BMC Pulmonary Medicine

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Comparison of initial empirical antibiotic regimens in severe community-acquired pneumonia: a network meta-analysis

Min Wang[1], Jing Zhang[1], Xiaoming Wang[2], Qian Wang[2], Lian Wang[2], Han Zhuang[2] and Ao Liu[2*]

Abstract

Background Severe community-acquired pneumonia (SCAP) remains a leading cause of morbidity and mortality worldwide. Identifying the optimal antibiotic regimen for treating SCAP is crucial for improving patient outcomes.

Methods We searched the PubMed, Embase, and Cochrane Central Register of Controlled Clinical Trials databases to identify studies reporting initial empirical antibiotic regimens in patients with SCAP. We performed a network meta-analysis to compare the relative efficacy of different antibiotic regimens in treating SCAP. The primary outcome was overall mortality. The second outcomes were 30-day mortality and in-hospital mortality.

Results This network meta-analysis included 1 randomized clinical trial and 13 observational studies with 8142 patients, categorized into five treatment groups: β-lactam antibiotics, β-lactam antibiotics plus doxycycline, β-lactam antibiotics plus fluoroquinolones, β-lactam antibiotics plus macrolides, and fluoroquinolones monotherapy. β-lactam antibiotics plus macrolides was ranked as the most effective treatment (surface under the cumulative ranking curve, 92.0%; mean rank, 1.3). The β-lactam antibiotics plus macrolides combination significantly reduced overall mortality compared to β-lactam antibiotics alone (RR, 0.79; 95% CI, 0.64–0.96) and β-lactam antibiotics plus fluoroquinolones (RR, 0.67; 95% CI, 0.64–0.82).

Conclusion Our findings suggest that β-lactam antibiotics plus macrolides may be the optimal treatment for SCAP. β-lactam antibiotics monotherapy and β-lactam antibiotics plus fluoroquinolones should not be recommended due to their inferior outcomes.

Keywords Severe community-acquired pneumonia, Network meta-analysis, B-lactam antibiotics, Macrolides, Fluoroquinolones, Mortality

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Introduction

Severe community-acquired pneumonia (SCAP) is the most life-threatening form of community-acquired pneumonia (CAP) and often necessitates intensive care unit (ICU) admission due to invasive mechanical ventilation or septic shock requiring vasopressors [1]. The overall mortality rate for SCAP exceeds 20%, and it is a leading cause of acute respiratory distress syndrome [2]. Studies indicate that early administration of antibiotics can reduce hospital mortality and ICU admission rates, so an appropriate initial antibiotic regimen is important for patients with SCAP [3].

The most frequently identified pathogens causing SCAP are Streptococcus pneumoniae, Staphylococcus aureus (including MRSA), Pseudomonas aeruginosa, and other gram-negative bacteria, viruses, and atypical pathogens [4, 5]. Understanding these pathogens is critical, as it informs the selection of appropriate initial empirical antibiotic regimens, which are essential for reducing mortality and ICU admissions in SCAP patients. The Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) and the latest European community-acquired pneumonia (CAP) guidelines recommend a β-lactam antibiotics plus a macrolides for patients with SCAP. The combination of a β-lactam antibiotics and a respiratory fluoroquinolones, however, remains controversial and lacks definitive evidence to support its superiority [6, 7]. Moreover, recent retrospective cohort studies have suggested that β-lactam antibiotics plus macrolides, fluoroquinolones monotherapy, and β-lactam antibiotics plus doxycycline may yield similar outcomes in non-severe CAP [8]. However, few studies have directly compared fluoroquinolones monotherapy and β-lactam antibiotics plus tetracycline in SCAP [9–11]. Despite the recommendations provided by guidelines, the optimal antibiotic regimen for SCAP remains a subject of ongoing debate. Questions persist regarding whether a β-lactam antibiotics plus macrolides combination is superior to a β-lactam antibiotics plus fluoroquinolones, and the efficacy of fluoroquinolones monotherapy and β-lactam antibiotics plus doxycycline as potentially suboptimal options is still unclear. Conventional pairwise meta-analyses, which rely on direct comparisons, are relatively limited and pose challenges in evaluating these antibiotic regimens. Therefore, we conducted a network meta-analysis (NMA) to gain a more comprehensive understanding of the outcomes associated with different antibiotic treatments.

Methods

Protocol and registration

This NMA was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analysis (PRISMA-NMA) guidelines (eTable 1) and was prospectively registered on PROSPERO (CRD42024574220) [12].

Literature search

We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Clinical Trials from inception to April 11, 2024, to identify relevant RCTs and observational studies evaluating empirical antibiotic therapy for SCAP. The complete search strategy is provided in eTable 2. Additionally, we conducted backwards citation searches by screening the reference lists of included studies for potentially relevant articles.

Study inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) SCAP defined as meeting IDSA/ATS criteria for SCAP or admitted to the ICU; (2) were RCTs or observational cohort studies comparing β-lactam antibiotics, fluoroquinolones, or β-lactam antibiotics based combination regimens; and (3) reported mortality outcomes for at least two antibiotic regimens. Studies were excluded if they lacked a comparator group, involved hospital-acquired pneumonia (HAP) or ventilator-acquired pneumonia (VAP), or focused on targeted therapy based on known pathogen-specific results.

Data extraction

Two independent reviewers (XW and LW) extracted study characteristics, patient demographics, treatment regimens, and mortality outcomes. Discrepancies were resolved by discussion.

Quality assessment

Two authors (HZ and QW) independently performed the assessment, with any disagreements resolved through discussion. The quality of the evidence was evaluated using the revised tool for risk of bias (ROB2) for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for observational studies [13, 14].

Outcome measure

The primary outcome was overall mortality, used to evaluate the effectiveness of different antibiotic regimens in SCAP treatment. When available, 30-day all-cause mortality was prioritized; otherwise, in-hospital all-cause mortality was used. Secondary

outcomes included 30-day all-cause mortality and in-hospital all-cause mortality analyzed separately.

Statistical analysis

This NMA was performed within a frequentist framework using a random-effects model in Stata (network and mvmeta packages) [15]. Mortality risk was estimated as relative risk (RR) with 95% confidence intervals (CIs), and results were visualized using forest plots and league tables. Treatment rankings for each outcome were determined by the surface under the cumulative ranking curve (SUCRA), where higher SUCRA values indicate better rankings [16]. To ensure result robustness, we evaluated inconsistency and heterogeneity [17]. Both overall and loop inconsistencies were assessed [15, 18], and heterogeneity was quantified using the restricted maximum likelihood method. A τ^2 value < 0.1 indicated low heterogeneity, 0.1–0.5 indicated moderate heterogeneity, and > 0.5 indicated high heterogeneity [19]. Small-study effects were examined via funnel plots, with Egger's test applied to detect publication bias. Statistical significance was set at $P < 0.05$.

Results

Characteristics of the studies

The flowchart of study selection for this network meta-analysis is shown in Fig. 1. In total, 1RCT and 13 observational studies with 8142 patients were included [9, 20–32], including 5 groups: β-lactam antibiotics, β-lactam antibiotics plus doxycycline, β-lactam antibiotics plus fluoroquinolones, β-lactam antibiotics plus macrolides, and fluoroquinolones alone. The basic characteristics of the included studies are summarized in Table 1. The quality of studies included is summarized in eTable 3 and eFigure 1.

Network geometry and synthesis of results

The network geometry for mortality is shown in Fig. 2. 5 studies reported 30-day mortality, 4 studies reported in-hospital mortality, and 7 studies reported both.

The SUCRA values and treatment ranks for overall mortality are presented in Fig. 3A. β-lactam antibiotics plus macrolides had the highest rank (SUCRA, 91.0%; mean rank, 1.3), followed by fluoroquinolones (SUCRA, 53.7%; mean rank, 2.9), β-lactam antibiotics plus doxycycline (SUCRA, 42.1%; mean rank, 3.3) and β-lactam antibiotics plus doxycycline (SUCRA, 41.6%; mean rank, 3.3). β-lactam antibiotics plus fluoroquinolones had the lowest rank.

β-lactam antibiotics plus macrolides didn't show a significant reducing mortality compared to fluoroquinolones (RR, 0.86; 95% CI, 0.66–1.44) and β-lactam antibiotics plus doxycycline (RR, 0.80; 95% CI, 0.43–1.48). β-lactam antibiotics plus macrolides was associated with a significant reduction in mortality compared to β-lactam antibiotics (RR, 0.79; 95% CI, 0.64–0.96) and β-lactam antibiotics plus fluoroquinolones (RR, 0.67; 95% CI, 0.64–0.82). The difference was not significant among other comparisons (Table 2A).

Secondary outcomes

To assess the effect of different antibiotic regimens on mortality over time, we evaluated both 30-day mortality (Table 2B) and in-hospital mortality (Table 2C). β-lactam antibiotics plus macrolides and fluoroquinolones ranked first and second for both 30-day mortality and in-hospital mortality (Fig. 3B and C). β-lactam antibiotics plus fluoroquinolones ranked the lowest.

For 30-day mortality, β-lactam antibiotics plus macrolides significantly reduced mortality compared to β-lactam antibiotics plus fluoroquinolones (RR, 0.73; 95% CI, 0.58–0.91) but not compared to β-lactam antibiotics alone (RR, 0.77; 95% CI, 0.59–1.01) (Table 2B).

For in-hospital mortality, β-lactam antibiotics plus macrolides also showed a better mortality compared to β-lactam antibiotics plus fluoroquinolones (RR, 0.67; 95% CI, 0.54–0.82) and β-lactam antibiotics alone (RR, 0.78; 95% CI, 0.64–0.96) (Table 2C).

Heterogeneity, inconsistency, and small-study effects

Heterogeneity and inconsistency are shown in Table 3. Heterogeneity was low for all outcomes. Loop inconsistency for β-lactam antibiotics, β-lactam antibiotics plus fluoroquinolones, and β-lactam antibiotics plus macrolides was found for overall mortality (indirect effect estimate, 0.42; 95% CI, 0.03–0.81; $P = 0.011$) and 30-day mortality (indirect effect estimate, 0.53; 95% CI, 0.14–0.91; $P = 0.000$) (eFigure 2 in the Supplement). A funnel plot was used to demonstrate small-study effects, revealing no publication bias visually (eFigure 3 in the Supplement).

Discussion

To the best of our knowledge, we are the first to combine both direct and indirect evidence to compare initial antibiotic options for patients with SCAP. Our analysis provides important insights to guide clinical decision-making regarding antibiotic choice for these patients. From our analysis, we derived several key findings: β-lactam plus macrolide emerged as the best choice for patients with SCAP, in alignment with international guidelines [6, 7] Fluoroquinolone monotherapy can be considered a reasonable alternative when β-lactam plus macrolide is not appropriate. However, β-lactam plus fluoroquinolone should be avoided.

Early antibiotic therapy has been shown to reduce mortality in patients with SCAP [33]. Although

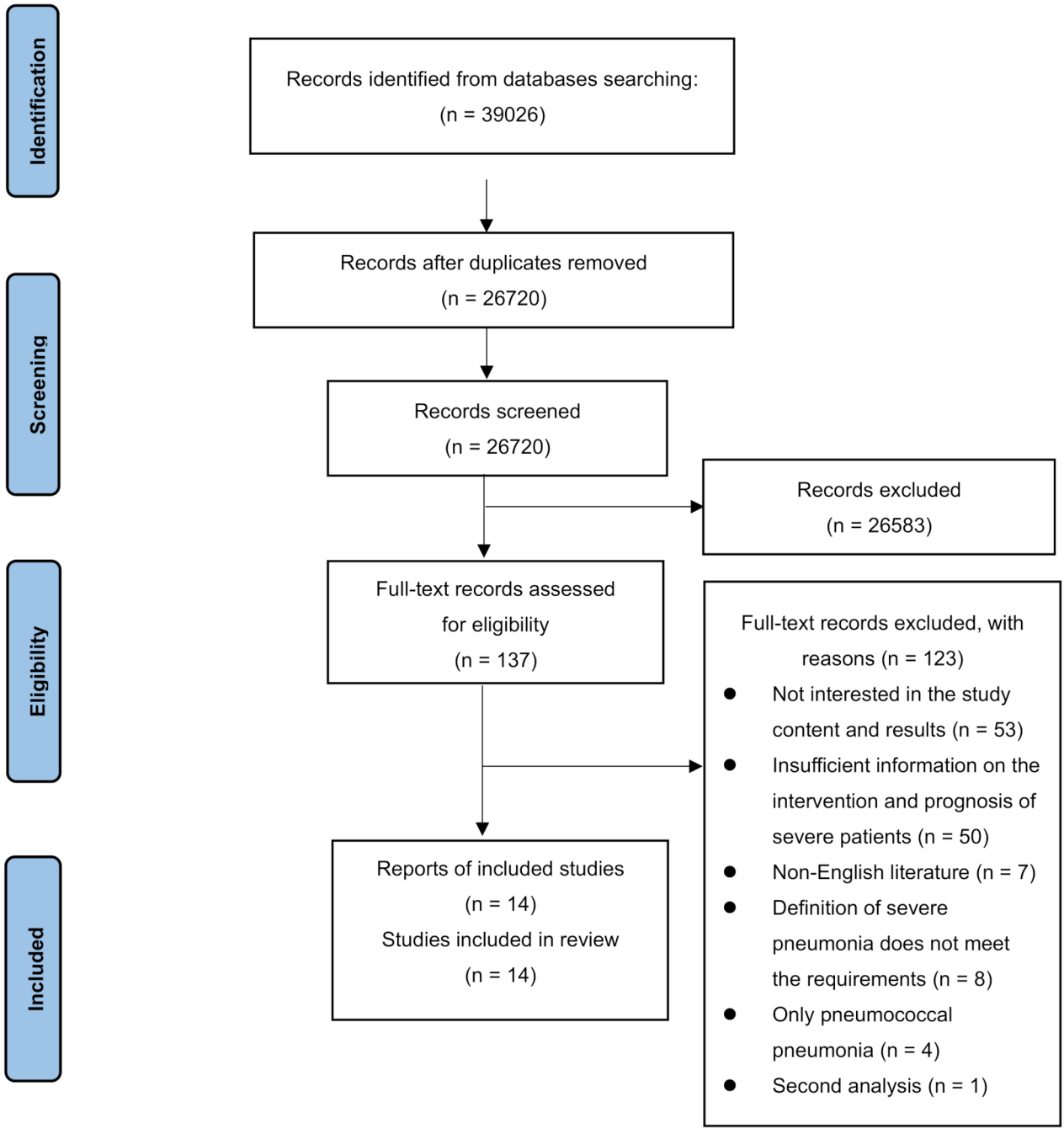

Fig. 1 PRISMA flowchart

atypical microorganisms are responsible for 8–20% of SCAP cases, their role in the disease process is significant [5, 34]. Therefore, empiric antibiotic treatment targeting atypical pathogens is associated with a reduction in clinical failure rates among hospitalized adults with CAP [35, 36]. In addition to their antibacterial effects, macrolides possess broad anti-inflammatory properties [37]. When combined with β-lactams, macrolides improve early clinical responses, reduce inflammation, enhance gas exchange, alleviate sepsis and organ failure, and lower mortality risk [38, 39]. Consistent with the result of a previous study [10], we recommend β-lactam plus macrolide as the preferred empirical antibiotic therapy for hospitalized patients with SCAP.

However, due to the increasing development of antibiotic resistance, especially to macrolides in countries with high prevalence of macrolides resistance [40, 41],

Table 1 Basic characteristics of included studies

Study	Country	Study design	Population	Disease severity score (mean)	Mechanical ventilation (%)	Severe sepsis or septic shock (%)	Interventions	Patients, No.	Mean age, (range), y	Reported mortality		Risk of bias*
										30-day (%)	In-hospital (%)	
Rello, 2002 [20]	Spain	Retrospective study	Patients admitted to ICU	APACHE II score 18.5	77.4	Septic shock (32.3%)	BL	31	NR	NR	35.5%	Low
				APACHE II score 18.8	92.1	Septic shock (31.5%)	F	38	NR	NR	26.3%	
				APACHE II score 19.1	46.1	Septic shock (0%)	BL + M	274	NR	NR	25.9%	
Leroy, 2005 [54]	International	Randomized controlled trials	Patients admitted to ICU	SAPS II score 34.0	51	Septic shock (0%)	BL + F	201	60	NR	22.4%	Low
				SAPS II score 33.0	51.6	Septic shock (0%)	F	194	60	NR	17.5%	
Bratzler, 2008 [22]	United States	Retrospective study	Patients admitted to ICU	NR	NR	NR	BL + F	207	NR	20.3%	15.9%	Low
							BL + M	693	NR	10.7%	6.9%	
							BL	509	NR	15.7%	12.6%	
							F	418	NR	15.6%	11.5%	
Martin, 2010 [23]	Spain	Prospective study	Patients meeting IDSA/ATS SCAP criteria	SAPS II score 49.2	100	Severe sepsis and septic shock (96.2%)	BL + F	54	57.1	46.3%	59.3%	High
				SAPS II score 44.3	100	Severe sepsis and septic shock (86.9%)	BL + M	46	58.2	26.1%	37.0%	
Wilson, 2012 [24]	United States	Retrospective study	Patients admitted to ICU	NR	43	Septic shock (27%)	BL + F	883	75	27.4%	NR	Low
				NR	37	Septic shock (20.7%)	BL + M	1106	74	24.2%	NR	
Adrie, 2013 [25]	France	Prospective study	Patients admitted to ICU	SAPS II score 47	72.2	Septic shock (40.1%)	BL	471	60	NR	26.1%	Low
				SAPS II score 43	58.3	Septic shock (58.3%)	BL + F	230	64	NR	31.3%	
				SAPS II score 37	44.5	Septic shock (44.5%)	BL + M	164	64	NR	21.3%	
Karhu, 2013 [26]	Finland	Retrospective study	Patients meeting IDSA/ATS SCAP criteria	IDSA/ATS SCAP criteria fulfilled (83.7%)	63.1	Septic shock (48.1%)	BL + F	104	54	16.3%	28.8%	Low
				IDSA/ATS SCAP criteria fulfilled (68.9%)	42.5	Septic shock (38.7%)	BL + M	106	55	24.5%	19.8%	
Ceccato, 2017 [27]	International	Retrospective study	Patients meeting IDSA/ATS SCAP criteria	PSI score 94.2	NR	NR	BL + F	78	61	NR	5.1%	High
				PSI score 132.3	NR	NR	BL + M	28	75	NR	21.4%	
Rahmel, 2017 [28]	Germany	Retrospective study	Patients admitted to ICU	SAPS II score 40	NR	NR	BL + F	44	41	33%	NR	Low
				SAPS II score 47	NR	NR	F	42	45	30%	NR	
Ito, 2019 [29]	Japan	Prospective study	Patients meeting IDSA/ATS SCAP criteria	NR	NR	NR	BL	236	NR	15.3%	NR	High
							BL + M	48	NR	6.3%	NR	
Suzuki, 2019 [30]	Japan	Retrospective study	Patients meeting IDSA/ATS SCAP criteria	IDSA/ATS SCAP criteria fulfilled (100%)	79.1	Septic shock (51.7%)	BL + F	560	72	20.7%	46.0%	Low
				IDSA/ATS SCAP criteria fulfilled (100%)	80	Septic shock (53.7%)	BL + M	560	73	19.3%	49.1%	
Kyriazopoulou, 2020 [31]	Greece	Retrospective study	Patients meeting IDSA/ATS SCAP criteria	APACHE II score 15.3	NR	Septic shock (18.5%)	BL + M	260	260	27.3%	NR	Low
				APACHE II score 16.8	NR	Septic shock (23.8%)	F	130	130	31.5%	NR	
				APACHE II score 16.1	NR	Septic shock (18.5%)	BL	130	130	36.2%	NR	

Table 1 (continued)

Study	Country	Study design	Population	Disease severity score (mean)	Mechanical ventilation (%)	Severe sepsis or septic shock (%)	Interventions	Patients, No.	Mean age, (range), y	Reported mortality		Risk of bias*
										30-day (%)	In-hospital (%)	
Greco, 2023 [9]	USA	Prospective study	Patients meeting IDSA/ATS SCAP criteria	APACHE IV score 35	53	Septic shock (34%)	BL + D	86	64	27.9%	27.9%	Low
				APACHE IV score 35	63	Septic shock (38%)	BL + M	63	58	22.2%	22.2%	
Oh, 2024 [32]	Korea	Retrospective study	Patients meeting IDSA/ATS SCAP criteria	PSI score 152.3	11.5	NR	BL	64	73	15.6%	25.0%	Low
				PSI score 158.2	21.4	NR	BL + F	84	75	27.4%	33.3%	

Legend: BL, β-lactam antibiotics; D, doxycycline; M, macrolides; F, fluoroquinolones; ICU, intensive care unit; NR, not reported; SCAP, severe community-acquired pneumonia; SAPS, simplified acute physiology score; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; APACHE, Acute Physiology and Chronic Health Evaluation; PSI, Pneumonia Severity Index. *The risk of bias in observational trials and randomized controlled trials was assessed using the Newcastle-Ottawa quality assessment scale (NOS) and the revised tool for risk of bias (ROB2) for randomized controlled trials, respectively

the use of macrolides in combination with β-lactams may no longer be a rational choice. While previous studies have suggested that β-lactam plus macrolide is more effective than β-lactam plus fluoroquinolone in reducing mortality and length of hospital stay in SCAP [10], this does not mean that β-lactam plus fluoroquinolone is an appropriate alternative. No studies have directly compared β-lactam plus fluoroquinolone with fluoroquinolone monotherapy or β-lactam combined with other antibiotics (e.g., doxycycline) targeting atypical microorganisms. Previous studies have reported that β-lactam plus macrolide, compared to fluoroquinolone or β-lactam plus doxycycline, results in similar in-hospital mortality rates for patients with non-severe CAP [8, 11, 42–44]. One prospective observational cohort study also found no significant differences in in-hospital and 30-day mortality between SCAP patients treated with β-lactam plus doxycycline or β-lactam plus azithromycin [9]. Our NMA results indicate that fluoroquinolone or β-lactam plus doxycycline may reduce mortality compared to β-lactam plus fluoroquinolone, although this difference was not statistically significant. Importantly, the evidence for β-lactam plus doxycycline comes from a single observational study [9], and further research is needed to confirm this finding. Therefore, if β-lactam plus macrolide is not the first choice due to high resistance, fluoroquinolone monotherapy could be a rational alternative.

Our results also showed that β-lactam plus fluoroquinolone did not significantly differ from β-lactam monotherapy in mortality outcomes. Several studies suggest that β-lactam monotherapy is associated with worse outcomes, including higher mortality and longer hospital stays [45–48]. However, this may be due to the lack of direct comparisons between β-lactam plus fluoroquinolone and other guideline-concordant treatments [22, 25, 49]. Given that β-lactam plus fluoroquinolone provides similar bacterial coverage to β-lactam plus macrolide, no significant question has been raised about the recommendation of using β-lactam plus fluoroquinolone in patients with SCAP. Our NAM results indicate that β-lactam plus fluoroquinolone may be associated with lower efficacy compared to fluoroquinolone monotherapy (RR,1.30; 95% CI, 0.99–1.70). The exact reasons for this reduced efficacy remain unclear. One possibility is that the combination does not provide broader coverage of pathogens compared to fluoroquinolone monotherapy. Additionally, overuse of antibiotics may lead to secondary infections, and disruption of the normal microbiota could exacerbate the inflammatory response, leading to worse outcomes [50, 51]. Therefore, based on our findings, we

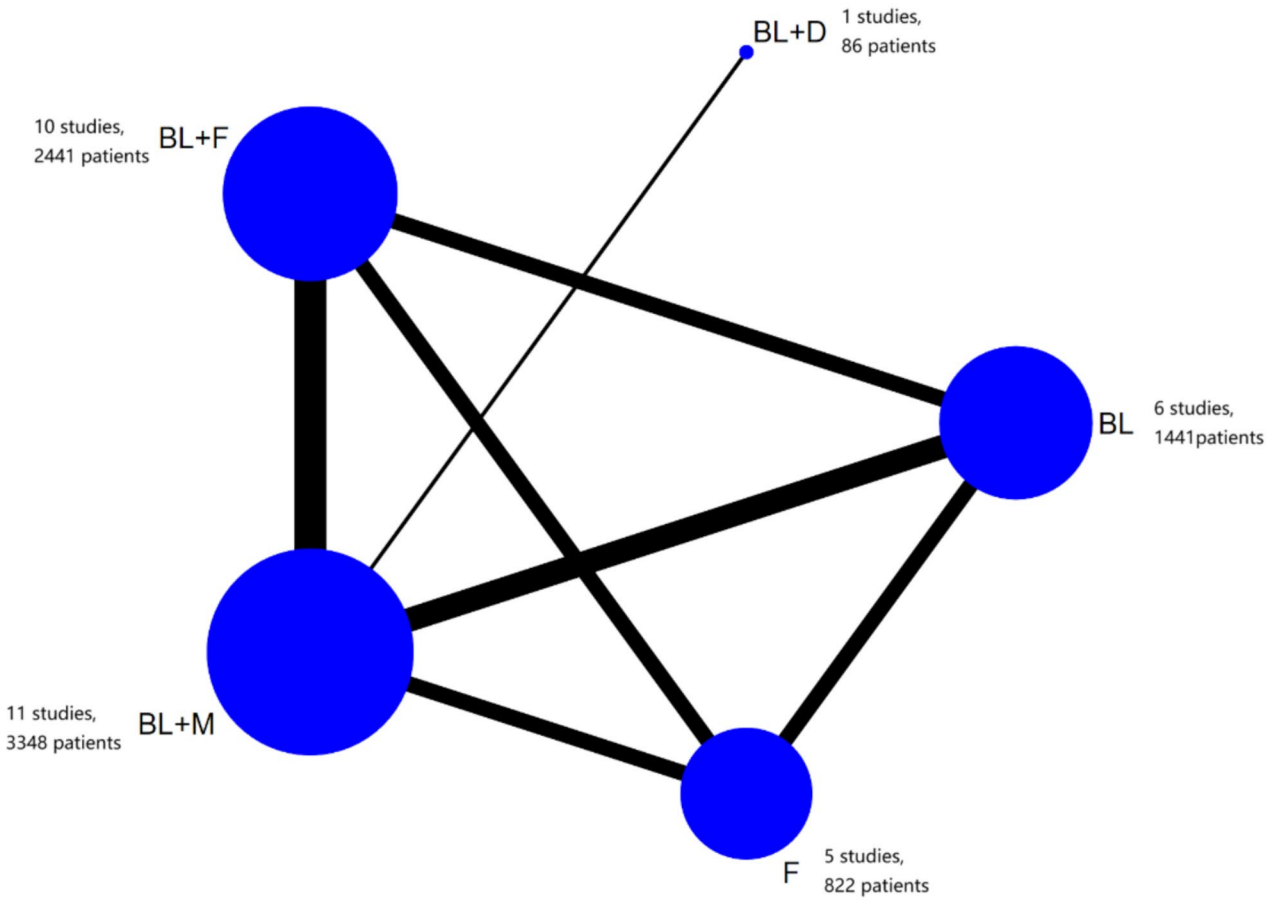

Fig. 2 Network diagrams of the network meta-analysis
Legend: BL, β-lactam antibiotics; D, doxycycline; M, macrolides; F, fluoroquinolones

recommend against using β-lactam plus fluoroquinolone as the treatment for SCAP.

In recent years, novel antibiotics such as delafloxacin and omadacycline have shown promising efficacy in treating CAP [52, 53]. However, these antibiotics should not be used as empirical treatments for SCAP in the initial stages due to insufficient clinical data supporting their effectiveness in severe cases. They should be reserved for situations with relevant risk factors or well-defined pathogen and resistance patterns.

Limitations

Our study has several limitations. Firstly, we included patients who were admitted to the ICU. Although the IDSA/ATS guidelines recommend that SCAP patients meet the criteria for severe pneumonia when admitted to the ICU, the studies included in our review did not explicitly state that the patients adhered to this specific recommendation. Instead, most of the ICU-admitted patients in these studies were included based on clinical judgment rather than strictly following the IDSA/ATS guidelines. Furthermore, some studies conducted subgroup analyses, which could introduce inconsistencies in baseline characteristics and potential bias. Secondly, 13 of the 14 studies included were observational, limiting our ability to draw definitive causal conclusions. Given the susceptibility of observational studies to confounding factors, future large-scale RCTs are needed to strengthen the evidence base and reduce bias. Thirdly, although guidelines recommend specific β-lactam antibioticss (e.g., cefotaxime, ceftriaxone) for ICU patients without high-risk drug-resistant pathogens, several studies used β-lactam antibioticss outside these recommended classes or did not specify the β-lactam antibiotics used. This inconsistency may have affected treatment efficacy. Lastly, the rising antimicrobial resistance, particularly to macrolidess, is a concern in treating SCAP. Unfortunately, none of the studies included provided data on macrolides resistance, preventing subgroup analyses based on resistance patterns. This data gap limits our ability to assess the real-world effectiveness of macrolidess in the context of resistance. Given these limitations, caution should be exercised in interpreting our findings,

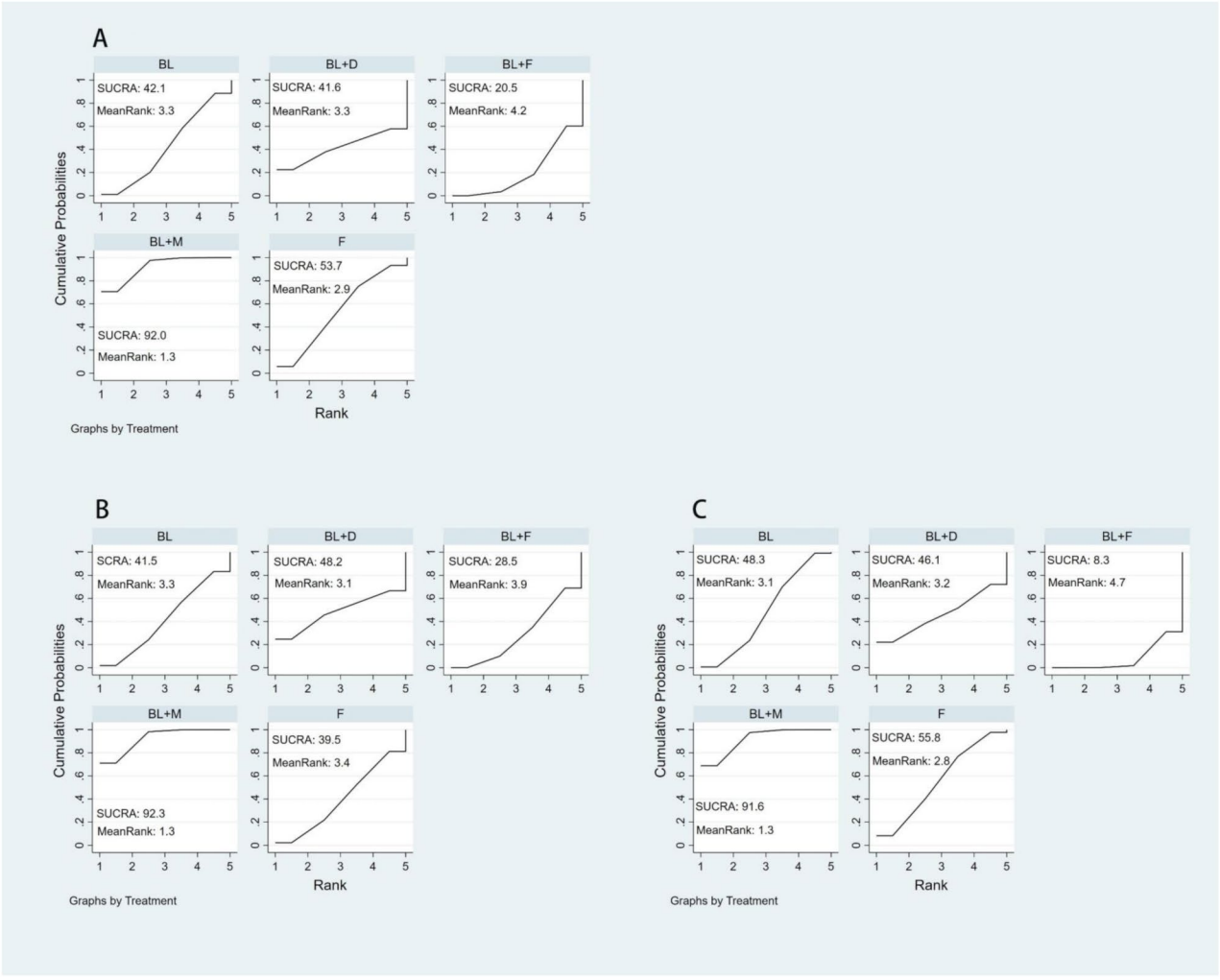

Fig. 3 SUCRA values and mean rank for each agent of each outcome
Legend: **A-C**: overall mortality, 30-day mortality, in-hospital mortaliy. BL, β-lactam antibiotics; D, doxycycline; M, macrolides; F, fluoroquinolones

Table 2 League tables of all outcomes

Panel A. Overall mortality				
LB + M	1.16 (0.88,1.53)	1.26 (0.67,2.34)	1.28 (1.05,1.57)	1.50 (1.22,1.84)
0.86 (0.66,1.14)	**F**	1.09 (0.55,2.14)	1.11 (0.83,1.48)	1.30 (0.99,1.70)
0.80 (0.43,1.48)	0.92 (0.47,1.82)	**BL + D**	1.02 (0.53,1.96)	1.20 (0.62,2.30)
0.78 (0.64,0.96)	0.90 (0.68,1.21)	0.98 (0.51,1.89)	**BL**	1.17 (0.94,1.47)
0.67 (0.54,0.82)	0.77 (0.59,1.01)	0.84 (0.43,1.61)	0.85 (0.68,1.07)	**BL + F**
Panel B. 30-day mortality				
BL + M	1.31 (0.99,1.73)	1.26 (0.65,2.43)	1.30 (0.99,1.70)	1.37 (1.10,1.72)
0.76 (0.58,1.01)	**F**	0.96 (0.47,1.97)	0.99 (0.73,1.34)	1.05 (0.79,1.40)
0.80 (0.41,1.54)	1.04 (0.51,2.13)	**BL + D**	1.03 (0.50,2.11)	1.09 (0.54,2.20)
0.77 (0.59,1.01)	1.01 (0.75,1.37)	0.97 (0.47,1.98)	**BL**	1.06 (0.79,1.43)
0.73 (0.58,0.91)	0.95 (0.71,1.27)	0.91 (0.45,1.84)	0.94 (0.70,1.27)	**BL + F**
Panel C. In-hospital mortality				
BL + M	1.16 (0.88,1.53)	1.26 (0.67,2.34)	1.28 (1.05,1.57)	1.50 (1.22,1.84)
0.86 (0.66,1.14)	**F**	1.09 (0.55,2.14)	1.11 (0.83,1.48)	1.30 (0.99,1.70)
0.80 (0.43,1.48)	0.92 (0.47,1.82)	**BL + D**	1.02 (0.53,1.96)	1.20 (0.62,2.30)
0.78 (0.64,0.96)	0.90 (0.68,1.21)	0.98 (0.51,1.89)	**BL**	1.17 (0.94,1.47)
0.67 (0.54,0.82)	0.77 (0.59,1.01)	0.84 (0.43,1.61)	0.85 (0.68,1.07)	**BL + F**

Legend: BL, β-lactam antibiotics; D, doxycycline; M, macrolides; F, fluoroquinolones. Significant results are indicated in bold

Table 3 Tests for inconsistency, heterogeneity, and small-study effects

Outcome	Inconsistency at the overall level		Heterogeneity	Small-Study Effects
	χ2	*P* value	τ^2	Egger's test *P* value
Overall mortality	14.37	0.072	0.013	0.891
30-day mortality	13.65	0.058	0.028	0.933
In-hospital mortality	0.94	0.998	0.008	0.844

Legend: Inconsistency and heterogeneity across studies was quantified using the restricted maximum likelihood (REML) method. Small-study effects were assessed using Begg's test

and further research is necessary to address these gaps and refine SCAP treatment strategies.

Conclusions

Our NMA suggests that β-lactam antibiotics plus macrolides may be the most effective treatment option for SCAP. The use of β-lactam antibiotics monotherapy and β-lactam antibiotics plus fluoroquinolones should be avoided, as these regimens demonstrated inferior efficacy in our analysis. However, the methodological limitations of the included studies and the limited availability of relevant clinical data preclude a definitive conclusion. Therefore, large-scale, well-designed RCTs are necessary to determine the most effective regimen for SCAP.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03695-w.

Supplementary Material 1

Author contributions

Ao Liu, Min Wang designed the study and supervised the overall project; Xiaoming Wang and Lian Wang participated in collecting data; Han Zhuang, Qian Wang participated in analysis; Ao Liu, Jing Zhang and Min Wang provided the statistical analysis and wrote the manuscript.

Funding

1 Henan Provincial Medical Science and Technology Research Project. Fund No.: SBGJ202303042.
2 Henan Provincial Key Research Projects of Higher Education Institutions. Fund No.: 24A320005.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This is a systematic review and meta-analysis; ethics approval and consent to participate are not applicable.

Consent for publication

Not applicable. The manuscript does not include the participant's identification image or other personal or clinical details.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

Received: 27 February 2025 / Accepted: 28 April 2025
Published online: 20 May 2025

References

1. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
2. Cilloniz C, Ferrer M, Liapikou A et al. Acute respiratory distress syndrome in mechanically ventilated patients with community-acquired pneumonia. Eur Respir J. 2018;51(3).
3. Phua J, Dean NC, Guo Q, et al. Severe community-acquired pneumonia: timely management measures in the first 24 hours. Crit Care. 2016;20(1):237.
4. Tsai D, Chiong F, Secombe P, et al. Epidemiology and microbiology of severe community-acquired pneumonia in central Australia: a retrospective study. Intern Med J. 2022;52(6):1048–56.
5. Wang S, Tang J, Tan Y et al. Prevalence of atypical pathogens in patients with severe pneumonia: a systematic review and meta-analysis. BMJ Open. 2023;13(4).
6. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. Am J Respir Crit Care Med. 2019;200(7):e45–67.
7. Martin-Loeches I, Torres A, Nagavci B et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Eur Respir J. 2023;61(4).
8. Bai AD, Srivastava S, Wong BKC, et al. Comparative effectiveness of first-line and alternative antibiotic regimens in hospitalized patients with nonsevere community-acquired pneumonia: a multicenter retrospective cohort study. Chest. 2024;165(1):68–78.
9. Greco Kinney A, Kovacic Scherrer N, Sarkar S, et al. β-Lactams plus Doxycycline versus Azithromycin for treatment of severe community-acquired pneumonia in critically ill patients. J Antimicrob Chemother. 2023;78(12):2816–23.
10. Lee JH, Kim HJ, Kim YH. Is β-Lactam plus macrolide more effective than β-Lactam plus fluoroquinolone among patients with severe community-acquired pneumonia? A systemic review and meta-analysis. J Korean Med Sci. 2017;32(1):77–84.
11. Uddin M, Mohammed T, Metersky M, et al. Effectiveness of beta-lactam plus doxycycline for patients hospitalized with community-acquired pneumonia. Clin Infect Dis. 2022;75(1):118–24.
12. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.
13. Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
14. Sterne JA, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366.
15. White IR. Network meta-analysis. Stata J. 2015;15(4):951–85.
16. Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163–71.
17. Higgins JPT, Jackson D, Barrett J, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synthesis Methods. 2012;3(2):98–110.

18. Shim S, Yoon B-H, Shin I-S et al. Network meta-analysis: application and practice using stata. Epidemiol Health. 2017;39.
19. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane database of systematic reviews. Int J Epidemiol. 2012;41(3):818–27.
20. Rello J, Catalán M, Díaz E, et al. Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia. Intensive Care Med. 2002;28(8):1030–5.
21. Leroy O, Saux P, Bédos JP, et al. Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest. 2005;128(1):172–83.
22. Bratzler DW, Ma A, Nsa W. Initial antibiotic selection and patient outcomes: observations from the national pneumonia project. Clin Infect Dis. 2008;47(Suppl 3):S193–201.
23. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med. 2010;36(4):612–20.
24. Wilson BZ, Anzueto A, Restrepo MI, et al. Comparison of two guideline-concordant antimicrobial combinations in elderly patients hospitalized with severe community-acquired pneumonia. Crit Care Med. 2012;40(8):2310–4.
25. Adrie C, Schwebel C, Garrouste-Orgeas M, et al. Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia: impact on survival and bacterial resistance. Crit Care. 2013;17(6):R265.
26. Karhu J, Ala-Kokko TI, Ohtonen P, et al. Severe community-acquired pneumonia treated with β-lactam-respiratory quinolone vs. β-lactam-macrolide combination. Acta Anaesthesiol Scand. 2013;57(5):587–93.
27. Ceccato A, Cilloniz C, Ranzani OT, et al. Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: a post-hoc exploratory analysis of a randomized controlled trial. PLoS ONE. 2017;12(6):e0178022.
28. Rahmel T, Asmussen S, Karlik J, et al. Moxifloxacin monotherapy versus combination therapy in patients with severe community-acquired pneumonia evoked ARDS. BMC Anesthesiol. 2017;17(1):78.
29. Ito A, Ishida T, Tachibana H, et al. Azithromycin combination therapy for community-acquired pneumonia: propensity score analysis. Sci Rep. 2019;9(1):18406.
30. Suzuki J, Sasabuchi Y, Hatakeyama S, et al. Azithromycin plus β-lactam versus levofloxacin plus β-lactam for severe community-acquired pneumonia: a retrospective nationwide database analysis. J Infect Chemother. 2019;25(12):1012–8.
31. Kyriazopoulou E, Sinapidis D, Halvatzis S, et al. Survival benefit associated with clarithromycin in severe community-acquired pneumonia: a matched comparator study. Int J Antimicrob Agents. 2020;55(1):105836.
32. Oh S, Jang W, Kim B. Is the fluoroquinolone combination necessary for empirical antibiotic regimen in severe community-acquired pneumonia? Postgrad Med. 2024.
33. Gattarello S, Lagunes L, Vidaur L, et al. Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study. Crit Care. 2015;19(1):335.
34. Raeven VM, Spoorenberg SMC, Boersma WG et al. Atypical aetiology in patients hospitalised with community-acquired pneumonia is associated with age, gender and season; a data-analysis on four Dutch cohorts. BMC Infect Dis. 2016;16(1).
35. Eljaaly K, Alshehri S, Aljabri A et al. Clinical failure with and without empiric atypical bacteria coverage in hospitalized adults with community-acquired pneumonia: a systematic review and meta-analysis. BMC Infect Dis. 2017;17(1).
36. Eljaaly K, Aljabri A, Rabaan AA et al. Efficacy of empiric antibiotic coverage in community-acquired pneumonia associated with each atypical bacteria: a meta-analysis. J Clin Med. 2021;10(19).
37. Kricker JA, Page CP, Gardarsson FR, et al. Nonantimicrobial actions of macrolides: overview and perspectives for future development. Pharmacol Rev. 2021;73(4):233–62.
38. Giamarellos-Bourboulis EJ, Siampanos A, Bolanou A, et al. Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2024;12(4):294–304.
39. Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in severe community-acquired pneumonia. N Engl J Med. 2023;388(21):1931–41.
40. Li J, Liu L, Zhang H, et al. Severe problem of macrolides resistance to common pathogens in China. Front Cell Infect Microbiol. 2023;13:1181633.
41. Wang G, Wu P, Tang R, et al. Global prevalence of resistance to macrolides in Mycoplasma pneumoniae: a systematic review and meta-analysis. J Antimicrob Chemother. 2022;77(9):2353–63.
42. Babonji AS, Alshehri SJ, Alturaiki AM. Clinical effectiveness and outcomes of azithromycin versus doxycycline containing regimen in inpatients with community acquired pneumonia: a retrospective cohort study. J Clin Pharm Ther. 2023;2023.
43. Aldhahri RK, Gabb SG, Shoaib OA, et al. Doxycycline vs. macrolides in combination with a β-lactam antibiotic for the treatment of community-acquired pneumonia in inpatients. Eur J Med Res. 2022;27(1):279.
44. Izadi M, Dadsetan B, Najafi Z, et al. Levofloxacin versus ceftriaxone and azithromycin combination in the treatment of community acquired pneumonia in hospitalized patients. Recent Pat Antiinfect Drug Discov. 2018;13(3):228–39.
45. Houck PM, MacLehose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 Western States: 1993, 1995, and 1997. Chest. 2001;119(5):1420–6.
46. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. Arch Intern Med. 2002;162(6):682–8.
47. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med. 2001;161(15):1837–42.
48. Aspa J, Rajas O, de Castro FR, et al. Impact of initial antibiotic choice on mortality from Pneumococcal pneumonia. Eur Respir J. 2006;27(5):1010–9.
49. Mortensen EM, Restrepo MI, Anzueto A, et al. The impact of empiric antimicrobial therapy with a β-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. Crit Care. 2005;10(1):R8.
50. Bhalodi AA, van Engelen TSR, Virk HS, et al. Impact of antimicrobial therapy on the gut microbiome. J Antimicrob Chemother. 2019;74(Supplement1):i6–15.
51. Zuttion MSSR, Parimon T, Bora SA et al. Antibiotic use during influenza infection augments lung eosinophils that impair immunity against secondary bacterial pneumonia. J Clin Investig. 2024;134(21).
52. McCurdy S, Nenninger A, Sheets A et al. Efficacy of delafloxacin versus moxifloxacin against atypical bacterial respiratory pathogens in adults with community-acquired bacterial pneumonia (CABP): data from the Delafloxacin phase 3 CABP trial. (1878–3511 (Electronic)).
53. Torres A, Garrity-Ryan L, Kirsch C, et al. Omadacycline vs moxifloxacin in adults with community-acquired bacterial pneumonia. Int J Infect Dis. 2021;104:501–9.
54. García Vázquez E, Mensa J, Martínez JA, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis. 2005;24(3):190–5.

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