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CASE REPORT

# Omadacycline for the Treatment of Severe *Legionella* Pneumonia Complicated with Multiple Organ Failure: A Case Report

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**Background:** Fluoroquinolones and macrolides are the preferred antibiotics for treating Legionnaires' disease. However, the limited utility of these antibiotics in cases of organ dysfunction is a major problem. Omadacycline is a novel tetracycline antibiotic with a good safety profile and in vitro antibacterial activity against *Legionella*, but it lacks validation by clinical data.

**Case Description:** Here, we report a case of severe pneumonia caused by *Legionella* infection. The patient was empirically treated with antibiotics, after admission but had a poor clinical outcome with severe hepatic and renal insufficiency. After *Legionella* infection was confirmed by metagenomic next-generation sequencing, the patient was switched to omadacycline antibiotic therapy and eventually discharged after recovery.

**Conclusion:** *The* results of this study suggest that metagenomic next-generation sequencing can facilitate early diagnosis of Legionnaires' disease, and omadacycline can be an alternative antibiotic treatment for severe Legionnaires' disease, especially in patients experiencing multiple organ failure.

**Keywords:** *Legionella* pneumonia, Legionnaires'disease, metagenomic next-generation sequencing, omadacycline, antibiotic therapy

## Introduction

Legionnaires' disease is an infection primarily caused by *Legionella pneumophila* and includes predominantly pneumonia-like manifestations that are often combined with damage to other extrapulmonary systems. It accounts for approximately 4.6% of cases of community-acquired pneumonia.[1] Patients are often severely ill and prone to developing multiple organ failure, and approximately 44% of these patients require intensive care unit (ICU) admission. The rate of morbidity and mortality for Legionnaires' disease is 10–15%,[2] hence, early diagnosis and timely and appropriate treatment are essential for reducing mortality. Diagnosis of Legionnaires' disease is often delayed or missed owing to the non-specificity of the clinical features and difficulty in obtaining timely and accurate pathological evidence.[3]

The preferred treatment for Legionnaires' disease is fluoroquinolones or macrolide antibiotic therapy. However, the limited utility of these antibiotics in cases of organ dysfunction is an important problem.[3,4] Omadacycline, a semisynthetic aminomethylcycline antibiotic derived from tetracycline, has good in vitro antibacterial activity against a wide range of atypical pathogens, including *Legionella pneumophila*, and is not affected by any previously known tetracycline resistance mechanisms such as ribosomal protection and efflux pumps.[5] Thus, it is a potential option for antibiotic treatment of patients with Legionnaires' disease. However, very few reports of Legionnaires' disease treated with omadacycline are published. Here, we report a patient with Legionnaires' disease who experienced severe hepatic and renal dysfunction secondary to initial therapy but improved following omadacycline treatment.

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## Case Presentation

An 81-year-old male was admitted to the Huizhou Central People's Hospital on September 18, 2022, with a principal complaint of fever and dyspnea. Three days before admission, the patient developed a fever with a maximum temperature of 39.5°C with no apparent cause. The fever was accompanied by dyspnea, chills, fatigue, muscle pain, and intermittent cough. The patient produced little sputum and did not complain of abdominal pain or diarrhea. The patient did not report marked improvement after self-medicating with oral cefuroxime and acetaminophen. One day prior, the patient visited the emergency department of our hospital. Chest computed tomography (CT) indicated a considerable consolidation in the left lung, patchy exudative lesions in the right lung, and a small amount of pleural effusion in the left lung (Figure 1A–C). The patient received piperacillin-sulbactam (4.5 g IV q.8 h) antibiotic injections, but the fever persisted, and the patient was subsequently admitted. The patient had a 5-year history of type 2 diabetes mellitus and was not taking hypoglycemic medication regularly.

Physical examination revealed a body temperature of 39.1°C; pulse, 95 beats/min; respiratory rate, 30 breaths/min; and blood pressure, 132/70 mmHg. The patient was conscious but described feeling in poor spirits; there was no evidence of rash, subcutaneous bleeding, or superficial lymph node enlargement. Breathing was slightly rapid, with coarse breath sounds in bilateral lungs and wet rales in the left lower lung. No other major abnormalities were noted.

Laboratory test results were as follows: blood gas analysis (FiO2 33%): pH, 7.505; pO2, 53 mmHg; pCO2, 27 mmHg; HCO3, 21.3 mmol/L; ferritin, >2000 μg/L (reference range: 13–150 μg/L); blood phosphorus, 1.52 mmol/L (reference range: 0.85–1.51 mmol/L); blood sodium, 145 mmol/L (reference range: 135–145 mmol/L); and urine erythrocytes, 530/μL (reference range: 0–17/μL). Other laboratory test results are shown in Table 1.

After admission, the patient was diagnosed with severe community-acquired pneumonia and administered meropenem injection (1.0 g IV q.8 h) and oseltamivir capsules (75 mg q. 12 h) as empirical antibiotic/antiviral treatment, hepatoprotective medication, and transnasal high-flow oxygen therapy. The patient's dyspnea was aggravated on the night of admission, with the oxygenation index falling to 62.5, leading to the initiation of emergency tracheal intubation and invasive mechanical ventilation. Given that the patient had a severe infection of unknown etiology, 10 mL of bronchoalveolar lavage fluid was collected via fiberoptic bronchoscopy on day 2 after admission for metagenomic next-generation sequencing (mNGS). During this period, antinuclear antibody panel, serum 1,3-β-D-glucan assay (G test), galactomannan (GM) assay, SARS-CoV-2 nucleic acid test, *Legionella* DNA test, and tests for IgM antibodies to respiratory pathogens (including *L. pneumophila, Mycoplasma pneumoniae, Rickettsia, Chlamydia pneumoniae*, adenovirus, respiratory syncytial virus, influenza A virus, influenza B virus, and parainfluenza virus) were all negative. Additionally, multiple sputum and blood cultures were negative. On day 4 after admission, the patient's temperature remained above 38.5°C, the dyspnea did not improve, cough and sputum increased, inflammatory indicators were higher than before, and severe liver and renal insufficiency was observed (Table 1). Chest CT re-examination indicated bilateral increases in lung lesions (Figure 1D–F). On day 4 after admission, mNGS results indicated the presence of *L. pneumophila* (76 sequences, coverage 32%) and *Candida albicans* (115 sequences, coverage 43%). According to the clinical manifestations and results of mNGS, severe *L. pneumophila* pneumonia was suggested. Given the severe hepatic and renal dysfunction, the antibiotic regimen was changed to omadacycline injection (first dose: 200 mg IV q.d., second dose: 100 mg IV q.d). Five days later, the dyspnea resolved completely, re-examination of inflammation and organ function indicators showed dramatic improvement (Table 1), and intravenous omadacycline was continued. On day 14, the patient was weaned from tracheal intubation, and transnasal high-flow oxygen therapy was administered. On day 22, all inflammation and organ function indicators had generally returned to normal, and chest CT indicated that the bilateral lung lesions were markedly resolved (Figure 1G–I). Omadacycline was discontinued, and the patient was discharged the following day. At the 2-month follow-up, the patient's general condition was satisfactory, with only occasional cough and no dyspnea. Chest CT indicated the lung lesions were almost entirely resolved, with only a few fibrotic streaks remaining (Figure 1J–L).

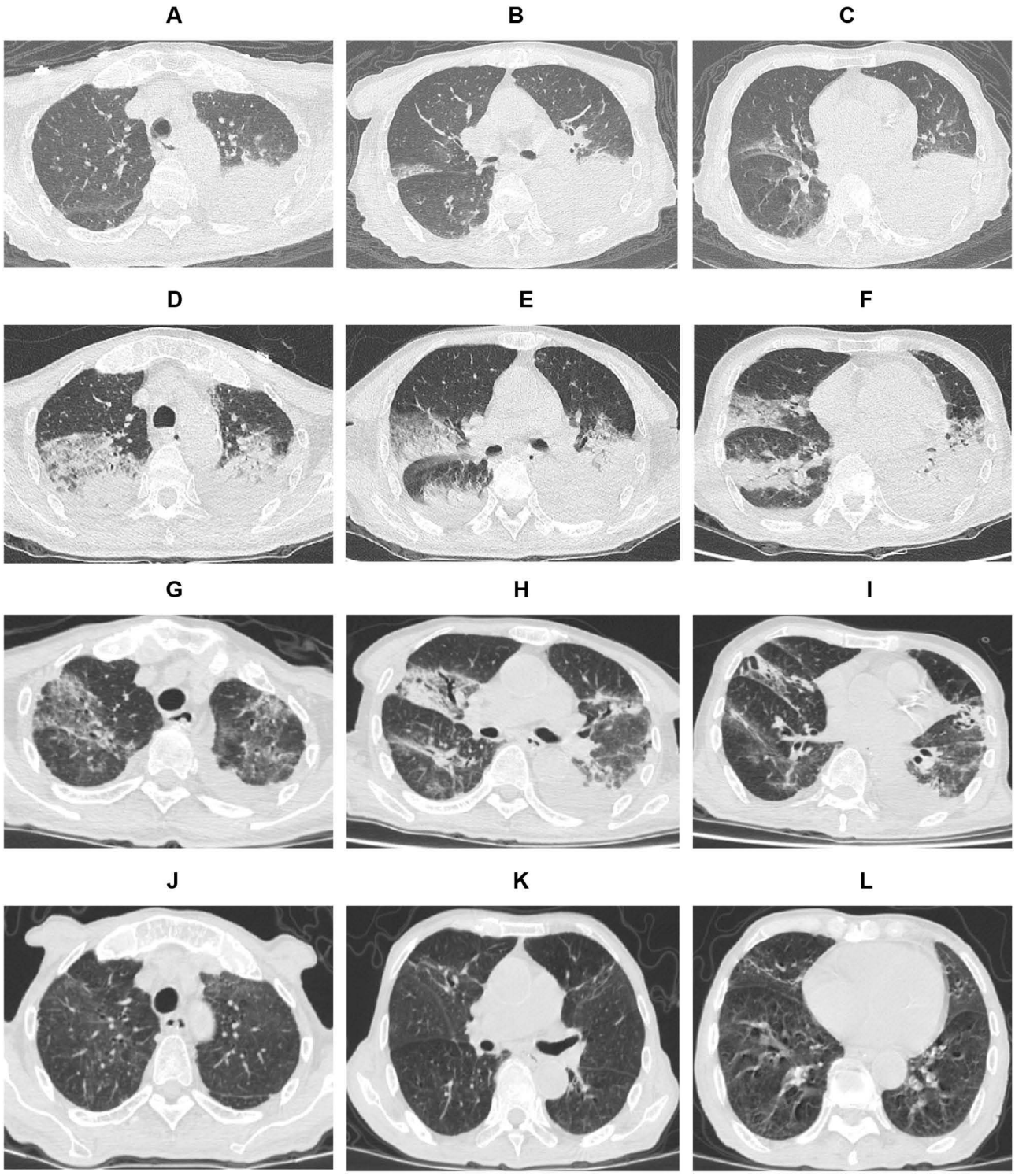


**Figure 1** Chest computed tomography (CT) images. (**A**–**C**) Chest CT 1 day before admission, showing a large consolidation in the left lung and patchy exudative lesions in the right lung, a small amount of pleural effusion in the left lung. (**D**–**F**) Chest CT on hospital day 4, showing bilateral increases in lung lesions. (**G**–**I**) Chest CT on hospital day 22, showing marked resolution of bilateral lung lesions. (**J**–**L**) Chest CT 2 months after discharge, showing almost complete resolution of the lung lesions, with only a few fibrotic streaks remaining.


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**Table 1** Results of Laboratory Tests of the Patient at Different Times

| Laboratory Test | Normal Range | First Day of Hospitalization | Fourth Day of Hospitalization | After 5 Days of Treatment with Omadacycline | One Day Before Discharge |
|---|---|---|---|---|---|
| Routine blood tests | | | | | |
| WBC ($\times 10^9$/L) | 4–10 | 21.8 | 25.3 | 11.6 | 5.9 |
| Neutrophil (%) | 40–75 | 96.2 | 98.1 | 78.2 | 65.1 |
| LYM ($\times 10^9$/L) | 1.1–3.2 | 0.49 | 0.33 | 1.26 | 1.69 |
| Inflammatory indexes | | | | | |
| C-reactive protein (mg/L) | 0–5 | 430.5 | 523.7 | 222.4 | 9.3 |
| Procalcitonin (ng/mL) | 0–0.05 | 3.03 | 3.74 | 0.76 | 0.06 |
| Interleukin-6 (pg/mL) | 0–7 | 275.3 | 289.5 | 75.0 | 4.6 |
| Biochemical indexes | | | | | |
| ALT (U/L) | 9–50 | 65 | 499 | 311 | 26 |
| AST (U/L) | 15–40 | 85 | 485 | 256 | 30 |
| CK (U/L) | 50–310 | 194 | 339 | 200 | 36 |
| LDH (U/L) | 109–245 | 393 | 547 | 304 | 180 |
| D-dimer (mg/L) | 0–500 | 2230 | 3580 | 1240 | 335 |
| BUN (mmol/L) | 3.2–7.1 | 15.8 | 11.2 | 5.7 | 2.3 |
| SCr (μmol/L) | 62–106 | 151 | 231 | 136 | 73 |
| BNP (pg/mL) | 0–100 | 438.2 | 397.1 | 185.2 | 113.7 |
| High-sensitivity troponin T (ng/mL) | 14–100 | 28.3 | 20.1 | 14.8 | 11.3 |

**Abbreviations**: ALT, alanine transaminase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; LDH, lactate dehydrogenase; LYM, lymphocytes; SCr, serum creatinine; WBC, white blood cells.

## Discussion

*Legionella* is an aerobic, gram-negative, intracellular, parasitic, opportunistic, and pathogenic bacterium often found in water supply systems and soil. Air conditioning condensate and circulating water from cooling towers are the primary sources of transmission. Inhaling aerosols containing *Legionella* can lead to pulmonary and extrapulmonary infections in humans. High-risk factors include advanced age, male sex, history of smoking, immunodeficiency, and comorbid cardiopulmonary disease.[2,3] After entering the body through the respiratory tract, *Legionella* first grows and multiplies in alveolar macrophages and then reaches the rest of the body through the bloodstream, causing systemic infections with pulmonary lesions and dysfunction of multiple organs.[6,7] The acute onset and rapid progression of the disease in the present case, with respiratory failure and hepatic and renal dysfunction developing within a short time, suggests that *Legionella* infection should be suspected in patients with community-acquired pneumonia who develop multi-organ dysfunction within a brief period. Legionnaires' disease has nonspecific clinical and imaging manifestations but can be strongly suspected based on several features,[2,8] including body temperature >38.9°C with a relatively slow pulse; erythrocyte sedimentation rate >90 mm/h or C-reactive protein >180 mg/L; elevated ferritin > double the normal level; hypophosphatemia; elevated creatine kinase > double the normal level; and microscopic hematuria on admission. In this case, more than three of these characteristics were noted, leading to Legionnaires' disease diagnosis by mNGS, further demonstrating that the Winthrop-University Hospital (WUH) scoring system can facilitate the identification of Legionnaires' disease at early stages.[8]

Currently, diagnosis of Legionnaires' disease relies on pathogen isolation and culture, urinary antigen testing, polymerase chain reaction (PCR) testing, and serum antibody testing.[2,3] *Legionella* isolation and culture are the gold standard for diagnosing Legionnaires' disease, but the culture conditions are harsh, and the positivity rate is affected by drug treatment. Urinary antigen testing can only detect type 1 *L. pneumophila* and is prone to missed diagnoses. In contrast, PCR testing is

rapid, sensitive, and specific but can detect only a single pathogen and is only performed when the clinician has a high suspicion of *Legionella* infection. Serum antibody testing is time-consuming and not suitable for the early diagnosis of *Legionella* infections.[2,3,9] In contrast, mNGS is an unbiased direct sequencing technique based on the shotgun method for clinical samples that do not require culture or specific amplification and covers a wide range of pathogenic microorganisms. It has excellent clinical utility in diagnosing rare infections, mixed infections, infections in immunosuppressed patients, and infections that are challenging to detect by conventional assays.[10,11] As *Legionella* is an intracellular pathogen, it must be considered a pathogenic agent even if the number of sequences detected is low,[10] and a diagnosis can be made in conjunction with other clinical manifestations. In the present case, the pathogenic agent was rapidly identified by mNGS, which guided antibiotic treatment and prevented further disease exacerbation and the unnecessary use of antibiotics.

As *Legionella* is an intracellular parasite, antibiotics with strong tissue penetration and high intracellular concentrations should be selected, which include fluoroquinolones, macrolides, and tetracyclines.[3,9] After admission, the patient had severe hepatic and kidney dysfunction, and treatment with fluoroquinolones, macrolides, and conventional tetracyclines was not appropriate. Therefore, omycycline was selected for anti-*Legionella* treatment. Omadacycline is a novel aminomethylcycline antibiotic that exerts antibacterial activity through specific binding to the 30S ribosomal subunit of bacteria. It has a broad-spectrum antibiotic activity, circumventing the common tetracycline resistance mechanisms of ribosomal protection and efflux pumps.[5,12,13] Omadacycline has a low rate of plasma protein binding and high tissue permeability, facilitating systemic antibacterial effects.[5] Excellent in vitro antibacterial activity of omadacycline against *Legionella* has been reported.[5,13] However, there have been few clinical reports on using omadacycline to treat Legionnaires' disease. Pharmacokinetic studies have shown the high bioavailability and safety of omadacycline, and it does not require dose adjustment for special populations such as elderly patients or those with hepatic and renal dysfunction.[5,14] Thus, omadacycline possesses important advantages in the antibacterial treatment of systemic infections combined with multiple organ failure. Legionnaires' disease is essentially a systemic disease prone to progressing to severe pneumonia with hepatic and renal dysfunction, which limits the use of fluoroquinolones, macrolides, and conventional tetracyclines such as doxycycline and minocycline to some extent.[2,15] In this case, treatment with fluoroquinolones was effective but led to the development of marked hepatic and renal dysfunction. Therefore, omadacycline treatment was started, the patient's symptoms improved, and inflammatory indicators gradually returned to normal; subsequently, the patient was discharged. This suggests that omadacycline can be a potential option for antibiotic treatment of Legionnaires' disease.

In general, if *Legionella* infection is suspected, *Legionella* urine antigen detection should be routinely performed. Unfortunately, the hospital where the patient was located did not have the necessary equipment and resources to conduct *Legionella* urine antigen detection.

For conditions such as Legionnaires' disease that lack specific clinical and imaging manifestations, mNGS can facilitate the early diagnosis of *Legionella* infection and omadacycline can be an alternative antibiotic treatment for severe Legionnaires' disease, especially in patients experiencing multiple organ failure.

## Data Sharing Statement

All relevant data are provided within the manuscript. All information in the article has been anonymized.

## Ethics Approval and Informed Consent

The Ethics Committees of Huizhou Central People's Hospital approved this study. Informed consents were obtained from the patient. Huizhou Central People's Hospital granted approval to publish the case details.

## Consent for Publication

Signed consent was obtained for the publication of the case details from the participant.

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## Disclosure

The authors report no conflicts of interest in this work.

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