RESEARCH PAPER

Ceftriaxone Monotherapy versus Ceftriaxone-Based Combination Therapy in Hospitalised Adults with Lower Respiratory Tract Infections: A Prospective Two-Centre Observational Study

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ABSTRACT

Background. Lower respiratory tract infections (LRTIs) are a leading cause of hospitalisation and death worldwide, and escalating antimicrobial resistance has renewed the debate over whether β-lactam–based combination therapy improves outcomes relative to monotherapy. Ceftriaxone, a third-generation cephalosporin, is a mainstay of empirical LRTI treatment.

Objective. To compare the effectiveness of ceftriaxone monotherapy with ceftriaxone-based combination therapy in hospitalised adults with LRTI, with respect to clinical cure, time to symptom improvement and length of hospital stay (LOS).

Methods. In a 6-month prospective observational study at two tertiary-care hospitals in Pune, India, 151 adults (≥18 years) admitted with LRTI were followed to discharge. Seventy-five received ceftriaxone monotherapy and 76 received ceftriaxone combined with a second agent (piperacillin/tazobactam, azithromycin, clarithromycin or doxycycline). Clinical severity and response were graded with the Clinical Global Impression–Severity (CGI-S) and –Improvement (CGI-I) scales; clinical cure was defined a priori as a CGI-I score ≤2 ("much" or "very much improved") at discharge. Serial white blood cell (WBC) counts and LOS were recorded. Between-group comparisons used Welch's t-test for continuous variables and the χ^2 test for categorical variables, with $p < 0.05$ considered significant.

Results. The two groups were comparable in age, sex, comorbidity burden and LRTI subtype. Combination therapy was associated with a higher clinical cure rate (92.1% vs 80.0%; $\chi^2 = 4.62$, $p = 0.032$; absolute risk reduction 12.1%, number-needed-to-treat ≈ 8), a shorter time to symptom improvement (4.2 ± 0.9 vs 6.5 ± 1.2 days; $p < 0.001$) and a shorter LOS (5.6 ± 1.8 vs 8.4 ± 2.5 days; $p < 0.001$). CGI-I at discharge was lower (better) with combination therapy (2.4 ± 0.8 vs 2.8 ± 1.0; $p = 0.008$). WBC counts declined significantly within both groups ($p \leq 0.002$), although the between-group difference at discharge and the ICU-admission rate did not reach statistical significance.

Conclusion. In this observational cohort, ceftriaxone-based combination therapy was associated with superior clinical outcomes and shorter hospitalisation compared with monotherapy, particularly relevant for severe or high-risk LRTI. Because treatment allocation was not randomised, confounding by indication cannot be excluded; adequately powered randomised multicentre trials are needed to confirm these findings.

Keywords: Ceftriaxone; combination antibiotic therapy; lower respiratory tract infection; community-acquired pneumonia; length of hospital stay; clinical cure; antimicrobial resistance; Clinical Global Impression.

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1. INTRODUCTION

Lower respiratory tract infections (LRTIs) — chiefly pneumonia, acute bronchitis and infective exacerbations of chronic obstructive pulmonary disease (COPD) — remain among the most frequent causes of morbidity, hospitalisation and death across all age groups [1,29]. Community-acquired pneumonia (CAP) alone is a persistently high-ranking cause of infection-related mortality, and the elderly, the immunocompromised and those with pre-existing cardiopulmonary disease bear a disproportionate share of the burden [1,2]. Beyond their clinical toll, LRTIs impose a substantial economic cost through admissions, diagnostic work-up and prolonged treatment, a burden that falls hardest on low- and middle-income settings where diagnostic and therapeutic resources are limited [2].

The management of LRTI is being reshaped by the steady rise of antimicrobial resistance (AMR). Key respiratory pathogens, including Streptococcus pneumoniae, Haemophilus influenzae and Pseudomonas aeruginosa, increasingly display reduced susceptibility to first-line agents, prolonging illness and complicating empirical therapy [3]. In this context, the choice between antibiotic monotherapy and combination therapy has become a central clinical question, particularly for patients with severe disease or risk factors for resistant organisms [4,6].

Ceftriaxone, a parenteral third-generation cephalosporin, is a cornerstone of empirical LRTI therapy. It exerts bactericidal activity by binding penicillin-binding proteins and inhibiting bacterial cell-wall synthesis, offers reliable activity against common Gram-positive and Gram-negative respiratory pathogens, achieves good pulmonary penetration, and its long half-life permits convenient once-daily dosing [7,21,22]. However, ceftriaxone lacks activity against atypical pathogens such as Mycoplasma pneumoniae, Chlamydophila pneumoniae and Legionella pneumophila, and its utility as sole therapy has been questioned as resistance rises [20]. Guidelines and observational data therefore support adding a macrolide, a tetracycline or a β-lactamase inhibitor combination to broaden coverage in moderate-to-severe CAP [6,8,20].

The rationale for ceftriaxone-based combination therapy is threefold: extended antimicrobial spectrum (notably coverage of atypical organisms by macrolides and doxycycline), potential immunomodulatory and anti-inflammatory effects of macrolides, and possible synergy against resistant or polymicrobial infection [6,9,26,27]. Several studies report lower mortality and faster recovery with combination regimens in bacteraemic pneumococcal pneumonia and severe CAP [6,8,14], whereas others find the incremental benefit modest in uncomplicated disease [4,17]. This uncertainty, together with the imperative of antimicrobial stewardship, makes head-to-head comparison of the two strategies clinically important.

The present study was designed to address this gap in a real-world Indian tertiary-care setting. We prospectively compared ceftriaxone monotherapy with ceftriaxone-based combination therapy in hospitalised adults with LRTI, evaluating three patient-centred outcomes: clinical cure, time to symptom improvement and length of hospital stay.

1.1 Aim and objectives

Aim: to study the effectiveness of ceftriaxone in monotherapy and in combination therapy for the treatment of lower respiratory tract infections.

Objectives: (i) to assess the effectiveness of ceftriaxone monotherapy versus combination therapy in treating LRTI; (ii) to determine the time required for symptom improvement; and (iii) to explore the impact of combination therapy on length of hospital stay.

2. MATERIALS AND METHODS

2.1 Study design and setting

This was a prospective observational study conducted over six months at two tertiary-care hospitals in Pune, Maharashtra, India (Lokmanya Hospital, Pune and Ruby Hall Clinic, Hinjewadi). An observational design was chosen to capture real-world prescribing and outcomes without experimental manipulation; treatment allocation was made by the treating physician according to routine clinical judgement. Patients in both treatment groups were followed prospectively from admission to discharge, and all data were collected in real time using a structured case-record form.

2.2 Ethical approval and consent

The study protocol was reviewed and approved by the Institutional Ethics Committee (Biomedical & Health Research) of the Poona Medical Research Foundation, constituted per Indian Council of Medical Research (ICMR) guidelines (approval reference RHC/BIOPMRFIEC/2025/559; Bio IEC/375; dated 19 March 2025). Written informed consent was obtained from every participant in English, Hindi or Marathi before enrolment. Participants received no compensation and were free to withdraw at any time.

2.3 Participants

Adults (≥18 years) admitted with a clinical diagnosis of LRTI (pneumonia, bronchitis, COPD exacerbation or related lower-airway infection) and presenting with symptoms such as cough, breathlessness, fever or sputum production, with or without comorbidities, were eligible. Patients with hypersensitivity to ceftriaxone or any study antibiotic, pregnant or lactating women, those unwilling to provide consent, and paediatric patients were excluded. The inclusion and exclusion criteria are summarised in Table 1.

Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
Adults ≥18 years with a clinical diagnosis of LRTI (pneumonia, bronchitis, COPD, etc.)	Hypersensitivity/allergy to ceftriaxone or any study antibiotic
Clinical symptoms (cough, breathlessness, fever, sputum production)	Pregnant or lactating women
Patients with or without comorbid conditions	Patients unwilling to provide informed consent
Admitted to a participating study centre	Paediatric patients (<18 years)

2.4 Treatment groups

A total of 151 patients were enrolled and analysed. The monotherapy group (n = 75) received intravenous ceftriaxone alone (1–2 g once or twice daily). The combination group (n = 76) received ceftriaxone together with one additional antibiotic selected on clinical grounds — piperacillin/tazobactam, azithromycin, clarithromycin or doxycycline — chosen to extend coverage against atypical, resistant or polymicrobial pathogens.

2.5 Variables and outcome measures

The independent variable was the treatment strategy (monotherapy vs combination). The pre-specified outcomes were: (1) clinical cure, defined as a CGI-I score ≤2 ("much" or "very much improved") at discharge; (2) time to symptom improvement in days, derived from serial CGI-I grading; and (3) length of hospital stay (LOS). Supporting measures included baseline severity (CGI-S), serial total white blood cell (WBC) counts on the day of admission (DOA) and day of discharge (DOD), and ICU admission. Age, sex, comorbidities, LRTI subtype and available laboratory values were recorded as covariates. The CGI-S and CGI-I instruments were anchored to LRTI-specific descriptors ranging from 1 (normal / very much improved) to 7 (most extremely ill / very much worse).

2.6 Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as counts and percentages. Between-group comparisons of continuous outcomes used Welch's two-sample t-test; categorical outcomes (clinical cure, ICU admission) were compared using the Pearson χ^2 test. Within-group change in WBC count (DOA vs DOD) was assessed by paired testing. For the primary effectiveness outcome, the absolute risk reduction (ARR) and number-needed-to-treat (NNT) were calculated. A two-sided $p < 0.05$ was considered statistically significant. Analyses were performed using standard statistical software.

3. RESULTS

3.1 Baseline characteristics

Of 151 patients, 75 received monotherapy and 76 combination therapy. The two groups were well matched at baseline (Table 2). The majority of patients in both arms were aged 51–70 years (33% and 37%, respectively), males predominated (54% overall), and comorbidities were present in roughly half of each group (49% vs 55%). The age distribution is shown in Figure 1.

Table 2. Baseline demographic and clinical characteristics of the two treatment groups.

Characteristic	Monotherapy (n=75)	Combination (n=76)	Total (n=151)
Age group			
18–30 years	12 (16%)	14 (18%)	26 (17%)
31–50 years	20 (27%)	18 (24%)	38 (25%)
51–70 years	25 (33%)	28 (37%)	53 (35%)
71+ years	18 (24%)	16 (21%)	34 (23%)
Sex			
Male	42 (56%)	39 (51%)	81 (54%)
Female	33 (44%)	37 (49%)	70 (46%)
Comorbidity status			
No comorbidity	38 (51%)	34 (45%)	72 (48%)
Comorbid	37 (49%)	42 (55%)	79 (52%)

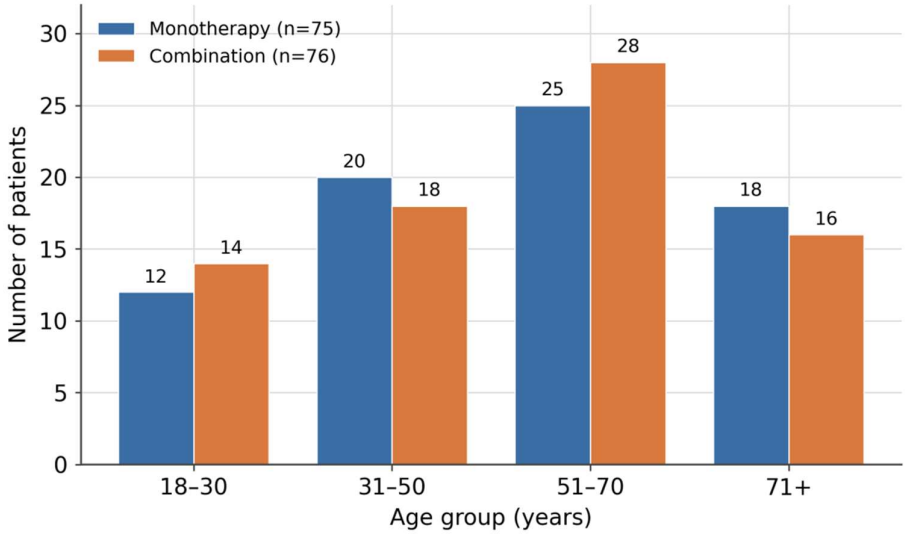

Figure 1. Age distribution of patients by treatment group.

Pneumonia was the most common LRTI subtype (44% overall), followed by bronchitis (25%), COPD (14%), combined pneumonia + COPD (7%) and other/viral LRTI (10%). The distribution was similar across the two groups (Table 3, Figure 2).

Table 3. Distribution of LRTI subtypes across treatment groups.

LRTI subtype	Monotherapy (n=75)	Combination (n=76)	Total (n=151)
Bronchitis	18 (24%)	20 (26%)	38 (25%)
Pneumonia	32 (43%)	34 (45%)	66 (44%)
COPD	12 (16%)	9 (12%)	21 (14%)
Pneumonia + COPD	5 (7%)	6 (8%)	11 (7%)
Other / viral	8 (10%)	7 (9%)	15 (10%)

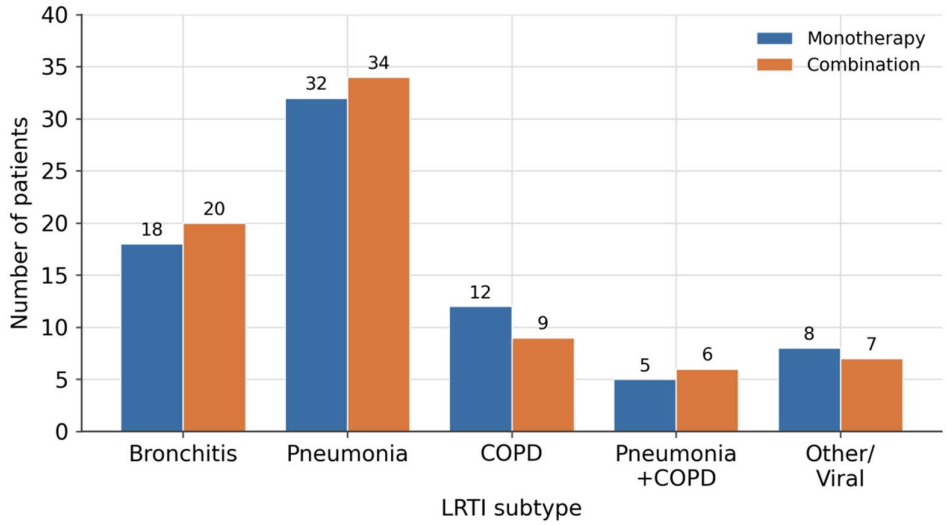

Figure 2. Distribution of LRTI subtypes by treatment group.

3.2 Inflammatory response (WBC counts)

Both groups presented with leukocytosis at admission and showed a significant fall in WBC count by discharge, consistent with resolving infection (Table 4, Figure 3). In the monotherapy group, WBC fell from 10,500 ± 2,200 to 8,500 ± 1,800 cells/mm³

(within-group p = 0.002); in the combination group, from 11,200 ± 2,500 to 9,000 ± 2,000 cells/mm³ (within-group p = 0.001). The between-group difference in discharge WBC did not reach statistical significance (p = 0.11), indicating comparable biochemical resolution of inflammation once treatment was completed.

Table 4. White blood cell counts (cells/mm³, mean ± SD) at admission and discharge.

Treatment group	WBC at admission (DOA)	WBC at discharge (DOD)	Within-group p
Monotherapy (ceftriaxone)	10,500 ± 2,200	8,500 ± 1,800	0.002
Combination therapy	11,200 ± 2,500	9,000 ± 2,000	0.001

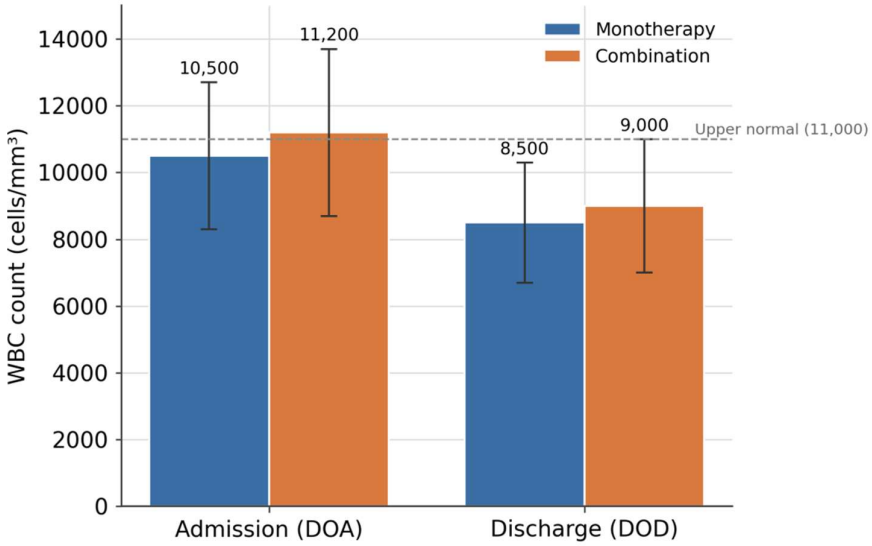

Figure 3. WBC count at admission (DOA) versus discharge (DOD) by treatment group. Dashed line marks the upper limit of the normal range.

3.3 Effectiveness: CGI-S and CGI-I

Baseline severity was similar between groups (CGI-S 5.2 ± 1.1 vs 5.1 ± 1.0). By discharge, the combination group achieved a lower (better) CGI-I score than the monotherapy group (2.4 ± 0.8 vs 2.8 ± 1.0; between-group p = 0.008), and a numerically greater mean improvement from baseline (2.7 ± 1.0 vs 2.4 ± 0.9; p = 0.055) (Table 5, Figure 4).

Table 5. Clinical Global Impression scores (mean ± SD). *Between-group comparison of CGI-I at discharge.

Treatment group	CGI-S (baseline)	CGI-I (discharge)	Mean improvement	p
Monotherapy (ceftriaxone)	5.2 ± 1.1	2.8 ± 1.0	2.4 ± 0.9	0.008*
Combination therapy	5.1 ± 1.0	2.4 ± 0.8	2.7 ± 1.0	0.008*

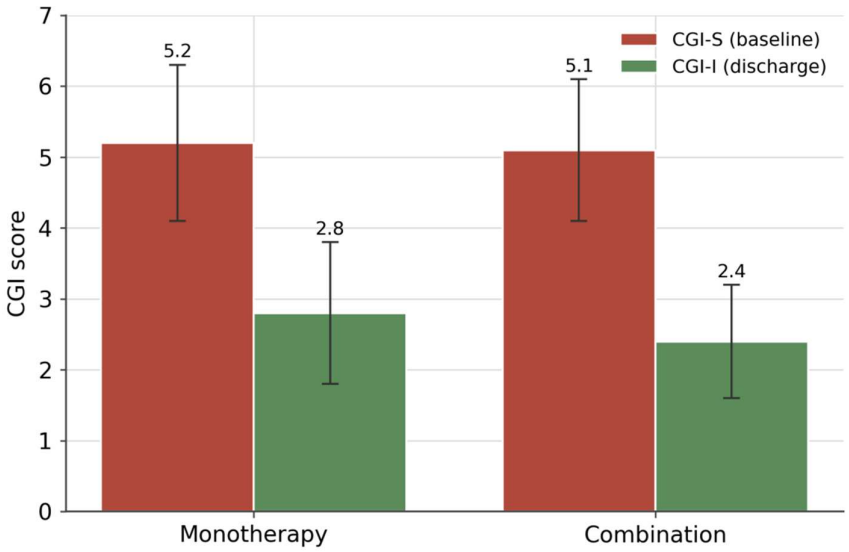

Figure 4. Baseline severity (CGI-S) and discharge improvement (CGI-I) scores by treatment group. Lower CGI-I indicates greater improvement.

3.4 Primary outcomes: cure, symptom improvement and LOS

Combination therapy outperformed monotherapy on all three primary outcomes (Table 6). The clinical cure rate was 92.1% with combination therapy versus 80.0% with monotherapy ($\chi^2 = 4.62$, $p = 0.032$), an absolute risk reduction of 12.1% and a number-needed-to-treat of approximately 8 (Figure 6). Time to symptom improvement was markedly shorter with combination therapy (4.2 ± 0.9 vs 6.5 ± 1.2 days; $p < 0.001$), as was LOS (5.6 ± 1.8 vs 8.4 ± 2.5 days; $p < 0.001$) — a mean reduction of 2.8 days (Figure 5). ICU-admission rates were low and did not differ significantly between groups (3/76, 4% vs 5/75, 7%; $p = 0.70$).

Table 6. Primary clinical outcomes by treatment group. ARR, absolute risk reduction; NNT, number-needed-to-treat.

Outcome	Monotherapy (n=75)	Combination (n=76)	Effect	p
Clinical cure, n (%)	60 (80.0%)	70 (92.1%)	ARR 12.1%; NNT ≈ 8	0.032
Time to symptom improvement (days)	6.5 ± 1.2	4.2 ± 0.9	−2.3 days	<0.001
Length of hospital stay (days)	8.4 ± 2.5	5.6 ± 1.8	−2.8 days	<0.001
ICU admission, n (%)	5 (7%)	3 (4%)	−3%	0.70

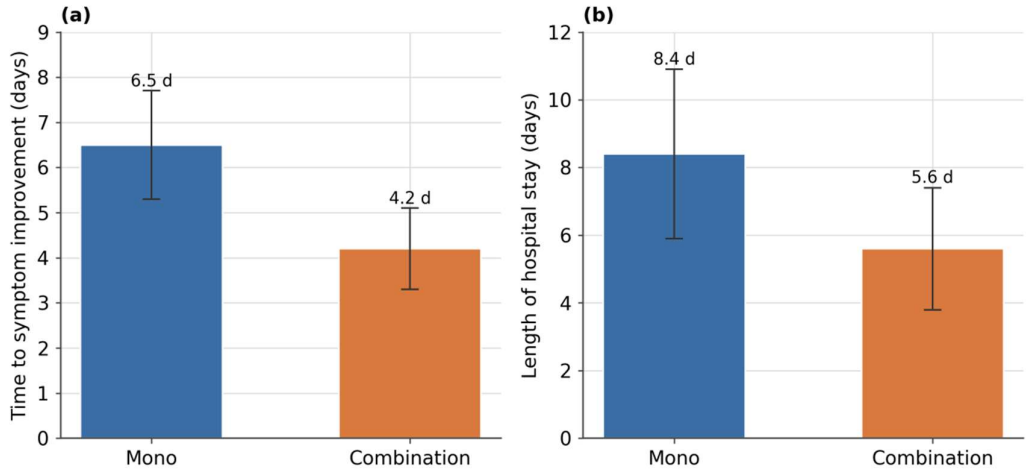

Figure 5. (a) Time to symptom improvement and (b) length of hospital stay by treatment group (mean ± SD).

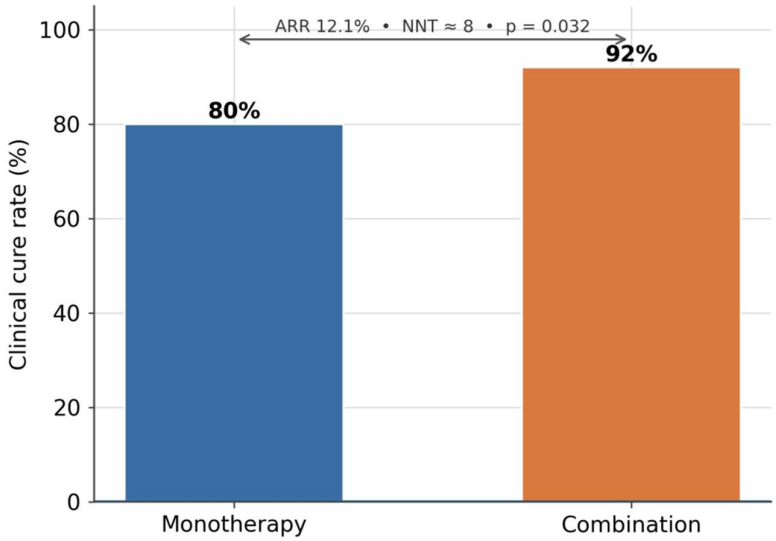

Figure 6. Clinical cure rate by treatment group, with absolute risk reduction, number-needed-to-treat and p-value.

4. DISCUSSION

In this prospective two-centre cohort of 151 hospitalised adults with LRTI, ceftriaxone-based combination therapy was associated with better clinical outcomes than ceftriaxone monotherapy across every pre-specified endpoint: a higher clinical cure rate, faster symptom improvement and a shorter hospital stay. Because the two groups were closely matched in age, sex, comorbidity and infection subtype, these differences are unlikely to be explained by gross baseline imbalance, although — as discussed below — residual confounding by indication remains possible in an observational design.

Our cure-rate finding (92% vs 80%; NNT ≈ 8) is consistent with the direction of several prior studies. De la Calle et al. reported significantly lower 30-day mortality with third-generation cephalosporin plus macrolide or fluoroquinolone versus cephalosporin monotherapy in bacteraemic pneumococcal pneumonia [6], and Flanders et al. found that ceftriaxone plus doxycycline was associated with reduced mortality in hospitalised CAP [8]. Ito et al. similarly observed a mortality benefit from adding azithromycin to a β-lactam in severe CAP defined by IDSA/ATS criteria, even where PSI- or CURB-65-based analyses were neutral [14]. The broader antimicrobial spectrum of combination regimens — in particular coverage of atypical pathogens (Mycoplasma, Chlamydophila, Legionella) by macrolides and doxycycline, which ceftriaxone does not cover — provides a coherent mechanistic explanation for improved cure [20,26,27].

The faster symptom resolution (4.2 vs 6.5 days) and shorter LOS (5.6 vs 8.4 days) observed here echo reports that adjunctive agents accelerate recovery. Doxycycline-containing regimens have been shown to shorten hospital stay and reduce cost in CAP [10], and macrolides exert anti-inflammatory, immunomodulatory and mucoregulatory effects that may hasten clinical improvement beyond their antibacterial action [26,27]. A shorter LOS is not only a marker of faster recovery but also carries direct economic and safety implications, reducing exposure to hospital-acquired complications and easing pressure on scarce inpatient resources — a consideration of particular weight in resource-constrained health systems.

Not all comparisons favoured combination therapy unequivocally, and it is important to report this even-handedly. The reduction in WBC count by discharge, though significant within each group, did not differ significantly between groups, suggesting that biochemical resolution of inflammation was ultimately comparable once therapy was completed. ICU-admission rates were low and statistically indistinguishable. These nuances align with the literature indicating that the incremental benefit of combination therapy is most evident in severe or high-risk disease and may be marginal in uncomplicated infection [4,17]. Frank et al., for example, found levofloxacin monotherapy to be as effective as azithromycin-plus-ceftriaxone in moderate-to-severe CAP [17]. The clinical message is therefore one of targeted, rather than universal, combination therapy — consistent with antimicrobial-stewardship principles and with the view that "universal pneumonia antibiotic" strategies should give way to individualised, resistance-informed choices [7].

The use of the CGI-S and CGI-I scales, anchored to LRTI-specific clinical descriptors, provided a simple, reproducible and patient-centred measure of severity and response that complemented objective markers such as WBC and LOS. Their responsiveness in this study supports their pragmatic use in real-world respiratory-infection research, where more elaborate severity instruments are not always feasible.

5. LIMITATIONS

Several limitations temper interpretation of these findings. First and most importantly, this was an observational study without randomisation; treatment was allocated at the physicians' discretion, so confounding by indication cannot be excluded, and the associations reported should not be read as proof of causation. Second, C-reactive protein and procalcitonin were unavailable for many patients, and pulmonary function tests were not routinely performed, limiting adjustment for infection severity and assessment of pulmonary recovery. Third, although data were drawn from two hospitals within one metropolitan region, the sample remains geographically and demographically limited, constraining generalisability to other regions with different resistance patterns and case-mix. Fourth, the combination arm pooled heterogeneous second agents (piperacillin/tazobactam, azithromycin, clarithromycin, doxycycline), so the analysis reflects an aggregate "combination" strategy rather than any single regimen, and the study was not powered to compare individual combinations. Fifth, potential drug–drug interactions and microbiological (culture-and-sensitivity) confirmation of pathogens and eradication were not systematically captured. Finally, follow-up ended at discharge, so recurrence, late complications and the longer-term impact on resistance were not assessed.

6. CONCLUSION

In hospitalised adults with LRTI, ceftriaxone-based combination therapy was associated with a higher clinical cure rate, faster symptom improvement and a significantly shorter hospital stay than ceftriaxone monotherapy, with a number-needed-to-treat of approximately eight for cure. These benefits appear most relevant for patients with severe or high-risk infection, in whom broadened antimicrobial coverage of atypical and potentially resistant organisms is likely to matter most. Given the observational design, the findings are hypothesis-strengthening rather than definitive: adequately powered, randomised, multicentre trials with longer follow-up and microbiological confirmation are needed to establish causality, define which patient subgroups derive the greatest benefit, and balance efficacy against the stewardship imperative of limiting unnecessary antibiotic exposure.

Declarations

Ethics approval and consent to participate. Approved by the Institutional Ethics Committee (Biomedical & Health Research), Poona Medical Research Foundation (RHC/BIOPMRFIEC/2025/559; Bio IEC/375; 19 March 2025). Written informed consent was obtained from all participants.

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Conflicts of interest. The authors declare no competing interests.

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