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Review Article

Comparing Several Treatments with Antibiotics for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: We aimed to review relevant randomized controlled trials to assess the relative clinical effects of antibiotic treatment of patients with community-acquired pneumonia (CAP).

Methods: In this meta-analysis, we identified relevant studies from PubMed, Cochrane, and Embase using appropriate keywords. Key pertinent sources in the literature were also reviewed and all articles published through Oct 2019 were considered for inclusion. For each study, we assessed the risk ratios (RRs) or mean difference combined with the 95% confidence interval (CI) to assess and synthesize outcomes.

Results: Overall, 36 studies were consistent with the meta-analysis, involving 17,076 patients. There was no significant difference in the mortality after subgroup analysis: individualized treatment vs. standard treatment; β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone; ceftaroline fosamil vs. ceftriaxone; combination therapy vs. monotherapy or high-dose vs. low-dose. The drug-related adverse event incidence was significantly higher in the ceftriaxone group than in the other drug groups (P<0.05) and also higher in the tigecyline group than in the levofloxacin group (P<0.05). Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the test-of-cure (TOC) visit in the clinically evaluable population, modified intent-to-treat efficacy (MITTE) population, microbiologically evaluable (ME) population and the microbiological MITTE (mMITTE) population (all P<0.05). Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the TOC visit in the mMITTE population of Gram positive-*Streptococcus pneumoniae* (P<0.05) and multidrug-resistant *S. pneumoniae* (P<0.05).

Conclusion: There was a limited number of included studies in the subgroup analysis, but it will still be necessary to conduct more high-quality randomized controlled trials to confirm the clinical efficacy of different antibiotics used to treat CAP.

Keywords: Antibiotics; Community-acquired pneumonia; Meta-analysis; β-lactams; Macrolides

Introduction

Community-acquired pneumonia (CAP) is an infectious inflammation of the lung parenchyma (including the alveolar wall, i.e. lung interstitial disease in a broad sense) outside the hospital, including pneumonia with a clear incubation period of pathogen infection and with an average incu-

bation period after admission. It can be caused by pathogenic microorganisms, immune damage, physical and chemical factors, drugs and/or allergies. Despite the development of ultra-broad-spectrum anti-microbial and strong bactericidal drugs, CAP is still an important disease threatening human health. Especially with the aging of social populations, the increase of hosts with impaired immune function, the dynamic changes of common pathogens in CAP and the rise of antibiotic resistance, the treatment of CAP is facing many problems and challenges. The incidence and fatality rates of CAP are high in all regions of the world, which not only threatens the health of individuals but also increases the burden on the national economy. According to the WHO estimation, there are about 450 million pneumonia patients in the world every year, and about 4 million die from this disease, accounting for about 7% of the total annual mortality rate. Children<5 yr old and elderly individuals aged ≥75 yr have the highest mortality rates, with developing countries having 5 times the death rate of more developed countries (1-5).

The treatment of CAP mainly relies on antibiotic therapy. The correct and appropriate administration of doses of antibiotics is the key to improving efficacy of therapy, reducing the incidence of adverse reactions and slowing down the rate of occurrence of bacterial resistance. Rational prescribing of antimicrobial therapy is a developing problem that needs to be paid great attention to in the clinic. In a previous meta-analysis (6), the clinical effects of ceftriaxone and ceftaroline/ceftobiprole were compared for the treatment of CAP. Tansarli (7) and You-Dong Wan (8) explored whether short-course antibiotic treatment for CAP would produce the most effective efficacy in adult patients. Huang (9) and Bi (10) explored the safety indexes and clinical effect of adjunctive corticosteroids for the treatment of serious CAP. The aim of the present study was to analyze all of the available literature to update our knowledge on the efficacy of antibiotics for the treatment of CAP, and to provide a rational basis for the selection of treatment. Clinical indexes such as mortality and hospital stays, drug-related adverse events, the clinical cure rate by study population or by baseline pathogens, were all analyzed.

Materials and Methods

Search strategy

To identify studies on the clinical results about antibiotic treatment of CAP, we reviewed the Cochrane, PubMed and Embase databases for relevant articles published through Oct 2019. We also reviewed the bibliographies of all identified articles for further relevant studies. The search terms were: CAP, community-acquired pneumonia, community acquired pneumonia, acquired pneumonia, antibiotic, biotic, anti-biotic, ceftriaxone, ceftaroline, tigecycline, levofloxacin, azithromycin, β-lactams, sitafloxacin, nemonoxacin, fluoroquinolone, random, randomized controlled trial, randomized and randomized controlled trial (RCT). In addition to being used alone, these terms were used in combination with "AND" or "OR" in the literature search. This literature review was performed independently by two investigators, with a third resolving any disputes if required.

According to the principle of PICOS (P: participants, I: interventions, C: comparisons, O: outcomes, S: study design), the main search terms included (P) patients with CAP, (I) treated with antibiotics, (C/O) compared the different antibiotic therapies and outcomes including the related clinical indexes, (S) randomized controlled trials.

Study selection criteria

Studies that met the following criteria were included: 1) randomized controlled trials; 2) the research individuals were patients with CAP; 3) antibiotic treatment; the dose and course were not limited; 4) English or Chinese language.

Studies were excluded according to the following criteria: 1) repeated articles or results; 2) clear data errors; 3) case reports, case-control studies, theoretical research, conference reports, systematic reviews, meta-analyses, and other forms of

research or comment not designed in a randomized controlled manner; 4) irrelevant outcomes.
Two investigators independently determined whether studies met the inclusion criteria, with a third investigator resolving any disputes if necessary.

Data extraction and quality assessment

For each included study, two categories of information were extracted, namely basic information and the primary study outcomes. Basic information relevant to the present meta-analysis included: author names, year of publication, sample size, therapy and Jadad scores. Primary clinical outcomes relevant to this analysis included: length of hospital stay; mortality; drug-related AE; test-of-cure (TOC) rates by clinically evaluable (CE) populations, microbiologically evaluable (ME) population, modified intent-to-treat efficacy (MITTE) population, microbiological modified intent-to-treat efficacy (mMITTE) population and the clinical cure rates by baseline pathogens at the TOC visit in a mMITTE population thus: Gram positive-*Streptococcus pneumoniae* (GPSP), multidrug-resistant *Streptococcus pneumoniae* (MDRSP), *Staphylococcus aureus* (SA), Gram negative-*Haemophilus influenzae* (GNHI), *Klebsiella pneumoniae* (KP), *Haemophilus parainfluenzae* (HP), *Escherichia coli* (EC).
Study quality was determined based on Jadad scores, evaluated based on how well each study satisfied the following criteria: included a specific statement regarding randomization; the method used to randomize patients was appropriate; the study was conducted in a double-blinded manner; the approach to double-blinding was appropriately described; information on any patients that withdrew from or dropped out of the study was provided. A Jadad score <3 was deemed to indicate a study of low-quality, and thus associated with a substantial risk of bias. The data extraction was performed independently by two investigators, with a third resolving any disputes if required.

Statistical analysis

STATA version 10.0 (TX, USA) was used for all analyses. The heterogeneity results of a study were assessed using chi-squared and I^2 tests and appropriate analysis models (fixed-effect or random-effect) were employed. If a chi-squared value of $P \leq 0.05$ and $I^2 > 50\%$ indicated that heterogeneity was high, a random effect model was used. A chi-squared value of $P > 0.05$ and $I^2 \leq 50\%$ indicated acceptable heterogeneity and therefore a fixed-effects model was used. Continuous variables are given as means ± standard deviations and were compared based on weighted mean difference (WMD), while categorical data are given as percentages and evaluated based on the risk ratio (RR)/odds ratio (OR). RR and 95% confidence interval (CI) were used to analyze all indexes except for the length of hospital stay.

Results

Overview of included studies

Overall, 1,215 articles identified by our initial keyword search were reviewed, of which 1,109 were excluded following title/abstract review. The remaining 106 articles were subject to a complete full-text assessment, leading to 70 articles being excluded for failing to meet the study inclusion criteria (*vide supra*). The reasons for exclusion of a study included: no clinical outcomes (50), no-qualified interventions (15), theoretical research (3), or repeated articles (2). We ultimately identified 36 studies (11-46) for inclusion in the meta-analysis that involved 17,076 patients. The selection process adopted is outlined in Fig. 1.

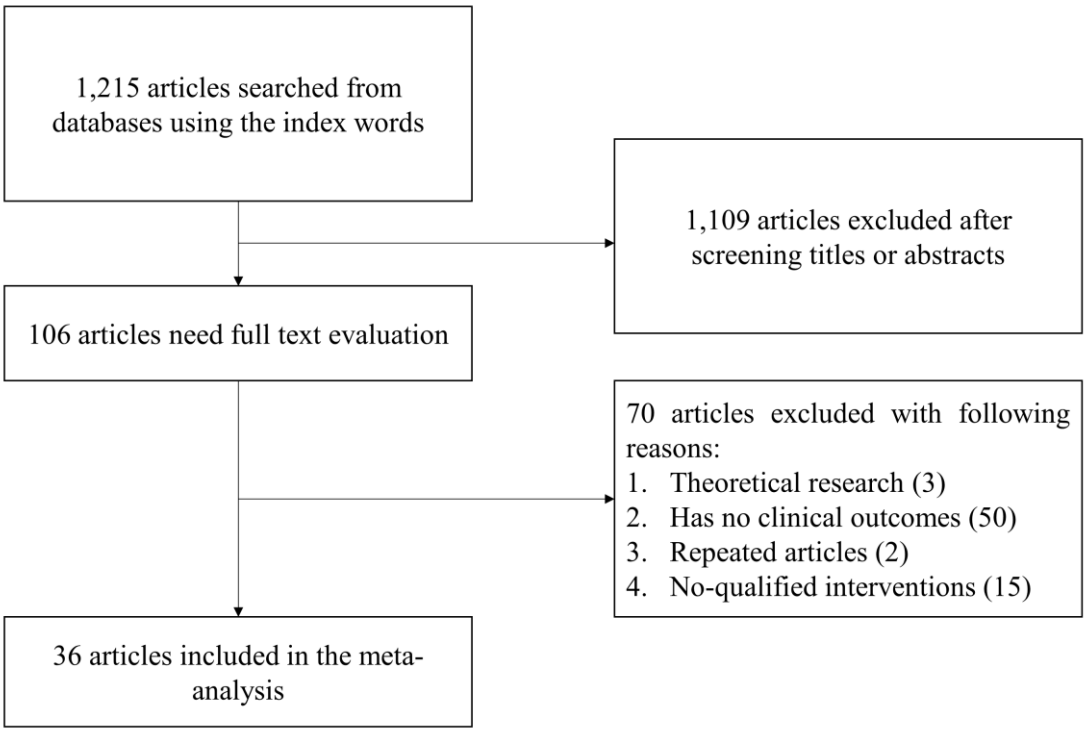

Fig.1: Literature search and selection strategy

According to interventions, studies were divided into the subgroup analysis thus: individualized treatment vs. standard treatment (11, 32, 40); β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone (13, 22, 35); high-dose vs. low-dose (21, 27, 37, 41, 44); ceftaroline fosamil vs ceftriaxone (17, 18, 23, 29, 36, 45); combination therapy vs. monotherapy (20, 26, 28, 31, 39, 42, 46); cethromycin vs clarithromycin (cethromycin 300 mg once daily vs clarithromycin 250 mg twice daily) (16); short-time therapy vs long-time therapy (15, 19, 33); ceftriaxone vs other drugs (30, 34); sulbactam/ampicillin vs. other drugs (24, 43); tigecycline vs levofloxacin (12, 38) and azithromycin *vs* other drugs (14, 25). The mean Jadad score for the selected studies was 3.76 indicating that the selected studies were all of high quality.

Length of hospital stay

Six studies (13, 15, 22, 32, 35, 40) comprising 4,302 patients reported on the length of hospital stays. There was no statistically significant difference in this index in the subgroup analysis: β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone (WMD: -0.00, 95% CI: -0.00 ~ 0.00), individualized treatment vs. standard treatment (WMD: -0.79, 95% CI: -2.85 ~ 1.26). Hospital stay was significantly decreased in the short-time therapy group compared to the long-time therapy group (WMD: -1.00, 95% CI: -1.04 ~ 0.96), but note the analysis only included one study (Fig. 2).

Mortality

Ten studies (11, 13, 22, 26, 32, 36, 37, 39, 40, 42) of 4,225 patients reported the results of mortality. There were no statistically significant differences in the incidences of mortality in the subgroup analysis: individualized treatment *vs* standard treatment (RR: 1.10, 95% CI: 0.49~2.44), β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone (RR: 1.27, 95% CI: 0.56~2.88), ceftaroline fosamil vs. ceftriaxone (RR: 1.25, 95% CI: 0.59~2.66), combination therapy *vs* monotherapy (RR: 1.09, 95% CI: 0.78~1.51), high-dose *vs* low-dose (RR: 0.58, 95% CI: 0.15~2.28) (Fig. 3).

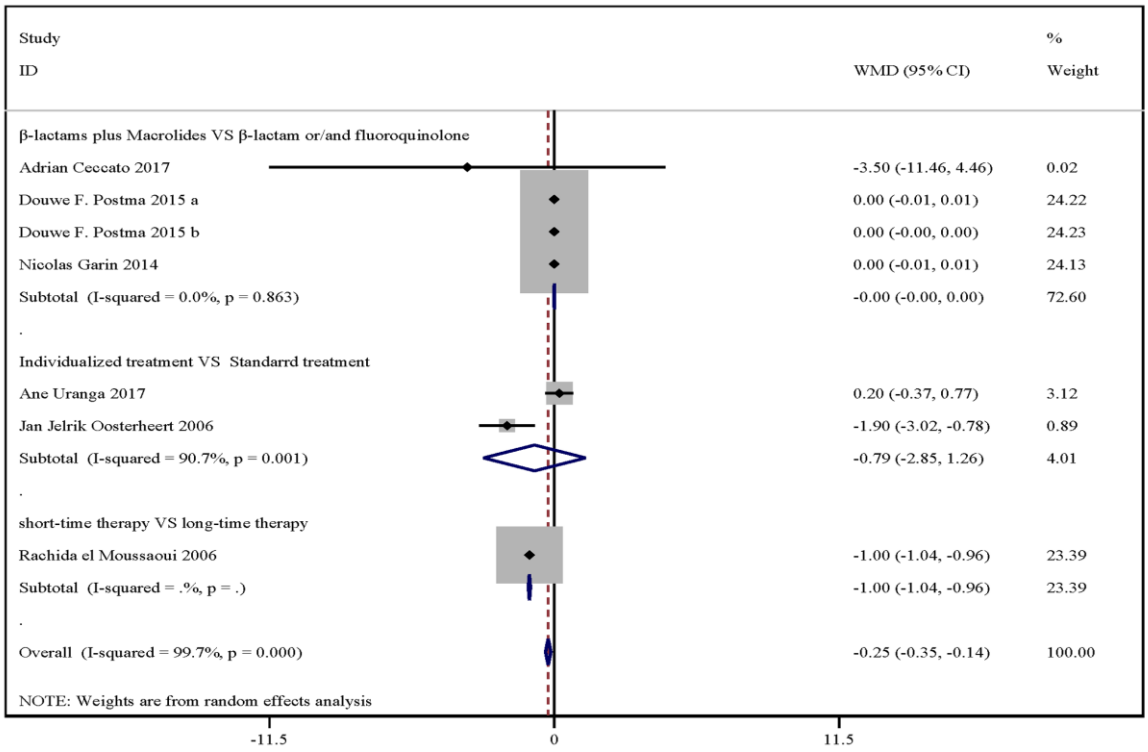

Fig. 2: Forest plot for the length of hospital stay
Abbreviation: WMD, weighted mean difference

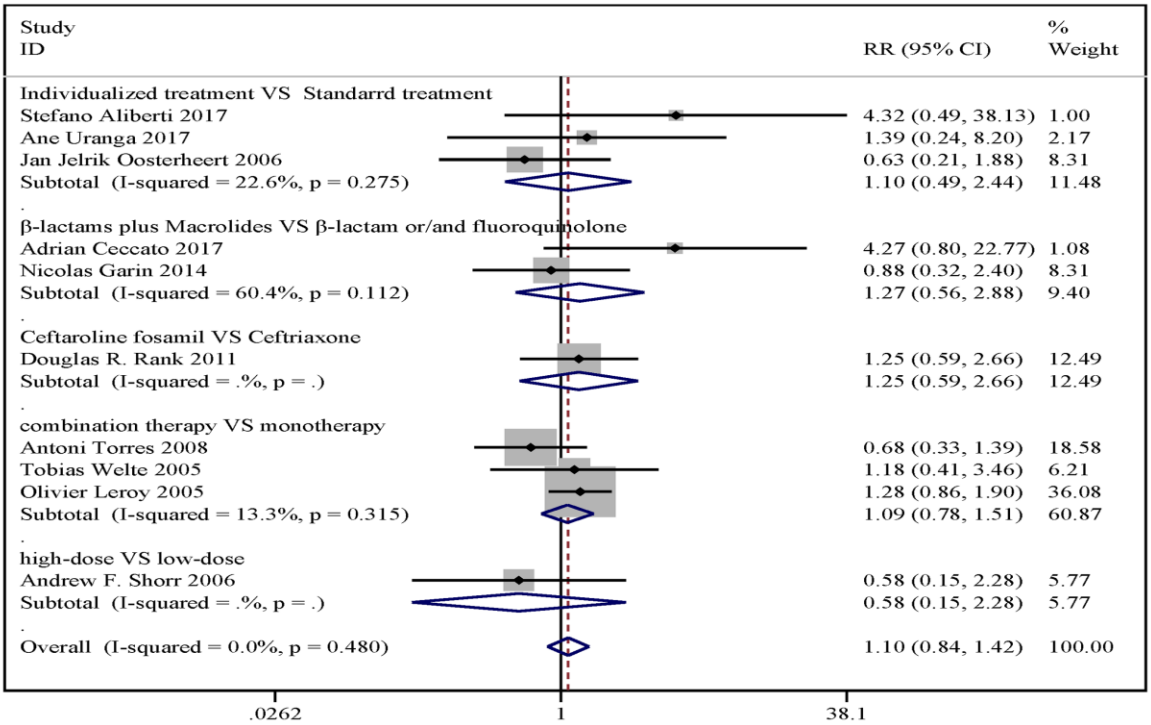

Fig. 3: Forest plot for mortality
Abbreviation: RR, risk ratio

Drug-related adverse events

Overall, 27 studies (11, 12, 14, 15, 17-19, 21, 25-31, 33-38, 40-45) of 13,898 patients reported the results of drug-related AEs. The subgroup analysis showed there was no statistically significance differences in the drug-related AE incidence: individual treatment *vs* standard treatment (RR: 0.82, 95% CI: 0.47~1.40), high-dose vs. low-dose (RR: 0.92, 95% CI: 0.81~1.05), β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone (RR: 1.08, 95% CI: 0.93~1.25), ceftaroline fosamil *vs* ceftriaxone (RR: 1.03, 95% CI: 0.95~1.11), combination therapy vs monotherapy (RR: 1.04, 95% CI: 0.85~1.27), short-time therapy vs long-time therapy (RR: 1.18, 95% CI: 0.90 ~ 1.56). The drug-related AE incidence was significantly higher in the ceftriaxone group than in other drug groups (RR: 1.21, 95% CI: 1.04 ~ 1.41). The drug-related AE incidence was significantly higher in the tigecyline group than in the levofloxacin group (RR: 1.23, 95% CI: 1.08~1.40) (Fig. 4).

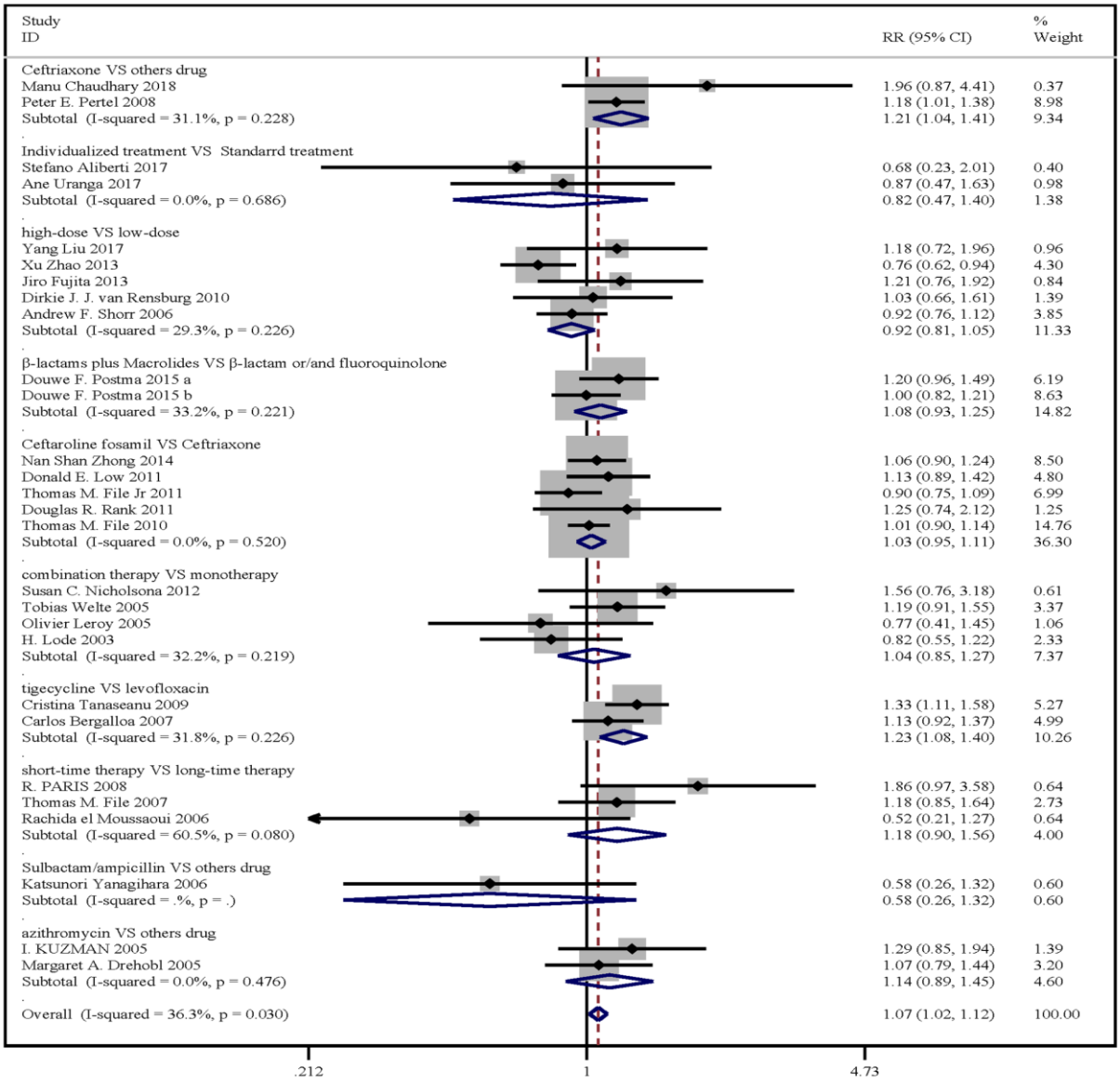

Fig. 4: Forest plot for drug-related adverse events
Abbreviation: RR, risk ratio

Clinical cure rates by study population at the TOC visit

Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the TOC visit in a CE population (RR: 1.083, 95% CI: 1.017 ~ 1.153), MITTE population (RR: 1.079, 95% CI: 1.017 ~ 1.144), ME population (RR: 1.135, 95% CI: 1.014 ~ 1.269) and mMITTE population (RR: 1.116, 95% CI: 1.000 ~ 1.246). The clinical cure rate at the TOC visit in the ME population was significantly increased in the ceftriaxone group than in other drug groups (RR: 1.173, 95% CI: 1.055 ~ 1.304) (Table 1). There was no significant difference in the clinical cure rate by study population at the TOC visit for other treatment subgroup analyses (data not listed in Table 1).

Table 1: Meta-analysis results of clinical cure rates by study population or by baseline pathogens

Index	*N (case/control)*	*Interventions*	*RR (95% CI)*	*P**	*I²*	*P#*	*P-value*	
							Begg's	Egger's
Clinical cure rates by study population at the TOC Visit								
CE								
	482/471	Ceftaroline fosamil *vs* ceftriaxone	1.083 (1.017, 1.153)	0.782	0.0%	0.013	0.602	0.644
MITTE								
	580/573	Ceftaroline fosamil *vs* ceftriaxone	1.079 (1.017, 1.144)	0.976	0.0%	0.011	0.317	-
ME								
	154/147	Ceftaroline fosamil *vs* ceftriaxone	1.135 (1.014, 1.269)	0.442	0.0%	0.027	0.317	-
	105/127	Ceftriaxone *vs* other drugs	1.173 (1.055, 1.304)	-	-	0.003	-	-
mMITTE								
	165/168	Ceftaroline fosamil *vs* ceftriaxone	1.116 (1.000, 1.246)	0.393	0.0%	0.050	0.317	-
Clinical cure rates by baseline pathogens at the TOC visit in mMITTE population								
GPSP								
	9/11	Ceftriaxone *vs* other drugs	0.470 (0.234, 0.941)	-	-	0.033	-	-
	160/155	Ceftaroline fosamil *vs* ceftriaxone	1.212 (1.076, 1.366)	0.434	0.0%	0.002	1.000	0.790
MDRSP								
	8/18	Ceftaroline fosamil *vs* ceftriaxone	3.341 (1.511, 7.386)	0.975	0.0%	0.003	1.000	0.978

Note: **P*-value of heterogeneity of chi-squared, #*P*-value of pooled statistics.

Abbreviations: CE, clinically evaluable; GPSP, Gram positive-*Streptococcus pneumoniae*; MDRSP, multidrug-resistant *Streptococcus pneumoniae*; ME, microbiologically evaluable; MITTE, modified intent-to-treat efficacy; mMITTE, microbiological modified intent-to-treat efficacy; TOC, test-of-cure

Clinical cure rates by baseline pathogens at the TOC visit in the mMITTE population

Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the TOC visit in the mMITTE population of GPSP (RR: 1.212, 95% CI: 1.076 ~ 1.366) and MDRSP (RR: 3.341, 95% CI: 1.511 ~ 7.386). The clinical cure rate of GPSP at the TOC visit in the mMITTE population was significantly lower in the ceftriaxone group compared to other drugs (RR: 0.470, 95% CI: 0.234 ~ 0.941) (Table 1). There was no significant difference in the clinical cure rates regarding EC, GNHI, HP, KP and SA subgroup analyses at the TOC visit (data not listed in Table 1)

Quality and bias assessment

Multiple complementary methods, including funnel plots, Begg's and Mazumdar's rank tests, and Egger's test were used to assess the quality of studies and the risk of bias. The log RR funnel plot of drug-related AEs for these studies was symmetric, suggesting a low publication bias risk (Fig. 5). The results of Begg's and Mazumdar's rank test (Z=0.10, *P*=0.921) and Egger's test (*P*=0.927) both suggested that there was not any significant risk of bias among the study results (Fig. 5).

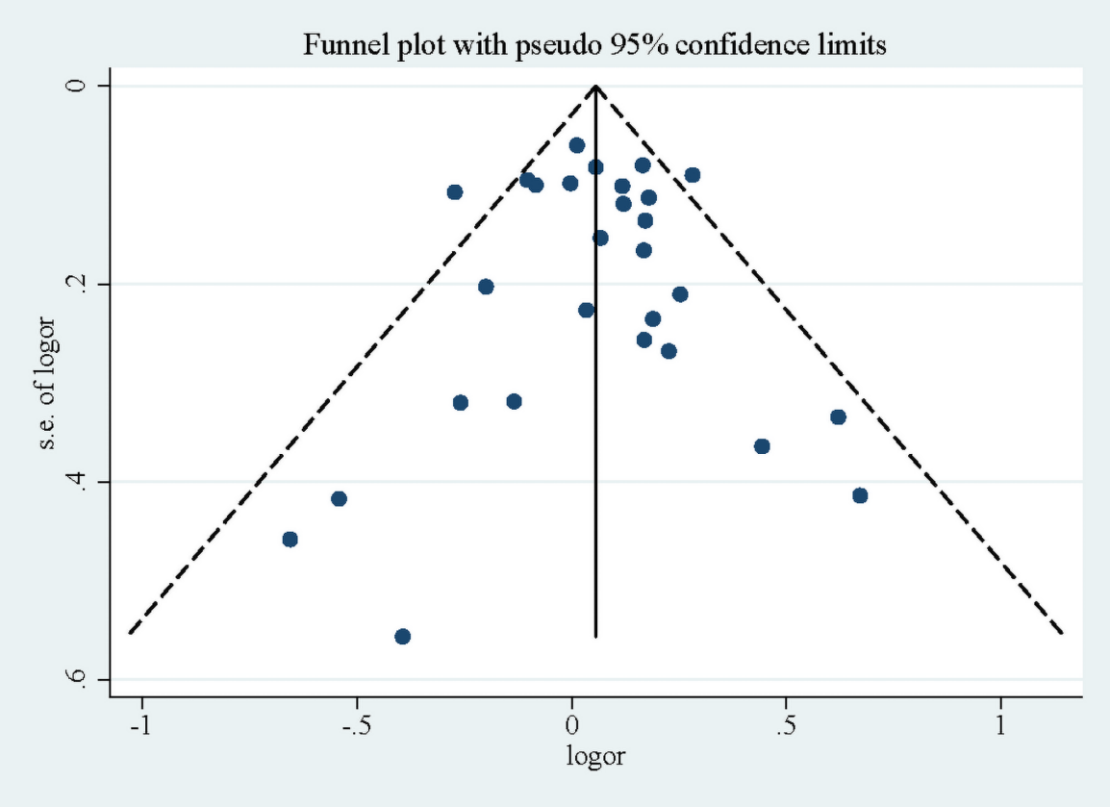

Fig. 5: Funnel plot analysis of the included studies

Discussion

In a previous study, Khalid Eljaaly (6) 5 RCTs analyzed and concluded that compared with ceftaroline or ceftobiprolec, eftriaxone use lead to a higher incidence of treatment failure in patients with methicillin-susceptible *Staphylococcus aureus pneumoniae*. Giannoula S. Compared with a long-course treatment, short-course treatment significantly decreased the incidence of serious AEs and mortality (7). It was safe to have short-term treatment with corticosteroids, which may

lower the risk of contracting acute respiratory distress syndrome, thus shortening the CAP course (8). Adjunctive corticosteroids significantly reduced all-cause mortality, the risk for adult respiratory distress syndrome and the need for mechanical ventilation (10).

In our study, there has no significant difference in the incidence of mortality in the subgroup analysis: individualized treatment vs. standard treatment, β-lactams plus macrolides vs. β-lactam and/or fluoroquinolone, ceftaroline fosamil vs. ceftriaxone, combination therapy vs. monotherapy or high-dose vs. low-dose. The drug-related AE incidence was significantly higher in the ceftriaxone group than in the other drug groups and also higher in the tigecyline group compared to the levofloxacin group. Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the TOC visit in the CE, MITTE, ME and mMITTE populations, findings consisted with another study (6). Compared with ceftriaxone, ceftaroline fosamil significantly increased the clinical cure rate at the TOC visit in the mMITTE populations of GPSP and MDRSP, results in agreement with the conclusion of El-jaaly (6).

Clinically 40%~60% of CAP patients have an unidentified pathogen, so in the case of etiology it is not clear whether empirical treatment is crucial or an empirical anti-infection program determination, generally speaking, should be combined with the following three aspects: 1) follow guidelines and strategies; 2) local microbial epidemic characteristics and drug susceptibility; 3) host factors.

Although in recent years the guidelines for CAP treatments have been revised in various countries, the protocol formulation process for each CAP patient is complex and individualized, so clinicians should understand the pharmacological effects of commonly used antibiotics as well as the guidelines. The clinical efficacy of antibiotics is influenced by many factors namely: previous health, being previously healthy, antibiotic use in the past 3 months, existing complications (chronic obstructive pulmonary disease, diabetes, kidney or heart failure, malignant tumor), and so on. The clinical efficacy of antibiotics depends not only on the antibacterial spectrum and antibacterial activity but also on their pharmacokinetic and pharmacodynamic properties.

The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of antibiotics are the main bases for assessing the bactericidal activity of antibiotics. However, the results of MIC and MBC are obtained by exposing bacteria to fixed antibiotic concentration in vitro, which does not necessarily reflect the dynamic effects of antibiotics in the human body. Therefore, the pharmacokinetic (PK) and pharmacodynamic (PD) effects of antibiotics were combined to study the relationship between the time process of antibiotic antibacterial activity changes in the human body and clinical efficacy. Accordingly, antibiotic PK/PD research can be roughly divided into concentration dependence, time dependence and the post-antibiotic effect (PAE). 1) concentration dependence includes aminoglycoside antibiotics, fluoroquinolone, ketone lactone class and amphotericin B; 2) dependence of antibiotics including most β-lactams, clindamycin, etc.; 3) time-dependent and relatively long PAE includes azithromycin and other macrolides, glycopeptides and azole antifungal drugs.

However, there are certain limitations to the present analysis, which are: 1) the limited number of included studies; 2) individual studies had variations in exclusion/inclusion criteria; 3) dosages and courses varied between studies; 4) the severity of CAP in patients varied between studies; 5) the quality of the included studies varies; 6) pooled data were analyzed, as individual patient data were not available, precluding more in-depth analyses.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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