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Case Report

Ceftobiprole in the Management of Severe *Legionella pneumophila* Pneumonia in Critically Ill Patients: Two Illustrative Case Reports

Novella Carannante [1,*], Michela Buonocore [2], Enza Napolitano [3], Angelantonio Maglio [4], Diana Abbenante [5], Alessandro Russo [6], Francesca Serapide [6], Giuseppe Fiorentino [7] and Anna Maria D'Ursi [3,*]

1 Emergency Infectious Diseases, Cotugno Hospital AO dei Colli, 80131 Naples, Italy
2 Department of Chemical Sciences, University of Naples "Federico II", Via Cinthia, 80126 Naples, Italy
3 Department of Pharmacy, University of Salerno, Via Giovanni Paolo II, 132, 84084 Fisciano, Italy
4 Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Via Salvador Allende, 43, 84081 Baronissi, Italy
5 Intensive Care Cotugno Hospital AO dei Colli, 80131 Naples, Italy
6 Department of Medical and Surgical Sciences, "Magna Graecia" University of Catanzaro, 88100 Catanzaro, Italy
7 Department of Respiratory Pathophysiology, Monaldi Hospital, Azienda Ospedaliera dei Colli, 80131 Naples, Italy
* Correspondence: novella.carannante@ospedaledeicolli.it (N.C.); dursi@unisa.it (A.M.D.)

Abstract

Legionella pneumophila is a pathogen responsible for severe 'atypical pneumonia' and is often associated with high mortality rates in hospitalized patients. Atypical pneumonia can progress to severe forms with fatal outcomes, causing multi-organ damage. The standard of care involves antibiotics such as fluoroquinolones and macrolides, therapies which can be limited by toxicity or emerging resistance. We report two complex cases of Legionella pneumonia not responsive to other antibiotics. Both cases involved ceftobiprole administration in combination with or following macrolide therapy, and in one case, also addressed a documented co-infection. In the first case, levofloxacin was discontinued due to neurotoxicity, and treatment was successfully switched to ceftobiprole combined with azithromycin, leading to complete clinical and radiological recovery. In the second case, ceftobiprole was administered for a concurrent *Staphylococcus aureus* infection, and a carbapenem-resistant *Acinetobacter baumannii* (CRAB) was subsequently managed with an alternative agent, eravacycline. This highlights the complexity of managing polymicrobial infections and the need for adaptable antimicrobial strategies. Ceftobiprole may represent a useful component of an individualized antimicrobial strategy in selected critically ill patients with severe Legionella pneumonia, particularly when first-line agents are contraindicated or concomitant bacterial infections require additional coverage. Although beta-lactams are generally not favored for Legionella due to poor intracellular penetration, the successful outcome in our first case suggests potential benefits in combination therapy. Furthermore, regional antibiotic resistance patterns, such as those observed in Campania (Italy), may favor the use of broad-spectrum agents like ceftobiprole. However, further clinical studies are warranted to define its precise role in this setting.

Keywords: *Legionella pneumophila*; atypical pneumonia; V generation cephalosporin

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Academic Editor: Alan G. Goodman

Received: 24 August 2026
Revised: 14 September 2026
Accepted: 23 September 2026
Published: 27 September 2026

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1. Introduction

Legionella is the only genus within the family of Legionellaceae, and *Legionella pneumophila*, particularly serogroup 1, is responsible for most human infections. These aerobic, Gram-negative bacilli were first identified following a 1976 outbreak among attendees of an American Legion conference [1]. Infections occur via inhalation of aerosolized droplets containing the organism, which primarily survives and replicates within alveolar macrophages.

Patients at greatest risk for Legionella infection include those with chronic cardiopulmonary conditions, immunosuppression, or advanced age [2]. Diagnosis is challenging and requires specific tests, including urinary antigen detection, serological assays, and culture on selective media. Radiological findings are often non-specific, and clinical features such as high fever, hyponatremia, and neurologic symptoms may offer diagnostic clues [3].

First-line antimicrobial agents include macrolides and fluoroquinolones due to their superior intracellular penetration, crucial for targeting Legionella residing within host cells [4,5]. Beta-lactam antibiotics are traditionally considered ineffective against *L. pneumophila* because of their limited intracellular penetration. However, recent real-life observations have prompted reconsideration of their role in complex clinical scenarios [6], and their use may occasionally become necessary in critically ill patients with polymicrobial infections or intolerance to first-line agents.

Ceftobiprole is a fifth-generation cephalosporin with broad-spectrum activity, including efficacy against methicillin-resistant *S. aureus* (MRSA) and various Gram-negative organisms [7]. While its use in Legionella pneumonia is not standard and evidence remains scarce, its excellent safety profile and broad-spectrum activity may justify off-label use in selected cases, particularly when co-infections are suspected or when standard treatments are contraindicated.

The possibility of Legionella co-infection with other bacterial pathogens has been increasingly recognized. In a series by Tan et al., several patients with *L. pneumophila* infection had concomitant bacteremia with *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or *Enterobacter cloacae* [4]. The study highlighted that Legionella may impair host immune defences, predisposing patients to secondary bacterial infections and complicating clinical management. This reinforces the need for broad-spectrum coverage in cases of severe pneumonia, especially in endemic regions or in patients with known risk factors, as also indicated in recent guidelines (https://www.cdc.gov/legionella/hcp/clinical-guidance, accessed on 15 July 2026).

Here, we report two cases of complicated *L. pneumophila* pneumonia treated with ceftobiprole in an intensive care setting. The first case involved intolerance to standard fluoroquinolone therapy, while the second case included a confirmed polymicrobial infection. These cases suggest a potential, though still unconfirmed, role for ceftobiprole in complex clinical scenarios involving atypical pathogens. The purpose of this report is not to directly demonstrate anti-Legionella activity of ceftobiprole, but rather to describe its use within individualized antimicrobial management in critically ill patients.

2. Detailed Case Description

2.1. Case 1

A 77-year-old woman with a history of chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (treated with CPAP), atrial fibrillation, and renal artery stenosis was admitted to the sub-intensive care unit with severe *L. pneumophila* pneumonia, confirmed by urinary antigen fluorescence immunoassay.

At admission, the patient presented with acute respiratory failure requiring non-invasive ventilation. Laboratory findings revealed elevated inflammatory markers, and chest imaging showed bilateral pulmonary consolidations. Initial antimicrobial ther-

apy consisted of intravenous levofloxacin in combination with intravenous azithromycin (500 mg/day), as indicated by the guidelines. However, after three days of treatment, levofloxacin was discontinued due to neuropsychiatric side effects (hallucinations). The antibiotic regimen was subsequently switched to intravenous ceftobiprole (500 mg every 8 h) in combination with full-dose azithromycin.

The patient experienced progressive clinical and radiological improvement over a 10-day course of combination therapy, as documented by a comprehensive assessment of clinical condition, respiratory status, radiological findings, biochemical parameters, and hemodynamic stability. She was successfully weaned from ventilatory support and discharged home in stable clinical condition.

2.2. Case 2

A 38-year-old man was transferred to our intensive care unit following a prolonged hospitalization for severe *L. pneumophila* pneumonia, with complications from other comorbidities. He had been tracheostomized and remained on mechanical ventilation at the time of transfer. The diagnosis of Legionella infection had been confirmed earlier by a urinary antigen fluorescence immunoassay.

At the referring hospital, the patient had received a three-week course of fluoroquinolones and macrolides, which was discontinued after severe hepatotoxicity developed. Upon admission to our unit, microbiological cultures yielded MRSA, confirming a concomitant bacterial infection. Based on the microbiological susceptibility profile and the need for effective anti-staphylococcal coverage, ceftobiprole was initiated at 500 mg every 8 h and continued for seven days.

During this period, liver function normalized, although the patient developed bilateral pneumothoraxes requiring chest tube placement. However, seven days after initiation of ceftobiprole, surveillance respiratory cultures yielded carbapenem-resistant *Acinetobacter baumannii* (CRAB), prompting a reassessment of antimicrobial therapy. Because of the newly isolated CRAB, together with persistent concern regarding ongoing infection, antimicrobial therapy with ceftobiprole was discontinued and changed to intravenous eravacycline (1 mg/kg every 12 h for 7 days). Within 48 h of this switch, the patient demonstrated marked improvement in respiratory function, and liver function remained stable. In this case as well, the improvement was documented through a comprehensive assessment that included clinical condition, respiratory status, radiological findings, biochemical parameters, and hemodynamic stability.

This case underscores the complexity of managing severe pneumonia with multiple coexisting pathogens and highlights the importance of individualized, dynamic antimicrobial strategies.

Table 1 provides a schematic comparison between the two cases.

Table 1. Comparison of the two patients with severe *Legionella pneumophila* pneumonia.

	Case 1	**Case 2**
Age	77	38
Sex	Female	Male
Legionella diagnosis	Confirmed by urinary antigen testing	Confirmed by urinary antigen testing
Clinical presentation	Acute respiratory failure	Severe pneumonia
Respiratory support	Non-invasive ventilation	Mechanical ventilation Tracheostomy

Table 1. *Cont.*

	Case 1	Case 2
Comorbidities	COPD Obstructive sleep apnea Atrial fibrillation Renal artery stenosis	Not reported
Initial antimicrobial therapy	Intravenous levofloxacin + azithromycin	Three-week course of fluoroquinolones + macrolides at the referring hospital
Reason for discontinuation of initial therapy	Hallucinations	Severe hepatotoxicity
Bacterial co-infection	Not reported	MRSA CRAB 7 days after treatment with ceftobiprole
Treatment and doses of antimicrobials	IV ceftobiprole 500 mg every 8 h Full-dose azithromycin	IV ceftobiprole 500 mg every 8 h, discontinued after 7 days and replaced by eravacycline 1 mg/kg every 12 h for 7 days
Outcome	Successfully weaned from ventilatory support and discharged home in stable clinical condition	Improvement in respiratory function Liver function remained stable

3. Discussion

The cornerstone of *L. pneumophila* pneumonia management is timely and effective antimicrobial therapy. Delayed or inappropriate treatment is associated with high mortality, particularly in hospitalized and critically ill patients [5,8]. Macrolides and fluoroquinolones are the mainstay of therapy due to their intracellular penetration, which is critical for targeting Legionella residing within alveolar macrophages [9,10]. However, therapeutic choices may be limited by drug-related toxicities or resistance, necessitating alternative strategies.

Our first case illustrates the challenges of maintaining effective antimicrobial therapy in a critically ill patient when a first-line fluoroquinolone must be discontinued due to side effects. Ceftobiprole was introduced as a replacement for levofloxacin while azithromycin was continued as Legionella-directed therapy. Following this therapeutic modification, the patient experienced a favorable clinical course. Although the independent contribution of ceftobiprole cannot be isolated from that of concomitant azithromycin, this observation is clinically relevant because it reflects a real-world therapeutic scenario in which the standard fluoroquinolone-based regimen could no longer be maintained in a critically ill patient. In such circumstances, the availability of an additional broad-spectrum agent may be valuable, particularly when concomitant bacterial pathogens are suspected or documented.

In our second case, ceftobiprole was appropriately used to treat a critically ill patient with severe *L. pneumophila* pneumonia with documented MRSA co-infection [11]. However, the subsequent identification of CRAB posed an additional microbiological challenge and led to modification of the antimicrobial regimen, replacing ceftobiprole with eravacycline. Clinical improvement was subsequently observed after this change. Rather than indicating failure of ceftobiprole against the initial bacterial co-infection, this clinical course illustrates the dynamic nature of severe polymicrobial infections in the intensive care setting, where antimicrobial therapy may need to be repeatedly reassessed in response to emerging microbiological findings and the patient's clinical evolution. Importantly, ceftobiprole provided broad-spectrum coverage during the initial phase of management, including activity against the documented MRSA co-infection.

Ceftobiprole is a fifth-generation cephalosporin with broad-spectrum antibacterial activity. As a beta-lactam antibiotic, it exerts its antibacterial effect by binding to penicillin-binding proteins (PBPs), thereby inhibiting bacterial cell-wall synthesis. Its spectrum includes several clinically relevant Gram-positive and Gram-negative pathogens, including MRSA. Although beta-lactams are not considered first-line agents for Legionella because of the pathogen's intracellular localization, ceftobiprole may still have clinical utility as part of a broader antimicrobial regimen in selected critically ill patients. In particular, its activity against concomitant bacterial pathogens may complement the activity of a Legionella-directed agent such as azithromycin. This potential complementary role provides a pharmacological rationale for its use in complex clinical situations, although the specific contribution of ceftobiprole to the treatment of Legionella infection cannot be established from the present cases.

Indeed, co-infection in legionellosis may be underdiagnosed. Tan et al. described six patients with *L. pneumophila* pneumonia and concurrent bacteremia from pathogens including *S. pneumoniae*, *S. pyogenes*, and *E. cloacae*. In several cases, initial empiric therapy failed, leading to complications and delayed recovery. The authors suggested that Legionella infection may impair local host defences, potentially predisposing patients to secondary bacterial infections. This immunomodulatory effect, though not fully understood, might partly explain the high rates of co-infection reported in severe community-acquired pneumonia [4]. In critically ill patients, polymicrobial infections frequently complicate the clinical course and require repeated microbiological reassessment. Therefore, antimicrobial modifications may reflect the emergence of additional pathogens rather than failure of the initial regimen alone.

These findings support the rationale for initiating empiric antimicrobial therapy that covers both typical and atypical pathogens. Such approach is also endorsed by major guidelines [8], and is particularly pertinent in intensive care settings where delays in adequate therapy can be fatal.

Furthermore, our clinical experience must be interpreted in the context of regional antimicrobial resistance patterns. Surveillance data from the Campania region (Southern Italy) in 2022 and 2024 showed alarmingly high rates of resistance among Gram-negative organisms to aminopenicillins, third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems. Notably, resistance to levofloxacin exceeds 64% among *Enterobacterales*, while fluoroquinolone resistance in Gram-positives surpasses 70% [12,13]. These figures underline the urgency of reconsidering traditional empiric regimens and explain the need to include broad-spectrum agents like ceftobiprole in selected scenarios. These surveillance data do not concern Legionella, but illustrate the epidemiological context in which empirical broad-spectrum agents like ceftobiprole are frequently required.

Lastly, ceftobiprole appears to exert a lower selective pressure on the gut microbiota compared to carbapenems, potentially reducing the risk of colonization or infection with ESBL- or AmpC-producing *Enterobacterales*, an important consideration in regions with high antimicrobial resistance.

This report has several limitations. The small number of cases and the absence of a control group preclude any definitive assessment of the efficacy of ceftobiprole against *L. pneumophila*. In Case 1, ceftobiprole was administered concomitantly with azithromycin, and therefore its individual contribution to clinical improvement cannot be established. In both cases, microbiological eradication of *L. pneumophila* was not systematically assessed after treatment, and culture-based isolation of the organism and direct antimicrobial susceptibility testing were not feasible in our clinical microbiology setting. Finally, no experimental studies evaluating macrophage penetration or intracellular activity of ceftobiprole

were performed. These limitations are inherent to the observational nature of this case report and highlight the need for further clinical and experimental investigation.

While ceftobiprole is not currently recommended as standard therapy for Legionella infections, our experience suggests that its broad-spectrum activity and tolerability profile may be clinically useful in selected critically ill patients with severe and complicated pneumonia, particularly when first-line agents cannot be continued because of toxicity or when concomitant bacterial infections require additional coverage. The value of these cases lies not in establishing the direct efficacy of ceftobiprole against *L. pneumophila*, but in illustrating how antimicrobial therapy may need to be individualized in real-world intensive care practice.

The clinical course of *L. pneumophila* pneumonia is dynamic and often unpredictable. A flexible, evidence-informed, and patient-centered antimicrobial strategy is essential, especially in high-risk populations and regions with complex resistance epidemiology. Further clinical observations and prospective studies will be important to determine whether ceftobiprole may have a broader role in such complex clinical settings.

Author Contributions: Conceptualization, N.C.; methodology, N.C.; validation, N.C.; formal analysis, N.C., E.N., A.M., D.A., A.R. and F.S.; investigation, N.C., E.N., A.M., D.A., A.R. and F.S.; resources, N.C. and A.M.D.; data curation, N.C. and M.B.; writing—original draft preparation, N.C. and M.B.; writing—review and editing, N.C., M.B., G.F. and A.M.D.; visualization, M.B.; supervision, N.C.; project administration, N.C. and A.M.D.; funding acquisition, A.M.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were not required for this study, as there has been no experimentation involving the drugs, but rather a simple 'good clinical practice' of first treatment with failure and after this a second line treatment. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article.

Acknowledgments: The authors would like to thank DHEAL—COM-Digital Health Solutions in Community Medicine under the Innovative Health Ecosystem (PNC)—National Recovery and Resilience Plan (NRRP) program funded by the Italian Ministry of Health.

Conflicts of Interest: The authors declare no conflicts of interest.

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