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**LEGIONNAIRES' DISEASE IN THE ERA OF  
MOLECULAR DIAGNOSTICS: IMPACT OF  
MULTIPLEX RESPIRATORY PANELS ON THE  
EARLY DETECTION OF LEGIONELLA  
PNEUMOPHILA MOLECULAR DIAGNOSIS OF  
LEGIONELLA PNEUMONIA**

ENFERMEDAD DEL LEGIONARIO EN LA ERA DEL  
DIAGNÓSTICO MOLECULAR: IMPACTO DE LOS PANELES  
RESPIRATORIOS MULTIPLEX EN LA DETECCIÓN  
TEMPRANA DE *LEGIONELLA PNEUMOPHILA* /  
DIAGNÓSTICO MOLECULAR DE LA NEUMONÍA POR  
LEGIONELLA

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## Legionnaires' Disease in the Era of Molecular Diagnostics: Impact of Multiplex Respiratory Panels on the Early Detection of Legionella pneumophila Molecular Diagnosis of Legionella Pneumonia

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### ABSTRACT

**Background:** Legionnaires' disease is a severe form of community-acquired pneumonia primarily caused by *Legionella pneumophila*. Although relatively uncommon, delayed diagnosis is associated with increased morbidity and mortality. Clinical suspicion is supported by extrapulmonary manifestations such as gastrointestinal symptoms, hyponatremia, and failure to respond to beta-lactam therapy. **Case presentation:** A 65-year-old male with hypertension and dyslipidemia developed fever, progressive dyspnea, and dry cough after environmental exposure to bird droppings. Laboratory tests showed leukocytosis, elevated C-reactive protein, and mild hyponatremia. After lack of response to amoxicillin-clavulanate and negative viral testing, multiplex PCR respiratory panel (FilmArray®) identified *Legionella pneumophila*. Targeted therapy with azithromycin led to rapid clinical improvement. **Discussion:** Legionella infection may mimic viral or typical bacterial pneumonia. Molecular multiplex diagnostic tools enable rapid pathogen identification. Early initiation of macrolides or fluoroquinolones significantly improves outcomes. **Conclusions:** Legionnaires' disease should be suspected in atypical pneumonia with systemic features and poor response to beta-lactams. Early molecular diagnosis and prompt intracellularly active antibiotic therapy are crucial determinants of prognosis.

**Keywords:** Legionella pneumophila; community-acquired pneumonia; hyponatremia; multiplex PCR; macrolides

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# **Enfermedad del Legionario en la Era del Diagnóstico Molecular: Impacto de los Paneles Respiratorios Multiplex en la Detección Temprana de *Legionella pneumophila* / Diagnóstico Molecular de la Neumonía por *Legionella***

## **RESUMEN**

Antecedentes: La enfermedad del legionario es una forma grave de neumonía adquirida en la comunidad, causada principalmente por *Legionella pneumophila*. Aunque es relativamente poco frecuente, el diagnóstico tardío se asocia con un aumento de la morbilidad y mortalidad. La sospecha clínica se apoya en manifestaciones extrapulmonares como síntomas gastrointestinales, hiponatremia y falta de respuesta a la terapia con betalactámicos. Presentación del caso: Un hombre de 65 años, con antecedentes de hipertensión y dislipidemia, desarrolló fiebre, disnea progresiva y tos seca tras exposición ambiental a excrementos de aves. Los estudios de laboratorio mostraron leucocitosis, elevación de proteína C reactiva e hiponatremia leve. Tras la falta de respuesta a amoxicilina-clavulánico y pruebas virales negativas, un panel respiratorio multiplex por PCR (FilmArray®) identificó *Legionella pneumophila*. El tratamiento dirigido con azitromicina condujo a una rápida mejoría clínica. Discusión: La infección por *Legionella* puede simular neumonía viral o bacteriana típica. Las herramientas diagnósticas moleculares multiplex permiten una rápida identificación del patógeno. El inicio temprano de macrólidos o fluoroquinolonas mejora significativamente los resultados clínicos. Conclusiones: La enfermedad del legionario debe sospecharse en neumonías atípicas con manifestaciones sistémicas y mala respuesta a betalactámicos. El diagnóstico molecular temprano y la terapia antibiótica oportuna con fármacos activos intracelularmente son determinantes clave del pronóstico.

**Palabras clave:** *Legionella pneumophila*; neumonía adquirida en la comunidad; hiponatremia; PCR multiplex; macrólidos

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## INTRODUCTION

Legionnaires' disease is a severe pneumonia predominantly caused by *Legionella pneumophila*, a facultative intracellular gram-negative bacillus that proliferates in artificial aquatic environments such as air-conditioning systems, cooling towers, and hospital water networks<sup>1</sup>. Since its first description in 1976, it has remained a significant cause of community-acquired pneumonia (CAP), with increasing incidence in several countries, partly attributed to improved diagnostic techniques and population aging<sup>2</sup>.

In Europe and North America, *Legionella* accounts for approximately 2–9% of hospitalized CAP cases; however, its prevalence increases in severe presentations or among patients requiring intensive care<sup>3</sup>. Reported mortality ranges from 4% to 18%, reaching higher rates in immunocompromised individuals or when appropriate antimicrobial therapy is delayed<sup>4</sup>.

The pathophysiology is based on inhalation of contaminated aerosols. Once in the lower respiratory tract, the bacterium invades alveolar macrophages using a type IV secretion system (Dot/Icm), which allows it to evade phagolysosomal fusion and replicate intracellularly<sup>5</sup>. This intracellular localization explains the limited efficacy of antibiotics that fail to achieve adequate intracellular concentrations.

Clinically, in addition to fever and respiratory symptoms, extrapulmonary manifestations are common and may include diarrhea, mild hepatic abnormalities, marked elevation of acute-phase reactants, and hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)<sup>6</sup>. The presence of these findings, together with lack of response to beta-lactam antibiotics, should increase clinical suspicion.

Traditional diagnosis relies on urinary antigen detection for *L. pneumophila* serogroup 1; however, this test does not identify other serogroups or species<sup>7</sup>. Currently, multiplex PCR techniques such as the FilmArray® Respiratory Panel enable identification of multiple respiratory pathogens with high sensitivity and specificity in approximately one hour<sup>8</sup>.

Recommended treatment according to international guidelines includes macrolides (azithromycin) or fluoroquinolones (levofloxacin), with a minimum duration of five days, extended in severe cases<sup>9</sup>.

We present the case of a patient with *Legionella pneumophila* pneumonia confirmed by molecular panel, highlighting the importance of early clinical recognition.



## CASE PRESENTATION

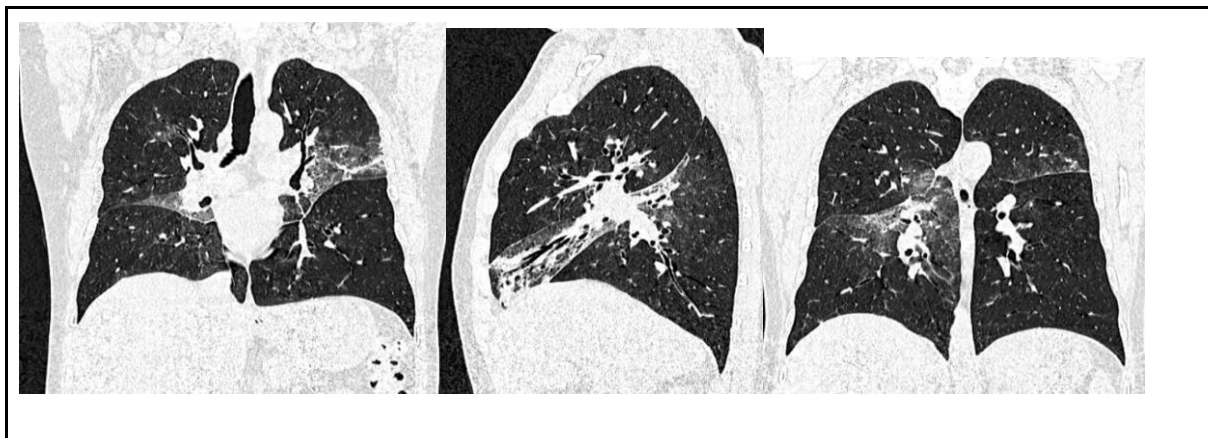
A 65-year-old male with a history of systemic arterial hypertension treated with losartan/hydrochlorothiazide and dyslipidemia under pharmacologic management presented to the hospital. He denied smoking and had no history of immunosuppression.

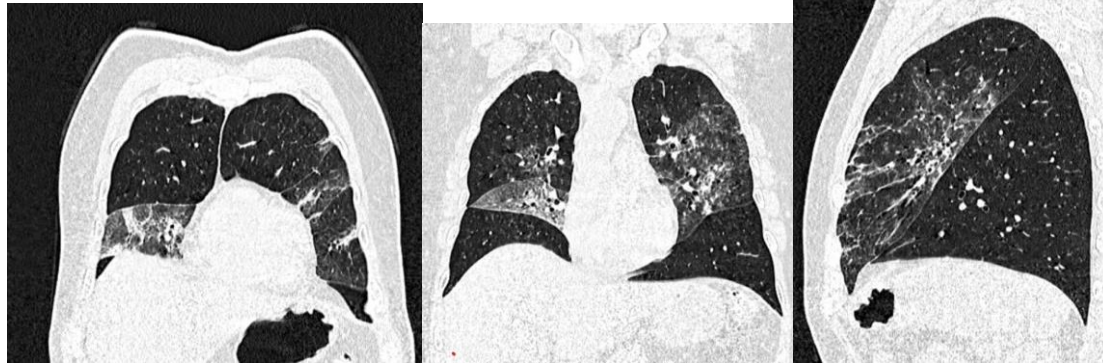
The patient developed unquantified fever, progressive dyspnea eventually occurring at rest, and persistent dry cough. He also reported dyspepsia and a recent history of cleaning a roof contaminated with bird droppings approximately five days prior to symptom onset.

At admission, respiratory rate was 24 breaths per minute, oxygen saturation was 90% on room air, and body temperature was 38.3°C. Pulmonary auscultation revealed crackles over the right mid-lung field. Initial laboratory tests demonstrated leukocytosis of 15,700/ $\mu$ L with neutrophilia (87%), C-reactive protein of 96 mg/L, serum sodium of 133 mEq/L, preserved renal function, and mildly elevated transaminases.

Chest radiography revealed ill-defined alveolar opacities, and empirical treatment with amoxicillin–clavulanic acid was initiated.

**Figure 1.** Chest Computed Tomography





Non-contrast chest computed tomography performed in lung window with coronal and sagittal reconstructions.

Coronal sections (upper row and lower left images) demonstrate areas of segmental parenchymal consolidation in the right lung, predominantly involving the lateral segment of the middle lobe (segment 5). The consolidation shows peripheral and subpleural distribution with visible air bronchograms. Multiple adjacent ground-glass opacities are also observed, displaying a patchy and poorly defined pattern.

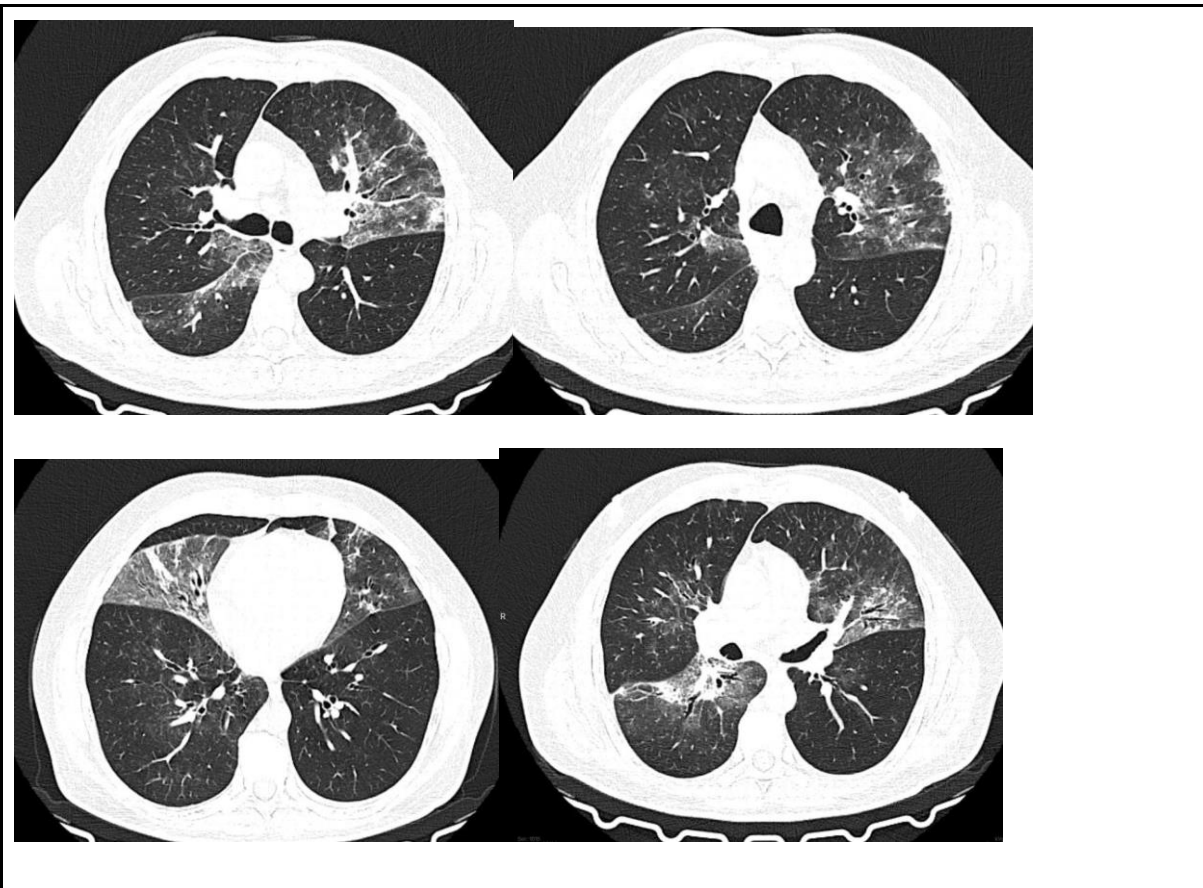
Sagittal sections (central and right images) confirm focal alveolar consolidation in the right middle lobe with extension toward the basal region, accompanied by mild interlobular septal thickening and areas of mixed ground-glass and consolidative pattern.

No significant pleural effusion, cavitation, or evident mediastinal lymphadenopathy is identified.

These findings are compatible with an acute alveolar–interstitial infectious process in the clinical context suggestive of atypical pneumonia caused by *Legionella pneumophila*.

Due to lack of clinical improvement and persistent fever, a chest computed tomography scan was performed, demonstrating consolidation in the right segment 5, initially suggestive of viral etiology. PCR tests for SARS-CoV-2, influenza, and respiratory syncytial virus were negative.

**Figure 2.** Chest Computed Tomography



Non-contrast chest computed tomography in lung window, axial sections.

Segmental and subpleural areas of alveolar consolidation are observed in the right lung, predominantly involving the middle lobe and the anterior basal segment of the right lower lobe. Air bronchograms are visible within the lesions. The consolidations have poorly defined margins and are associated with extensive perilesional ground-glass opacities, creating a mixed alveolar–interstitial pattern.

Additional bilateral patchy opacities are identified, with right-sided predominance and mild adjacent interlobular septal thickening. No cavitation, significant pleural effusion, or mediastinal lymphadenopathy is observed in these sections.

These radiologic findings are consistent with acute pneumonia of probable atypical etiology, concordant with *Legionella pneumophila* infection in the clinical context described.

A molecular respiratory panel (FilmArray®) was requested and returned positive for *Legionella pneumophila*. Treatment with azithromycin 500 mg orally every 24 hours for seven days was initiated, with evident clinical improvement within 48 hours, resolution of fever, and progressive normalization of inflammatory markers.

The patient was discharged without complications.

## DISCUSSION

Legionnaires' disease represents a diagnostic challenge due to its nonspecific clinical presentation<sup>10</sup>. In this case, the combination of gastrointestinal symptoms, hyponatremia, and lack of response to beta-lactam therapy suggested the presence of an atypical pathogen.

Hyponatremia is reported in up to 40% of cases and is attributed to inappropriate secretion of antidiuretic hormone induced by inflammatory cytokines<sup>11</sup>. Additionally, elevated C-reactive protein levels (>100 mg/L) have been associated with a higher probability of *Legionella* etiology<sup>12</sup>.

The FilmArray® respiratory panel demonstrated rapid diagnostic utility. Recent studies have shown sensitivity exceeding 95% for the detection of bacterial and viral respiratory pathogens<sup>13</sup>. Its use in severe pneumonia allows earlier adjustment of antimicrobial therapy and reduction of unnecessary broad-spectrum antibiotic use<sup>14</sup>.

ATS/IDSA guidelines recommend empirical coverage against *Legionella* in moderate-to-severe CAP<sup>9</sup>. Delayed initiation of macrolides or fluoroquinolones has been associated with increased hospital mortality<sup>15</sup>.

Compared with recent reports, our case is consistent with the literature regarding patient age, clinical presentation, and rapid response to macrolide therapy<sup>16–18</sup>.

Furthermore, in recent years an increase in the reported global incidence of legionellosis has been described, a phenomenon attributed both to population aging and to the greater availability of highly sensitive molecular diagnostic methods. Several epidemiological studies have indicated that the increasing use of molecular respiratory tests has enabled the identification of cases that previously remained underdiagnosed, particularly in patients hospitalized with community-acquired pneumonia presenting with atypical clinical evolution<sup>19</sup>. This shift in the diagnostic approach has contributed to a

better characterization of the true burden of the disease and has allowed optimization of targeted therapeutic strategies.

On the other hand, the integration of rapid diagnostic tools into the clinical approach to severe respiratory infections has become a key element of precision medicine in infectious diseases. Early identification of the etiologic agent not only allows selection of the most appropriate antibiotic therapy but also helps reduce the unnecessary use of broad-spectrum antimicrobials and supports antimicrobial stewardship strategies<sup>20</sup>. In this context, respiratory molecular panels represent a particularly useful diagnostic tool in patients with atypical pneumonia or with poor response to initial empirical therapy.

## CONCLUSION

Legionnaires' disease should be considered in the differential diagnosis of community-acquired pneumonia, particularly in patients presenting with atypical systemic manifestations such as gastrointestinal symptoms, hyponatremia, marked elevation of acute-phase reactants, and lack of clinical response to empirical regimens based exclusively on beta-lactam antibiotics. Recognition of these clinical features may facilitate early suspicion of *Legionella pneumophila* infection and prevent diagnostic delays associated with increased morbidity and mortality.

In recent years, multiplex molecular diagnostic tools have transformed the approach to respiratory infections by enabling rapid and simultaneous detection of multiple pathogens with high sensitivity and specificity. Their implementation in cases of moderate-to-severe pneumonia or in patients with atypical clinical evolution facilitates early initiation of targeted antimicrobial therapy, optimizes antimicrobial stewardship, and contributes to reduced hospital length of stay and complications.

Timely initiation of antimicrobials with adequate intracellular penetration, such as macrolides or fluoroquinolones, remains a cornerstone of therapy due to the intracellular localization of the microorganism within alveolar macrophages. The combination of clinical suspicion, radiological support, and molecular confirmation significantly improves prognosis, reduces mortality, and strengthens comprehensive management strategies for atypical pneumonia.

This case reinforces the importance of integrating clinical evaluation with advanced diagnostic tools in contemporary medical practice. Early recognition of Legionnaires' disease continues to be a challenge, but it also represents an opportunity for timely, evidence-based intervention.



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