

Annals of Infectious Diseases and Therapy

Review Article

Impact of combination antibiotic therapy on Quality of Life in Patients with bacterial pneumonia

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Received: 15 March 2026; Accepted: 10 June 2026; Published: 13 September 2026.

Citation of this article: Ferrari D, Gallo G, Greco G (2026) Impact of combination antibiotic therapy on Quality of Life in Patients with bacterial pneumonia. Ann Infect Dis Ther, 7(1): 01-06. DOI: [10.5281/zenodo.22812052](https://doi.org/10.5281/zenodo.22812052)

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Abstract

Background: Combination beta-lactam-macrolide therapy is recommended for moderate-to-severe bacterial pneumonia largely on mortality and readmission data, while its effect on patient-reported quality of life is studied far less directly.

Objective: This review synthesizes comparative trial evidence on combination versus monotherapy antibiotic strategy for bacterial pneumonia alongside the separate literature on post-pneumonia quality of life.

Methods: We conducted a narrative synthesis of randomized trials, meta-analyses, and cohorts comparing antibiotic strategies for pneumonia, together with cohorts measuring health-related quality of life after pneumonia.

Findings: Combination therapy reduces 30-day readmission and, in severely ill or atypical-pathogen-infected patients, mortality, with little added benefit in lower-severity populations; quality of life after pneumonia recovers slowly regardless of regimen and is shadowed for up to a year by elevated cardiovascular risk, but no trial has measured quality of life directly as an antibiotic-strategy endpoint.

Conclusions: The case for combination therapy improving quality of life is presently inferential; a trial powered on a validated quality-of-life instrument is needed to close this gap.

Keywords: bacterial pneumonia; combination antibiotic therapy; quality of life; community-acquired pneumonia; macrolide

1. Introduction

Bacterial pneumonia remains one of the few acute infections for which the choice of initial antibiotic regimen is still argued over decades after effective antimicrobials became routine, and the argument has shifted only partially from survival to what survival actually feels like afterward. Guideline bodies converge on a severity-stratified approach: outpatient monotherapy for low-risk disease, and either a respiratory fluoroquinolone or a beta-lactam paired with a macrolide for patients admitted to a ward or an intensive care unit, a structure now codified in the most recent American Thoracic Society guidance on adults with community-acquired pneumonia [1] and echoed in the European severe-pneumonia guideline jointly issued by the ERS, ESICM, ESCMID and ALAT [2]. That stratification itself depends on severity tools, principally the Pneumonia Severity Index derived by Fine and colleagues [3] and the simpler CURB-65 score validated by Lim and colleagues [4] and folded into the British Thoracic Society's own guideline update [5], both of which were built to predict mortality rather than recovery quality, a distinction that matters once the argument turns to quality of life.

The rationale for combination therapy, almost always a beta-lactam plus a macrolide, was built on two overlapping claims: that macrolides cover atypical pathogens a beta-lactam alone misses, and that macrolides carry an immunomodulatory effect independent of antibacterial activity that blunts the inflammatory injury driving prolonged illness. The earlier consensus statement from the Infectious Diseases Society of America and American Thoracic Society [6] and the parallel European lower-respiratory-tract-infection guideline [7] both incorporated this reasoning well before the trial evidence on patient-centered outcomes matured. What has accumulated since is a body of randomized and propensity-matched evidence that speaks increasingly to readmission, symptom burden and health-related quality

of life (HRQoL) rather than mortality alone, alongside a separate and largely disconnected literature on how HRQoL actually behaves in the weeks and months after a pneumonia episode regardless of which regimen was used. This review draws those two strands together, asking specifically what combination antibiotic therapy is shown to do for quality of life in patients with bacterial pneumonia, as distinct from what it does for mortality, where the trial evidence is more familiar and considerably less equivocal.

2. Methods

We conducted a narrative synthesis of the published clinical trial, propensity-matched cohort, meta-analytic and prospective-cohort literature addressing combination (beta-lactam plus macrolide) versus monotherapy antibiotic strategies for bacterial community-acquired pneumonia, and the separate literature quantifying health-related quality of life, symptom recovery and post-discharge morbidity after pneumonia. Search terms combined "community-acquired pneumonia," "combination therapy," "macrolide," "beta-lactam," "quality of life," "SF-36," "health-related quality of life" and "readmission" across general medical and pulmonary/critical-care journals, supplemented by the reference lists of major society guidelines. We prioritized randomized trials and meta-analyses for the therapy-comparison question, and prospective cohort studies using validated HRQoL instruments for the recovery-trajectory question, since randomized evidence on quality of life specifically, as opposed to mortality or clinical cure, remains comparatively scarce for this population.

3. Results

Combination therapy and clinical cure versus mortality endpoints

The trial evidence on combination therapy is more consistent for process and readmission outcomes than for mortality. The pragmatic, cluster-randomized CAP-START

trial found that a strategy of beta-lactam monotherapy was noninferior to strategies incorporating a beta-lactam-macrolide combination or fluoroquinolone monotherapy on 90-day mortality across seven Dutch hospitals, with the absolute difference between strategies falling within the prespecified noninferiority margin [8]. Garin and colleagues, in a randomized noninferiority trial confined to moderately severe ward-admitted patients, could not establish noninferiority of monotherapy and instead found that combination therapy was associated with a substantially lower 30-day readmission rate, 3.1% against 7.9% with beta-lactam alone, a difference concentrated among patients with atypical pathogens (Figure 1) [9]. The 2012 meta-analysis by Asadi and colleagues, pooling observational and randomized data on macrolide-containing regimens, found a modestly but significantly lower mortality with macrolide-based therapy than without it [10], while the more recent randomized-controlled-trial-only meta-analysis by Prizão and colleagues found that adding a macrolide to a beta-lactam improved treatment success rates without producing a significant difference in in-hospital mortality or length of stay [11]. A large Japanese multicenter propensity-score analysis by Nakashima and colleagues reached a broadly consistent conclusion, that combination therapy conferred a measurable outcome advantage over monotherapy once baseline severity was accounted for, an advantage that was most apparent among the more severely ill stratum of their cohort [12] (Table 1).

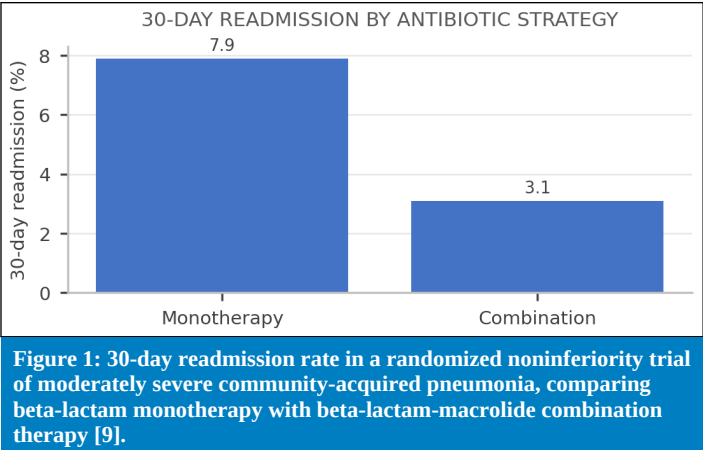
Table 1: Summary of comparative evidence on combination (beta-lactam-macrolide) versus monotherapy antibiotic strategy for bacterial community-acquired pneumonia [8,9,10,11,12].			
Study	Design	Population	Key finding
[8]	Cluster-randomized, crossover, noninferiority	Ward-admitted, 7 Dutch hospitals	Beta-lactam monotherapy noninferior to combination/fluoroquinolone strategy on 90-day mortality

Study	Design	Population	Key finding
[9]	Randomized noninferiority trial	Moderately severe, ward-admitted	Noninferiority of monotherapy not established; 30-day readmission 3.1% (combination) vs 7.9% (monotherapy)
[10]	Systematic review and meta-analysis	Hospitalized CAP, mixed severity	Modestly but significantly lower mortality with macrolide-containing regimens
[11]	Meta-analysis of randomized controlled trials	Hospitalized CAP, 6 RCTs	Improved treatment success; no significant difference in mortality or length of stay
[12]	Propensity score-matched multicenter cohort	Hospitalized CAP, Japan	Combination therapy advantage most apparent in the more severely ill stratum

Short-term recovery and readmission as intermediate quality-of-life markers

Readmission and treatment failure function, in effect, as coarse proxies for quality of life, since both events interrupt recovery and impose additional physical and psychological burden on a patient who believed they were discharged well. The Garin trial's readmission signal is the clearest single data point linking combination therapy to a patient-relevant, if indirect, quality-of-life outcome (Figure 1) [9], and it is consistent with the broader clinical logic behind atypical-pathogen coverage: a patient whose Mycoplasma or Legionella infection is inadequately treated by a beta-lactam alone is a patient at elevated risk of a second, more debilitating illness episode within a month of the first. Symptom-based recovery data reinforce how slow that first episode's resolution already is even when treatment succeeds. Metlay and colleagues, tracking hospitalized and ambulatory CAP patients with the SF-36 and a structured symptom diary, found that most patients had not returned to their baseline level of functioning by 28 days, with fatigue and physical role limitation the domains slowest to normalize, and with older age and comorbid illness the strongest predictors of delayed recovery [13]. El Moussaoui and colleagues, following mild-to-moderately severe hospitalized patients

prospectively, found that a majority still reported at least one persistent respiratory or constitutional symptom at day 28, with health-related quality of life continuing to improve incrementally through day 90 rather than plateauing immediately after clinical cure [14]; a companion randomized trial from the same Amsterdam group established that shortening antibiotic duration from eight days to three, once early clinical improvement was reached, did not compromise that same recovery trajectory, evidence that duration and choice of regimen are related but distinguishable levers on recovery quality [15].



Longitudinal quality-of-life trajectories after pneumonia

Two recent prospective cohorts extend this recovery literature into more contemporary populations and instruments. Rysrø and colleagues followed a hospitalized CAP cohort with serial HRQoL assessment and found measurable deficits relative to population norms that persisted well beyond hospital discharge, with the pace and completeness of recovery varying by baseline severity and comorbidity burden [16]. Hegelund and colleagues, studying the overlapping population of patients with chronic obstructive pulmonary disease hospitalized for CAP, found that HRQoL measured at or near admission independently predicted subsequent mortality risk in that group, indicating that quality-of-life measurement carries

prognostic as well as descriptive value rather than being merely a downstream consequence of how severe the acute illness turned out to be [17] (Table 2). None of these longitudinal HRQoL cohorts were designed to compare antibiotic regimens directly, which is itself a notable gap: the trial literature establishes readmission and mortality differences between combination and monotherapy strategies, while the HRQoL literature characterizes the shape and pace of recovery, but very little published work sits at the intersection of the two, measuring HRQoL as a primary or even secondary endpoint within a randomized comparison of antibiotic strategy.

Table 2: Health-related quality-of-life and symptom-recovery findings from prospective cohorts of community-acquired pneumonia, independent of antibiotic strategy [13,14,16,17].			
Study	Instrument / measure	Population	Recovery finding
[13]	SF-36 and structured symptom diary	Hospitalized and ambulatory CAP	Most patients not back to baseline function by day 28; fatigue slowest domain to normalize
[14]	Symptom checklist and HRQoL survey	Mild-to-moderately severe, hospitalized	Majority report a persistent symptom at day 28; HRQoL continues improving through day 90
[16]	Prospective serial HRQoL assessment	Hospitalized CAP	HRQoL deficits versus population norms persist beyond discharge; pace varies by severity/comorbidity
[17]	HRQoL at/near admission	COPD patients hospitalized with CAP	Admission HRQoL independently predicts subsequent mortality risk

Long-term mortality and cardiovascular sequelae

The consequences of a pneumonia episode extend well past the weeks captured by most HRQoL follow-up windows. Holter and colleagues, in a five-year prospective follow-up of hospitalized CAP patients, identified older age, comorbidity burden and markers of persistent inflammation as independent predictors of long-term mortality well beyond the index admission [18], a finding consistent with Yende and colleagues' earlier observation

that inflammatory markers measured at hospital discharge, not just at admission, independently predicted subsequent mortality after pneumonia and sepsis [19]. Corrales-Medina and colleagues, pooling data from large community cohort studies, found that the risk of incident cardiovascular disease was sharply elevated in the interval immediately following pneumonia hospitalization and then declined progressively over the following year, a time-varying hazard rather than a fixed one (Figure 2) [20], a pattern broadly corroborated by Tralhão and Póvoa's systematic review and meta-analysis of cardiovascular events after community-acquired pneumonia across dozens of observational cohorts [21]. Musher and Thorner's synthesis of pneumonia pathophysiology situates this cardiovascular signal within the acute-phase inflammatory response itself, plausibly the same inflammatory cascade that combination therapy's immunomodulatory rationale was intended to blunt [22], while Welte and colleagues' analysis of the disease's clinical and economic burden across Europe underscores how much of that burden is carried in the months after discharge rather than during the inpatient stay itself [23].

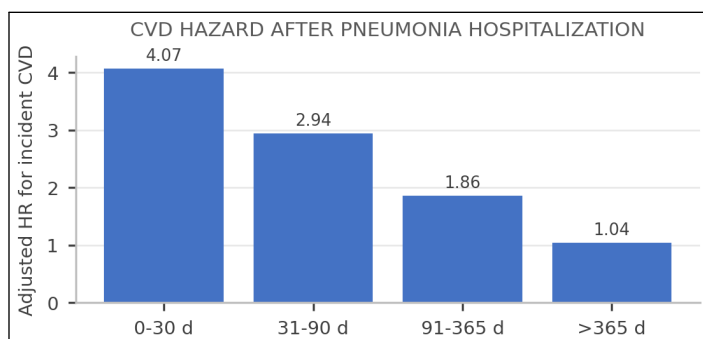


Figure 2: Adjusted hazard ratio for incident cardiovascular disease among pneumonia-hospitalization survivors relative to matched pneumonia-free controls, by interval since hospitalization, showing risk concentrated in the weeks immediately following the acute episode [20].

4. Discussion

Read together, this literature supports a specific and fairly narrow claim rather than a sweeping one: combination beta-lactam-macrolide therapy has reasonably strong evidence behind it for reducing readmission and possibly

mortality in more severely ill or atypical-pathogen-infected patients [9,10,12], modest or absent evidence for improving in-hospital length of stay or mortality in less severely ill, ward-level populations where monotherapy performs comparably [8,11], and essentially no direct randomized evidence, positive or negative, on health-related quality of life as a measured endpoint. Everything connecting combination therapy to quality of life in the existing literature is inferential, built by combining a therapy-comparison trial's readmission or mortality signal with a separate cohort's demonstration that readmission, prolonged symptoms and cardiovascular sequelae are themselves markers of, or contributors to, poor quality of life [13,14,16,20]. That inferential chain is plausible, and clinically it is probably the best available basis for decision-making given the absence of a direct trial, but it should not be mistaken for direct evidence, a distinction that matters because the mechanisms plausibly linking combination therapy to better quality of life, principally macrolide immunomodulation blunting the same inflammatory response implicated in slow symptom recovery and post-pneumonia cardiovascular risk [22,19,21], remain biologically plausible rather than demonstrated in patient-reported outcome data.

Several practical implications follow even from this incomplete evidence base. First, the population most likely to benefit from combination therapy on quality-of-life grounds, atypical-pathogen-infected and more severely ill patients [9,12], is a population current severity tools like the Pneumonia Severity Index and CURB-65 [3,4] were not built to identify, since both were validated against mortality rather than pathogen type or subsequent HRQoL trajectory, an unresolved mismatch between how regimen decisions get made at the bedside and what the decision is now understood to affect. Second, the recovery literature consistently shows that clinical cure, defined by resolution of fever and radiographic improvement, precedes functional and

quality-of-life recovery by weeks to months regardless of regimen [13,14], meaning that a trial powered only on 30-day mortality or clinical cure, the traditional regulatory endpoints, is structurally unable to detect a quality-of-life difference even if one exists. Third, the elevated but time-limited cardiovascular hazard documented after pneumonia hospitalization [20,21,18] suggests that quality-of-life follow-up windows shorter than six to twelve months, common in the existing HRQoL cohorts, may be systematically missing the period during which a genuine treatment-strategy effect on long-term recovery would most plausibly appear. A dedicated randomized trial powered on a validated HRQoL instrument, following patients for at least a year and stratified by baseline severity and pathogen, would close a gap that guideline bodies [1,2,6,7] have so far had to fill with mortality and readmission data serving, not entirely comfortably, as proxies for what patients actually experience after they go home.

5. Conclusion

Combination beta-lactam-macrolide antibiotic therapy for bacterial pneumonia has a reasonably solid evidence base for reducing readmission and, in more severely ill or atypical-pathogen-infected patients, mortality, but it has essentially no direct randomized evidence on health-related quality of life as a measured endpoint, an evidence gap concealed by the intuitive but unproven assumption that reducing readmission and mortality must also improve how patients feel during recovery. The separate literature on post-pneumonia quality of life is unambiguous that recovery is slow, incomplete at 28 days for most patients, and shadowed for up to a year by elevated cardiovascular risk, findings that make a stronger case for measuring quality of life directly in future antibiotic-strategy trials than for inferring it from mortality and readmission data alone. Until such a trial exists, clinicians selecting between monotherapy and combination therapy for bacterial pneumonia are, on the quality-of-life question specifically, working from

plausible inference rather than direct evidence, a gap the field is well positioned to close given how mature the surrounding mortality, readmission and HRQoL-instrument literatures already are.

6. Acknowledgements

The authors thank the clinical and administrative staff of the participating departments for their support in the preparation of this manuscript.

7. Funding

This work received no external or internal grant funding, and no funding body had any role in the design, analysis, or writing of this review.

8. Conflict of Interest

The authors declare that they have no competing interests, financial or otherwise, related to the subject matter of this manuscript.

9. Author Contributions

Ferrari D conceived the review and drafted the manuscript. Gallo G performed the literature synthesis and prepared the tables and figures. Greco G critically revised the manuscript for intellectual content. All authors approved the final version for submission.

10. Ethics Statement

This review synthesizes previously published, publicly available literature and did not involve new data collection from human or animal subjects; institutional ethics approval was therefore not required.

11. Data Availability

No new datasets were generated for this review. All data discussed are available in the cited original publications.

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