP, 16 mg/dl; GOT, 86 UI/l; GPT, 123 UI/l; γ-GT, 100 UI/l	None	1	UAT	Levofloxacin	15	15	DISCH	NEG
5	50	F	Gilbert syndrome, idiopathic gastritis	Fever with chills, intense asthenia	4	RUL consolidation	CRP, 21 mg/dl; PCT, 3.16 mcg/l	None	1	UAT	Levofloxacin	16	16	DISCH	NEG
6	51	M	Hypertension, nephrolithiasis	Fever, cough	2	RLL consolidation	CRP, 10.8 mg/dl; WBC, 14,800 cells/mm^3; CPK, 489 UI/l; γ-GT, 131 UI/l; GOT, 61 UI/l	None	1	UAT	Levofloxacin	17	17	DISCH	NEG

Table I. Continued.

Case no.	Age, years	Sex	Underlying diseases	Symptoms	Time form onset to hospitalization (days)	Imaging findings	Other abnormal laboratory findings	Oxygen use	Hospitalization to diagnosis (days)	Diagnostic methods	Antibiotic regimen	Treatment duration (Days)	Days of hospitalization	Outcome	6-Month follow-up status
7	55	M	None	Fever, asthenia, dyspnea	5	RML consolidation	CRP, 5.32 mg/dl	None	1	UAT	Levofloxacin	15	2	AMA	NEG
8	47	F	Hypertension, SLE, endometrial polyps	Fever, pharyngodynia	7	RLL, LLL consolidation	Sodium, 134 mEq/l; CRP, 35 mg/dl; PCT, 13.3 mcg/l; WBC, 14,300 cells/mm^3	None	2	UAT	Levofloxacin	21	26	DISCH	NEG
9	78	M	Atrial flutter, prostate cancer	Fever, cough	10	LLL consolidation, left pleural effusion	CRP, 22 mg/dl; WBC, 28,000 cells/mm^3; GOT, 170 UI/l; GPT, 196 UI/l; γ-GT, 156 UI/l	None	1	UAT	Clarithromycin	21	16	DISCH	NEG
10	68	M	HIV infection, HCV infection, occult HBV infection, smoking	Fever, cough, asthenia	2	RUL, LLL consolidation, right pleural effusion	Sodium, 162 mEq/l; CRP, 30 mg/dl; PCT, 1.57 mcg/l	HFNC	1	UAT	Levofloxacin	21	25	DISCH	NEG

HBV, hepatitis B virus; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; HCV, hepatitis C virus; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe; RML, right middle lobe; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count; PLT, platelets; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; γ-GT, γ-glutamyl transpeptidase; CPK, creatine phosphokinase; VM, Venturi mask; HFNC, high-flow nasal cannula; UAT, urinary antigen test; AMA, discharge against medical advice; DISCH, discharge; NEG, negative.

media which are difficult to prepare, such as buffered charcoal yeast extract (20-24).

The nucleic acid-based detection (PCR method) has a higher sensitivity and specificity compared to the aforementioned techniques, allowing for the rapid diagnosis of all known *Legionella* species, with better performance on respiratory samples; however, PCR is relatively costly, it requires specialized personnel, and it is not standardized for testing urine or blood (21,25). Ricci *et al* (26) predicted an increase of 18% in the diagnosis of legionellosis when real-time PCR was used in combination with UAT.

The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines for community-acquired pneumonia (CAP) recommend that only those patients with epidemiological indications or severe cases should be tested for *Legionella* spp. with UAT (27), whereas other guidelines recommend testing all patients admitted with CAP (28,29).

The present study reports the clinical image and outcomes of 10 patients with legionellosis admitted to the Infectious Diseases Unit of the ARNAS Garibaldi Hospital, between January, 2017 and September, 2022. Although the majority of the cases in the present study were not severe and only 2 patients required oxygen support, based on imaging along with biochemical parameters (particularly inflammatory markers and hyponatremia), as well as the clinical conditions of the patients, *Legionella* UAT was successfully performed soon after hospitalization, identifying all the cases as Legionaries' disease.

Initial symptoms in patients with *Legionella* pneumonia are non-specific and do not allow for the differentiation of legionellosis with other forms of community acquired pneumonia (3). In according with this, in the present study, fever, cough and asthenia represented the most common symptoms reported.

As regards the imaging findings in legionellosis, chest computed tomography often describes ground-glass opacities, consolidation and pleural effusion (30). Pulmonary features are better highlighted with computed tomography than X-ray, which may be less sensitive, particularly at symptom presentation (31). Severe characteristics were found in the cohort in the present study, in which 4 patients had bilateral pneumonia and half of the patients presented pleural effusion, which may be linked to the high prevalence of predisposing comorbidities. In total, 2 patients presented immunosuppression factors (AIDS and systemic lupus erythematosus), and 2 patients had cancer. Of note, as indicated in the literature (32), immunosuppressed patients tend to exhibit an atypical presentation and signs, such as lung cavitations (33-36).

As regards laboratory examinations, hyponatremia and high levels of inflammatory markers were the most frequent abnormalities observed in the cohort in the present study, along with an increase in the levels of transaminases and abnormal procalcitonin levels.

As previously reported, other non-specific laboratory test abnormalities may occur in patients with legionellosis, that are consistent with pneumonia (37). These include hypophosphatemia, hyperbilirubinemia, increased levels of liver-associated enzymes, thrombocytopenia, leukopenia/leukocytosis, disseminated intravascular coagulation, pyuria, elevated creatine kinase, and elevated lactate dehydrogenase levels (38).

Furthermore, patients with legionellosis are more likely to have hyponatremia than those with pneumonia due to other causes; however, serum sodium levels are too variable to function as diagnostic markers (37,38).

Legionnaires' disease accounts for 2-9% of pneumonia cases (24), although the exact incidence worldwide may be underestimated mainly due to misdiagnosis and under-reporting. The detection of clusters of Legionnaires' disease requires the awareness of clinicians and the understanding of the clinical characteristics of Legionnaires' disease, sound disease reporting, as well as effective notification and investigation systems. Severe *L. pneumophila* pneumonia is associated with high rates of mortality and ICU admissions (39). Early, targeted therapy improves outcomes, and the timely investigation and intervention for potential sources limit the scale and recurrence of outbreaks (40).

Several studies have highlighted the association between the starting time of therapy and the prognosis of patients with legionellosis, also demonstrating the need of ICU care when appropriate antibiotic treatment is delayed (41). In the setting of CAP, when UAT is not available, initial antimicrobial treatment should include drugs active against *Legionella*. All patients in the present study had a communitarian CAP, two of them requiring oxygen administration, and *Legionella* UAT was performed within 2 days from the time of hospitalization.

The effective selection of antibiotic therapy, traditionally fluoroquinolones or macrolides represents the elective therapy against *Legionella* (24). Current guidelines recommend either a macrolide (azithromycin or clarithromycin) or a fluoroquinolone (moxifloxacin or levofloxacin) as a first-line treatment regimen for legionellosis (27,42). Although the majority of studies are retrospective and there are only a limited number of randomized trials, there are no clear data available supporting the use of levofloxacin rather than azithromycin, which are the preferred choice among the recommended classes, since there are no benefits in terms of clinical cure (43,44). In the same manner, despite the *in vitro* synergy of the fluoroquinolone/macrolide combination, as well as the positive effect of rifampin addition to the fluoroquinolone regimens, data on combination therapy are limited and unclear (45,46). In the present study, 9 of the 10 patients were treated with levofloxacin, whereas 1 patient received clarithromycin. The mean duration of antibiotic therapy was 17 days, which was longer than the duration suggested by other studies (7-10 days for moderate to severe *Legionella* pneumonia and 21 days for immunocompromised hosts) (47). All the patients we discussed were successfully discharged with no recurrences during a follow-up of 6 months.

In conclusion, it is suggested that testing for *Legionella* infection should be performed for all patients with community-acquired pneumonia, even in the absence of risk factors highlighted by the guidelines, particularly given the severity of this disease.

Due to its simplicity and rapidity, it is considered that UAT should be performed for all patients who visit the hospital with a diagnosis of pneumonia (confirmed with imaging together with a clinical evaluation). When the UAT results are negative, either in the presence of risk factors or if the clinical evaluation and imaging are compatible, it would be advisable to not *a priori* exclude legionellosis, guaranteeing an appropriate antibiotic

regimen and/or performing more sensitive tests (qPCR or culture) to unveil the possible presence of other SGs or species.

As regards antibiotic treatment, levofloxacin or clarithromycin exhibit the same efficacy, leading to positive clinical outcomes. It would be appropriate for antibiotic therapy to cover *Legionella* until diagnostic exclusion, to avoid worthless delays which could compromise clinical outcomes. Eventually, the development of rapid, cost-effective and broad-spectrum tests would be desirable.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors (AM, SS, EC, MC, AZ, MG, LL, GN and BC) contributed to the conception and design of the study. AM and SS were involved in the conceptualization of the study. EC was involved in the study methodology. AZ, LL and MG were involved in the investigative aspects of the study. MC was involved in data curation. MG and LL were involved in the writing and preparation of the original draft of the manuscript. AZ was involved in the writing, review and editing of the manuscript. GN and BC supervised the study. GN and BC confirm the authenticity of all the raw data. All authors have read and agreed to the published version of the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from all the patients whose data are presented herein. Ethics approval was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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