

The Efficacy and Safety of Omadacycline plus β -Lactam versus Moxifloxacin plus β -Lactam for the treatment of Severe Community-Acquired Pneumonia: A Multicenter, Prospective, Randomized Controlled Trial

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Abstract

Background: Severe community-acquired pneumonia (sCAP) is associated with high morbidity and mortality. Current empirical antimicrobial regimens are increasingly challenged by rising antimicrobial resistance and safety concerns (e.g., fluoroquinolone-related adverse events). Omadacycline, a novel aminomethylcycline antibiotic, exhibits broad-spectrum activity against common respiratory pathogens (including drug-resistant strains) and a favorable safety profile. However, its efficacy and safety when combined with β -lactams for the treatment of sCAP remain insufficiently explored.

Methods: This is a multicenter, prospective, randomized, open-label, active-controlled, non-inferiority trial conducted across 8 tertiary hospitals in China. Eligible participants are adult patients (≥ 18 years old) who meet the IDSA/ATS 2019 diagnostic criteria for sCAP, with no contraindications to the study drugs (omadacycline, β -lactams, or moxifloxacin) and able to complete follow-up. A total of 248 patients will be recruited and randomized in a 1:1 allocation ratio to either of the two arms. The experimental arm will receive omadacycline (200mg iv once daily for the first day, then 100mg iv q24h) plus β -lactam therapy (piperacillin-tazobactam 4.5g iv q8h or meropenem 1g iv q8h). The control arm will receive moxifloxacin (400mg iv q24h) plus the same β -lactam regimen. The treatment duration for both groups will be 7–14 days, adjusted based on clinical response. The primary endpoint is early clinical response at 72–96 hours (defined as improvement in ≥ 2 major clinical symptoms/signs of pneumonia without worsening of any other major symptom/sign). Secondary endpoints include clinical cure at the end of treatment, 28-day all-cause mortality, epidemiology of pathogens of severe CAP, time to clinical stability, incidence of adverse events, and length of hospital stay. This trial has obtained ethical approval from the Ethics Committee of the leading center (Approval Number: [KY-2025-8-167-1]). The study protocol has been filed with the Ethics Committees of all other participating hospitals in accordance with relevant regulatory requirements, and all patients will provide written informed consent prior to enrollment.

Discussion: This trial aims to evaluate whether omadacycline combined with β -lactam is noninferior to the standard β -lactam plus moxifloxacin regimen in the treatment of sCAP. If confirmed, this combination may provide a safer and broader-spectrum alternative for sCAP, addressing unmet needs in the context of increasing antimicrobial resistance.

Trial registration: Chinese Clinical Trial Registry ChiCTR2500109407. Registered on 17 September 2025.

Key messages

- At present, clinical studies of omadacycline for the treatment of CAP are largely limited to mild-to-moderate disease; robust evidence regarding its efficacy in sCAP, its potential synergistic effects with β -lactams, and its impact on clinical outcomes remains lacking.
- The design of this ongoing RCT is intended to provide robust, evidence-based support for optimizing the clinical use of omadacycline in the management of sCAP and to address a critical gap in the current clinical evidence.

Introduction (Background and rationale)

Community-acquired pneumonia (CAP) is a major type of lower respiratory tract infection, ranking as the fourth leading cause of global mortality and the second in low-income countries [1]. Severe CAP (sCAP), which often requires intensive care unit (ICU) admission, presents a critical public health burden with high incidence, acute and long-term complications, and substantial healthcare costs [2]. Mortality rates remain unacceptably high, reaching up to 47% in the ICU and exceeding 30% in patients requiring both invasive mechanical ventilation and shock management. While pathogen resistance prevalence remains relatively low, its emergence complicates empirical antibiotic selection[3–4]. Current guidelines recommend β -lactam combined with a macrolide or respiratory fluoroquinolone [5–6], yet rising macrolide resistance (especially in *Mycoplasma pneumoniae*) and fluoroquinolone-related safety risks (e.g., tendinopathy, cardiovascular events) significantly limit their clinical utility [7–10].

Omadacycline, a novel semisynthetic aminomethylcycline derived from minocycline, exhibits broad-spectrum activity against common and resistant respiratory pathogens, including penicillin- and macrolide-resistant streptococci, methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-producing Enterobacterales, and macrolide-resistant atypical bacteria [11–13]. In vitro studies have demonstrated that omadacycline is 3–5 times more potent than vancomycin and linezolid against *Staphylococcus* species, highlighting its potential to address unmet needs in antibiotic therapy [14]. Preclinical and early-phase clinical data have confirmed omadacycline's ability to overcome macrolide resistance and avoid fluoroquinolone-related adverse events, supporting its potential as an alternative treatment for sCAP [15, 16]. However, large-scale randomized controlled evidence specifically evaluating omadacycline in sCAP patients remains limited, leaving a critical gap in understanding its optimal role in this high-risk population. Existing studies have primarily focused on mild-to-moderate CAP or other infections, and their findings cannot be directly extrapolated to the complex pathophysiology and pathogen profiles of sCAP [17, 18].

Therefore, we aim to conduct a multicenter, randomized controlled trial to evaluate the efficacy and safety of omadacycline-based therapy compared to standard guideline-recommended regimens in patients with severe community-acquired pneumonia. This study will address the unmet clinical need for effective, well-tolerated antibiotic options that can overcome the limitations of current therapies, providing high-quality evidence to inform the management of sCAP.

Methods

Study design

This was an open-label, multicenter, non-inferiority randomized controlled trial (RCT) conducted to compare the efficacy and safety of omadacycline combined with β -lactam versus fluoroquinolone (moxifloxacin) combined with β -lactam in adults with severe community-acquired pneumonia (SCAP). A total of 248 eligible patients will be recruited from 8 participating hospitals in China between September 2025 and December 2026. Participants will be randomized 1:1 to the experimental arm (omadacycline

combination therapy) or the control arm (moxifloxacin combination therapy) using block randomization. This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) guidelines[19-20]. The study design is depicted in Figure 1, and detailed procedures for enrollment, interventions, and outcome assessments are summarized in Table 1.

Ethics and Registration

The protocol was approved by the Ethics Committee of the Chinese PLA General Hospital (No. KY-2025-8-167-1) and prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2500109407). The study will be performed in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Any protocol modifications will be submitted to the Ethics Committee for reapproval. Written informed consent will be obtained from all participants or their legal representatives prior to enrollment. Trial results will be published in peer-reviewed journals and presented at academic conferences.

Eligibility Criteria

Enrolled patients were adults (18–85 years) of either sex with ≥ 2 community-acquired pneumonia-related symptoms (cough, purulent sputum, dyspnea, or pleuritic chest pain), meeting the diagnostic criteria for SCAP per the Diagnosis and Treatment Guidelines for Community-acquired Pneumonia in Adults[6] and 2019 IDSA/ATS guidelines. SCAP was defined as meeting either 1 major criterion or ≥ 3 minor criteria:

Major criteria: Septic shock requiring vasopressors; Respiratory failure requiring mechanical ventilation.

Minor criteria: Respiratory rate >30 breaths/min; $\text{PaO}_2/\text{FIO}_2 < 250$ mmHg; Multilobar infiltrates; Confusion/disorientation; Uremia (blood urea nitrogen >20 mg/dl); Leukopenia (white blood cell count $<4,000$ cells/ml); Thrombocytopenia (platelet count $<100,000$ /ml); Hypothermia (core temperature $<36^\circ\text{C}$); Hypotension requiring aggressive fluid resuscitation.

Inclusion Criteria

Age 18–85 years;

Fulfills sCAP diagnostic criteria per the 2019 IDSA/ATS guidelines;

Willing to provide written informed consent and complete the study follow-up.

Exclusion Criteria

Patients were excluded if they met any of the following:

1. Prior use of fluoroquinolones or omadacycline for >3 days before enrollment;
2. History of hypersensitivity to β -lactams, fluoroquinolones, or omadacycline;

3. Severe liver failure;
4. QT interval >450 ms (male) or >470 ms (female) at admission, or known long QT syndrome;
5. Severe immunosuppression (primary immunodeficiency, active malignancy [except localized non-melanoma skin cancer/early-stage malignancies] within 1 year, current chemotherapy/radiotherapy, HIV infection with CD4⁺ T-lymphocyte count <200/ μ L or percentage <14%, solid organ/hematopoietic stem cell transplantation history, systemic corticosteroid use [$\geq$ 20 mg prednisone equivalent daily for $\geq$ 14 days or cumulative dose >600 mg] or immunosuppressants/biological immunomodulators within 3 months)[21];
6. Suspected/confirmed infection with pathogens unresponsive to study drugs (e.g., *Pneumocystis jirovecii*, fungi, viruses);
7. Suspected/confirmed empyema (excluding parapneumonic effusion) or lung abscess;
8. Prior hospitalization >48 hours before current admission;
9. Pregnancy or lactation;
10. Anticipated inability to complete treatment due to personal reasons;
11. Severe structural lung disease;
12. Microbiological evidence of *Pseudomonas aeruginosa* or *Staphylococcus aureus* infection within 1 year.

Recruitment

Participants will be recruited from 8 hospitals: the First, Fourth, Fifth, Seventh, Eighth, and Ninth Medical Centers of the PLA General Hospital, China Aerospace Science and Industry Corp 731 Hospital, and Beijing Huimin Hospital. Clinicians at each site will screen hospitalized sCAP patients for eligibility, with supplementary recruitment via social media platforms (e.g., WeChat™).

Randomization and Blinding

Randomization will be performed using a computer-generated random-number sequence (Beijing Medlive Technology Co., Ltd; <http://dct.meddb.cn/>) with block randomization to allocate participants 1:1 to the two arms. The randomization code will serve as the unique identifier for each participant. Blinding will be maintained for investigators involved in data analysis (laboratory quantification and statistical analysis) to minimize detection bias; clinicians administering interventions will be unblinded due to the open-label design.

Interventions

Both arms will receive empirical β -lactam therapy, with subsequent adjustments based on etiological findings and antimicrobial susceptibility testing (AST) results. The minimum duration of study drug administration is 3 days, and the total anti-infective course is 7–14 days per the National Guidelines for Antimicrobial Therapy (Second Edition)[22].

Experimental arm: β -lactam (piperacillin–tazobactam 4.5 g IV q8h or meropenem 1g IV q8h, adjusted for renal function; meropenem preferred for hemodynamically unstable patients) + omadacycline (200 mg IV loading dose on Day 1, then 100 mg IV qd; may switch to oral 300 mg qd if clinically stable).

Control arm: β -lactam (same as experimental arm) + moxifloxacin (400 mg IV qd; may switch to oral 400 mg qd if clinically stable).

Outcome Measures

Primary Outcome

Early treatment response, assessed 72–96 hours after the first study drug dose, defined as: (1) Resolved: any 50% or more decrease in respiratory symptom severity score compared with baseline without need to change Initial standard-of-care treatment[23], or (2) any 30% or more decrease in Sequential Organ Failure Assessment (SOFA) score compared with baseline or favourable change in procalcitonin kinetics (defined as $\geq 80\%$ decrease in procalcitonin compared with baseline or blood procalcitonin < 0.25 ng/mL), without antibiotic escalation; (2) Ineffective: worsening symptoms/signs, elevated infection markers, radiological progression, antibiotic escalation, or death.

Secondary Outcomes

Treatment endpoint evaluation (24–48 hours post-final study drug dose): Treatment remission rate ($\geq 80\%$ PCT reduction, $\geq 50\%$ SOFA score reduction vs. baseline, complete resolution of severe CAP symptoms), and mortality rate.

Treatment post-evaluation (5–10 days post-final study drug dose): Treatment remission rate (complete resolution of all severe CAP symptoms) and mortality rate.

Safety evaluation: Adverse events (AEs), renal function, and liver function during treatment.

The epidemiology of pathogens of severe CAP.

28-day survival rate.

Sample Size Calculation

Sample size was calculated based on previous studies, assuming an early clinical response rate of 80% in both arms. With a 10% dropout rate, 124 patients per arm (total 248) will provide 80% power (one-

sided $\alpha=2.5\%$) to demonstrate non-inferiority with a 15% margin using the Miettinen and Nurminen method.

Data Management and Statistical Analysis

In this study, source data will be recorded on printed Case Report Forms (CRFs). An electronic data capture (EDC) system (Beijing Medlive Technology Co., Ltd) will subsequently be established to capture all information transcribed from the CRFs. Independent double data entry and secondary verification will ensure data integrity and accuracy. To maintain rigorous oversight, medical staff independent of the study team will be responsible for trial monitoring. These monitors will have access to the database to verify adherence to the study protocol, ensure the protection of participant rights and well-being, and confirm the accuracy and completeness of the study data.

Statistical analyses will be performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics will summarize demographic and outcome data: continuous variables as mean $\pm$ SD or median (IQR) (per distribution), categorical variables as frequencies (percentages). Univariate comparisons will use Student's t-test, ANOVA, or rank-sum test (continuous variables) and χ^2 test (categorical variables). All tests will be two-sided, with $P<0.05$ considered statistically significant. Efficacy analyses will include modified intention-to-treat (mITT), per-protocol (PP), and safety set (SS) populations.

Safety Monitoring

All study drugs are commercially available and administered per routine clinical practice, with foreseeable AEs (consistent with guideline-recommended agents for CAP). Clinicians will monitor AEs closely; moderate-to-severe AEs will prompt immediate study drug discontinuation and appropriate treatment. All AEs will be reported to the project leader and Ethics Committee.

Quality Control

Pre-study investigator training will standardize sampling and data collection. Site Principal Investigators will ensure procedural adherence and data integrity. The lead investigator will conduct regular monitoring and audits of clinical data and sample collection to maintain study quality.

The data monitoring committee, comprising representatives from the medical ethics committee and the Clinical Trial Management Department of the Fifth Medical Center of Chinese PLA General Hospital, has been established to oversee trial conduct. Throughout the study, this committee will review accumulating data and may issue recommendations regarding protocol modifications, continuation, or termination of the trial. Any amendments to the protocol will be promptly communicated to all relevant stakeholders by the committee to maintain protocol integrity. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Discussion

This multicenter, open-label, non-inferiority randomized controlled trial (RCT) compared the efficacy and safety of β -lactam combined with omadacycline versus β -lactam combined with fluoroquinolone in adults with severe community-acquired pneumonia (sCAP). Its primary purpose is to generate definitive evidence, thereby providing robust, evidence-based support for optimizing the clinical use of omadacycline in the management of sCAP and addressing a critical gap in the current clinical evidence

sCAP remains associated with high mortality (16%–36% across clinical cohorts), despite advances in its understanding, and empiric antibiotic selection is a key determinant of patient outcomes [24-28]. Omadacycline, a third-generation semisynthetic aminomethylcycline derived from minocycline, has distinct advantages that make it a promising candidate for sCAP treatment. Approved in the United States and China for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), it exhibits potent activity against core sCAP pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, atypical organisms) [29]. Notably, it retains efficacy against doxycycline- and macrolide-resistant *S. pneumoniae* (accounting for 20%–40% of North American isolates) and demonstrates in vitro activity against Enterobacterales and methicillin-resistant *Staphylococcus aureus* (MRSA)-pathogens that complicate sCAP treatment due to rising resistance [30]. Compared with fluoroquinolones and macrolides, omadacycline avoids QTc interval prolongation and has a lower propensity for *Clostridioides difficile* infection (CDI), addressing key safety concerns of existing regimens [31]. Prior trials (OPTIC, OPTIC 2) have confirmed its noninferiority to moxifloxacin for CABP and its efficacy as monotherapy in hospitalized CABP patients, further supporting its clinical potential [32-33].

The mechanistic rationale for evaluating omadacycline-based combination therapy lies in the unmet need for safe, effective regimens amid growing antimicrobial resistance in China. Local data show alarmingly high resistance rates: non-meningitis *S. pneumoniae* and *Mycoplasma pneumoniae* have macrolide resistance exceeding 90% and 80%, respectively, while adult *Haemophilus influenzae* strains also exhibit high macrolide resistance [34-38]. Although β -lactams are preferred, combination therapy improves outcomes in pneumococcal bacteremia [39-40], and fluoroquinolones—currently recommended in guidelines—are limited by serious, potentially permanent adverse effects (tendons, muscles, joints, central nervous system) [41-42]. Omadacycline's broad antimicrobial spectrum, activity against resistant strains, and favorable safety profile address these challenges, justifying its evaluation in sCAP.

This study has several limitations. First, as an open-label trial, it may be subject to bias in outcome assessment, despite standardized evaluation protocols. Second, while it leverages national antimicrobial resistance data, regional variations in resistance patterns may affect the generalizability of its findings to specific populations. Third, the study focuses on β -lactam-combined regimens and does not evaluate omadacycline monotherapy in sCAP, leaving gaps in understanding its optimal dosing and administration strategies in critically ill patients. Finally, long-term outcomes (e.g. post-discharge mortality, recurrence) are not assessed, which may limit insights into its sustained efficacy.

In conclusion, this non-inferiority RCT directly addresses the evidence gap in sCAP management by evaluating omadacycline-based combination therapy, aligning with the need for optimized empiric treatment amid rising antimicrobial resistance. If non-inferiority to fluoroquinolone-based combinations is demonstrated, omadacycline could serve as a viable alternative—particularly for patients with resistance concerns or intolerance to existing regimens. Additionally, this research will refine empirical pathogen coverage, inform updates to domestic sCAP treatment guidelines aligned with local resistance patterns, and contribute to improved clinical outcomes and public health strategies for severe pneumonia.

Trial status

Recruiting has be started in September 2025. Patient recruitment is estimated to be completed around December 2026.

Declarations

Acknowledgements

None.

Author contributions

Xin Y initiated the project and is the principal investigator. Xin Y, Xin Z, Li X, Fu W, Dan S and Wen N participated in the design of the study. Xin Z and Xin Y wrote the protocol. Yin S, Yue Z and Rui X carried out the pilot study under supervision of Xin Y. Xin Z and Yun F implemented the project into clinical rouine. Xin Z will carry out statistical analyses. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Ethics approval and consent to participate

The studies involving humans were approved by the medical ethics committee of the Chinese PLA General Hospital (Registration No. KY-2025-8-167-1) or the responsible ethics committee of each respective study center and conducted in accordance with the revised Declaration of Helsinki. Written informed consent was obtained from the patients or a legal representative.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Table 1

Table 1 is available in the supplementary files section

Figures

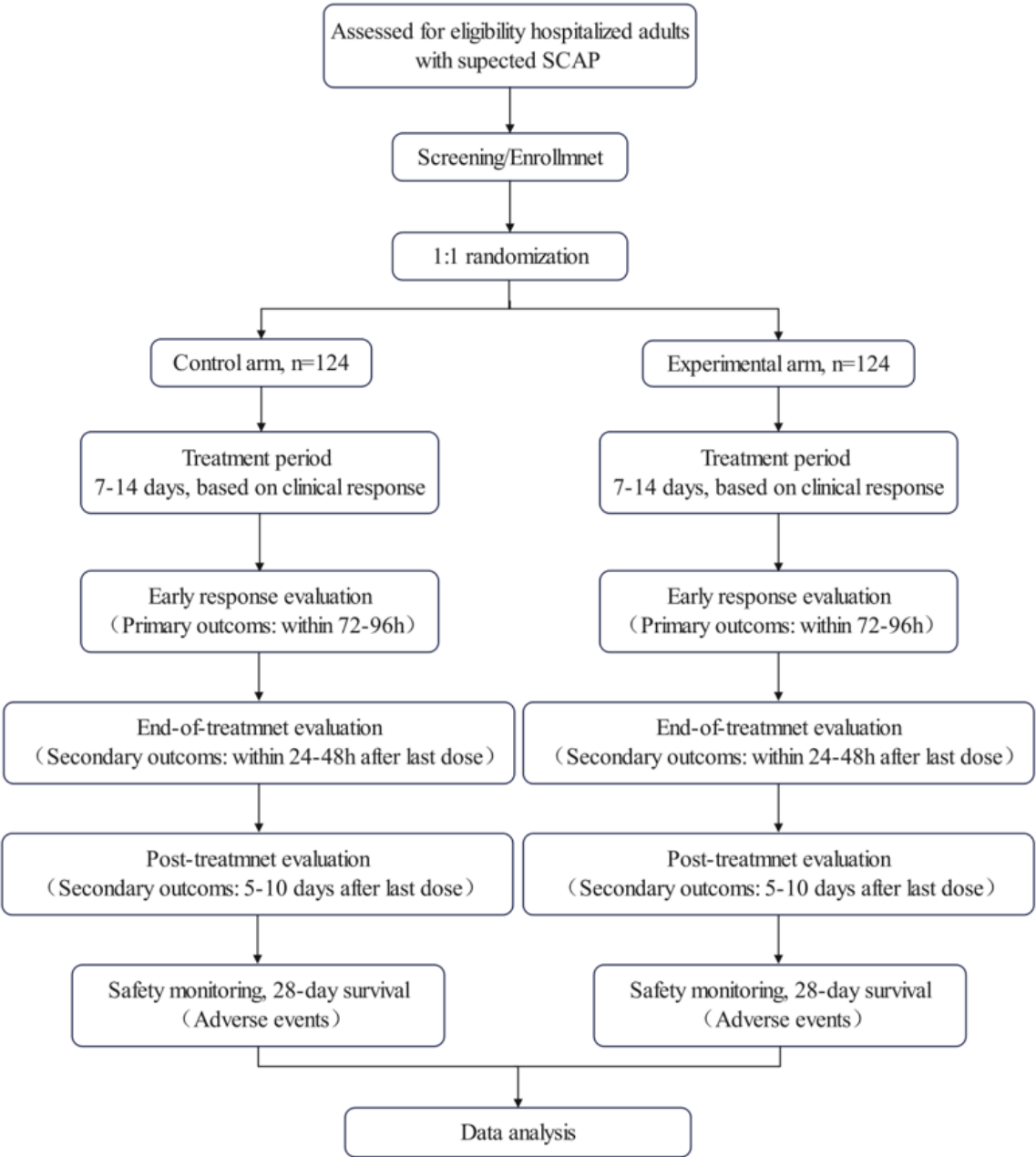


Figure 1

Flowchart of the study protocol

Supplementary Files

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- [Table1.docx](#)