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

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(Received 10 Nov 2020; accepted 11 Jan 2021)

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 tigecycline 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 incubation period of 3-7 days.
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, microbiologically modified intent-to-treat efficacy (mMITTE) population and the clinical cure rates by baseline pathogens at the TOC visit in a mMITTE population.

The remaining studies were 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.

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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 tigecycline 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

| Study ID | RR (95% CI) | Weight |
|----------|-------------|--------|
| Ceftriaxone VS others drug | 1.96 (0.87, 4.41) | 0.37 |
| Peter J. Pern et al, 2008 | 1.18 (1.01, 1.38) | 8.98 |
| Subtotal (I-squared = 31.1%, p = 0.228) | 1.21 (1.04, 1.41) | 9.34 |
| Individualized treatment VS Standard treatment | | |
| Stefano Aliberti, 2017 | 0.68 (0.23, 2.01) | 0.40 |
| Ane Uranga, 2017 | 0.87 (0.47, 1.63) | 0.98 |
| Subtotal (I-squared = 0.9%, p = 0.686) | 0.82 (0.47, 1.40) | 1.38 |
| High-dose VS low-dose | | |
| Yang Liu, 2017 | 1.18 (0.72, 1.39) | 0.96 |
| Xu Zhao, 2013 | 0.76 (0.62, 0.94) | 4.30 |
| Tino Fujita, 2011 | 1.21 (0.76, 1.92) | 0.84 |
| Dirk J. J. van Rensburg, 2011 | 1.03 (0.66, 1.61) | 0.39 |
| Andrew F. Shier, 2005 | 0.92 (0.76, 1.12) | 3.85 |
| Subtotal (I-squared = 9.3%, p = 0.226) | 0.92 (0.81, 1.05) | 11.33 |
| β-lactams plus Macrolides VS β-lactam or/and fluoroquinolone | | |
| Douwe F. Postma, 2013 a | 1.20 (0.96, 1.49) | 6.19 |
| Douwe F. Postma, 2013 b | 1.00 (0.82, 1.21) | 8.63 |
| Subtotal (I-squared = 33.2%, p = 0.221) | 1.08 (0.93, 1.25) | 14.82 |
| Ceftriaxone fosamil VS Ceftriaxone | | |
| Nan Shao, Zhong, 2011 | 1.06 (0.90, 1.24) | 8.50 |
| Donald E. Low, 2011 | 1.13 (0.89, 1.42) | 4.80 |
| Thomas M. File Jr., 2011 | 0.90 (0.75, 1.09) | 6.99 |
| Douglas R. Raan, 2011 | 1.28 (0.74, 2.21) | 1.25 |
| Thomas M. File, 2010 | 1.01 (0.99, 1.04) | 14.76 |
| Subtotal (I-squared = 0.9%, p = 0.520) | 1.03 (0.99, 1.17) | 36.30 |
| Combination therapy VS monotherapy | | |
| Susan C. Nichols, 2012 | 1.56 (0.76, 3.18) | 0.61 |
| Tobias Welte, 2005 | 1.19 (0.91, 1.55) | 3.37 |
| Oliver Leroy, 2005 | 0.77 (0.41, 1.45) | 1.06 |
| H. Lode, 2003 | 0.82 (0.55, 1.22) | 2.33 |
| Subtotal (I-squared = 32.2%, p = 0.219) | 1.04 (0.85, 1.27) | 7.37 |
| Tigecycline VS levofloxacine | | |
| Cristina Tananeau, 2009 | 1.33 (1.11, 1.59) | 5.27 |
| Carlos Bergall, 2007 | 1.13 (0.92, 1.37) | 4.99 |
| Subtotal (I-squared = 31.8%, p = 0.226) | 1.23 (1.08, 1.40) | 10.26 |
| Short-time therapy VS long-time therapy | | |
| R. PARIS, 2008 | 1.86 (0.97, 3.58) | 0.64 |
| Thomas M. File, 2007 | 1.18 (0.85, 1.64) | 2.73 |
| Rachid el Moussouni, 2006 | 0.52 (0.21, 1.27) | 6.64 |
| Subtotal (I-squared = 60.5%, p = 0.080) | 1.18 (0.90, 1.56) | 4.00 |
| Ceftriaxone VS others drug | | |
| Subtotal (I-squared = %, p =) | 0.58 (0.26, 1.32) | 0.60 |
| Subtotal (I-squared = %, p =) | 0.58 (0.26, 1.32) | 0.60 |
| Azithromycin VS others drug | | |
| I. KUZMAN, 2005 | 1.29 (0.85, 1.94) | 1.39 |
| Margaret A. Drobatz, 2005 | 1.07 (0.79, 1.44) | 3.20 |
| Subtotal (I-squared = 0.9%, p = 0.476) | 1.14 (0.89, 1.45) | 4.60 |
| Overall (I-squared = 36.3%, p = 0.030) | 1.07 (1.02, 1.12) | 100.00 |

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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* | E | P# | P-value |
|---------------------------------------------------------------------|------------------|-----------------------------|----------------------|----|---|----|---------|
| Clinical cure rates by study population at the TOC Visit CE         |                  |                              |                      |    |   |    |         |
| 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                                                             | Ceftaroline fosamil vs other drugs | 1.173 (1.055, 1.304)      | -                    | -   | 0.0% | 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 |                  |                              |                      |    |   |    |         |
| 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).

![Funnel plot with pseudo 95% confidence limits](image)

**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

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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 tigecycline 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 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 andazole 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.
Acknowledgements

This research was supported by Natural Science Foundation of Liaoning Province (Guidance Program) (Grant No. 20180551234), Research Foundation of Shenyang Science and Technology Bureau (Grant No. 18-400-4-09) and Science and Technology Program of Liaoning Province (Grant No. 2017225076). The funders had no role in the design of the study or the collection, analysis, and interpretation of data, or in writing the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Ho J, Ip M (2019). Antibiotic-Resistant Community-Acquired Bacterial Pneumonia. Infect Dis Clin North Am, 33(4):1087-103.
2. Voiriot G, Philippot Q, Elabbadi A, et al (2019). Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients. J Clin Med, 8(6):786.
3. Esposito S, Principi N (2019). Defining the aetiology of paediatric community-acquired pneumonia: an unsolved problem. Expert Rev Respir Med, 13(2):153-61.
4. Nascimento-Carvalho AC, Nascimento-Carvalho CM (2019). Clinical management of community-acquired pneumonia in young children. Expert Opin Pharmacother, 20(4):435-42.
5. Welte T, Kantecki M, Stone G, Hammond J (2019). Ceftriaxone fosamil as a potential treatment option for Staphylococcus aureus community-acquired pneumonia in adults. Int J Antimicrob Agents, 54(4):410-22.
6. Eljaaly K, Wali H, Baslimi A, Alharbi A, Asfour HZ (2019). Clinical cure with ceftriaxone versus ceftriazone or cefotibiprole in the treatment of staphylococcal pneumonia: a systematic review and meta-analysis. Int J Antimicrob Agents, 54(2):149-53.
7. Tansarli GS, Mylonakis E (2018). Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults. Antimicrob Agents Chemother, 62(9): e00635-18.
8. Wan Y-D, Sun T-W, Liu Z-Q, et al (2016). Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia. Chest, 149(1):209-19.
9. Huang J, Guo J, Li H, et al (2019). Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: A systematic review and meta-analysis. Medicine (Baltimore), 98(13):e14636.
10. Bi J, Yang J, Wang Y, et al (2016). Efficacy and Safety of Adjunctive Corticosteroids Therapy for Severe Community-Acquired Pneumonia in Adults: An Updated Systematic Review and Meta-Analysis. PLoS One, 11(11):e0165942.
11. Aliberti S, Ramirez J, Giuliani F, et al (2017). Individualizing duration of antibiotic therapy in community-acquired pneumonia. Palm Pharma Ther, 45:191-201.
12. Bergallo C, Jasovich A, Teglia O, et al (2009). Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. Diagn Microbiol Infect Dis, 63(1):52-61.
13. Ceccato A, Cilloniz C, Ranzani OT, et al (2017). Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: A post-hoc exploratory analysis of a randomized controlled trial. PLoS One, 12(6):e0178022.
14. Drehobl M, De Salvo M, Lewis D, Breen J (2005). Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest, 128(4):2230-7.
15. el Moussaoui R, de Borgie C, van den Broek P, et al (2006). Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ, 332(7554):1355.
16. English M, Fredericks C, Milanesio N, et al (2012). Ceftriamycin versus clarithromycin for community-acquired pneumonia: comparative efficacy and safety outcomes from two double-blinded, randomized, parallel-group, multicenter, multinational noninferiority studies. Antimicrob Agents Chemother, 56(4):2037-47.

17. File TM, Jr., Low DE, Eckburg PB, et al (2010). Integrated Analysis of FOCUS 1 and FOCUS 2: Randomized, Doubled-Blinded, Multicenter Phase 3 Trials of the Efficacy and Safety of Ceftrarone Fosamil versus Ceftriaxone in Patients with Community-Acquired Pneumonia. Clin Infect Dis, 51(12):1395-405.

18. File TM, Jr., Low DE, Eckburg PB, et al (2011). FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftrarone fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother, 66 Suppl 3:ii9-32.

19. File TM, Mandell LA, Tillotson G, et al (2007). Gatifloxacin once daily for 5 d versus 7 d for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. J Antimicrob Chemother, 60(1):112-20.

20. File TM, Jr., Segreti J, Dunbar L, et al (1997). A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefotaxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother, 41(9):1965-72.

21. Fujita J, Niki Y, Kadota J, et al (2013). Clinical and bacteriological efficacies of sitafloxacin against community-acquired pneumonia caused by Streptococcus pneumoniae: nested cohort within a multicenter clinical trial. J Infect Chemother, 19(3):472-9.

22. Garin N, Genné D, Carballo S, et al (2014). β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia. JAMA Intern Med, 174(12):1894-901.

23. Jandourek A, Smith A, Llorens L, et al (2014). Efficacy of ceftrarone fosamil for bacteremia associated with community-acquired bacterial pneumonia. Hosp Pract (1995), 42(1):75-8.

24. Kohno S, Yanagihara K, Yamamoto Y, et al (2013). Early switch therapy from intravenous sulbactam/ampicillin to oral garenoxacin in patients with community-acquired pneumonia: a multicenter, randomized study in Japan. J Infect Chemother, 19(6):1035-41.

25. Kuzman I, Daković-Rode O, Oremuš M, Banaszak AM (2005). Clinical Efficacy and Safety of a Short Regimen of Azithromycin Sequential Therapy vs Standard Cefuroxime Sequential Therapy in the Treatment of Community-Acquired Pneumonia: An International, Randomized, Open-Label Study. J Chemother, 17(6):636-42.

26. Leroy O, Saux P, Bédos J, Caulin E (2005). Comparison of levofloxacin (L) and cefotaxime (C) combined with ofloxacin (O) for treatment of severe community-acquired pneumonia (CAP) in the intensive care unit. Crit Care, 8(Supplement 1):230.

27. Liu Y, Zhang Y, Wu J, et al (2017). A randomized, double-blind, multicenter phase II study comparing the efficacy and safety of oral nemonoxacin with oral levofloxacin in the treatment of community-acquired pneumonia. J Microbiol Immunol Infect, 50(6):811-20.

28. Lode H, Magyar P, Muir J, et al (2004). Once-daily oral gatifloxacin vs three-times-daily co-amoxiclav in the treatment of patients with community-acquired pneumonia. Clin Microbiol Infect, 10(6):512-20.

29. Low DE, File TM, Jr., Eckburg PB, et al (2011). FOCUS 2: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftrarole fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother, 66 Suppl 3:iii33-44.

30. Manu C, G, AS, A. MM (2018). Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. J Infect Public Health, 11(5):691-7.

31. Nicholson SC, Welte T, Jr TMF, et al (2012). A randomised, double-blind trial comparing ceftrubiprocol medecaril with ceftriazone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. Int J
Antimicrob Agents, 39(3):240-6.

32. Oosterheert J, Bonten M, Schneider M, et al. (2006). Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ, 333(7580):1193.

33. Paris R, Confalonieri M, Dal Negro R, et al (2008). Efficacy and Safety of Azithromycin 1 g Once Daily for 3 Days in the Treatment of Community-Acquired Pneumonia: an Open-Label Randomised Comparison with Amoxicillin-Clavulanate 875/125 mg Twice Daily for 7 Days. J Chemother, 20(1):77-86.

34. Pertel P, Bernardo P, Fogarty C, et al (2008). Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis, 46(8):1142-51.

35. Postma DF, van Werkhoven CH, van Elden LJ, et al (2015). Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults. N Engl J Med, 372(14):1312-23.

36. Rank DR, Friedland HD, Laudano JB (2011). Integrated safety summary of FOCUS 1 and FOCUS 2 trials: Phase III randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with community-acquired pneumonia. J Antimicrob Chemother, 66 Suppl 3iii53-9.

37. Shorr AF, Khashab MM, Xiang JX, et al (2006). Levofloxacin 750-mg for 5 days for the treatment of hospitalized Fine Risk Class III/IV community-acquired pneumonia patients. Respir Med, 100(12):2129-36.

38. Tanaseanu C, Milutinovic S, Calistru P, et al (2009). Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med, 9:44.

39. Torres A, Garau J, Arvis P, et al (2008). Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study—a randomized clinical trial. Clin Infect Dis, 46(10):1499-509.

40. Uranga A, España P, Bilbao A, et al (2016). Duration of Antibiotic Treatment in Community-Acquired Pneumonia: A Multicenter Randomized Clinical Trial. JAMA Intern Med, 176(9):1257-65.

41. van Rensburg D, Perng R, Mitha I, et al (2010). Efficacy and safety of nemonoxacin versus levofloxacin for community-acquired pneumonia. Antimicrob Agents Chemother, 54(10):4098-106.

42. Welte T, Petermann W, Schurmann D, et al (2005). Treatment with Sequential Intravenous or Oral Moxifloxacin Was Associated with Faster Clinical Improvement than Was Standard Therapy for Hospitalized Patients with Community-Acquired Pneumonia Who Received Initial Parenteral Therapy. Clin Infect Dis, 41(12):1697-705.

43. Yanagihara K, Fukuda Y, Seki M, et al (2006). Clinical Comparative Study of Sulbactam/Ampicillin and Imipenem/Cilastatin in Elderly Patients with Community-Acquired Pneumonia. Intern Med, 45(17):995-9.

44. Zhao X, Wu J, Xiu Q, et al (2014). A randomized controlled clinical trial of levofloxacin 750 mg versus 500 mg intravenous infusion in the treatment of community-acquired pneumonia. Diagn Microbiol Infect Dis, 80(2):141-7.

45. Zhong NS, Sun T, Zhuo C, et al (2015). Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. Lancet Infect Dis, 15(2):161-71.

46. Lin TY, Lin SM, Chen HC, et al (2007). An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia. Chang Gung Med J, 30(4):321-32.