Short-course vs long-course antibiotic treatment for community-acquired pneumonia

A literature review

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Short-course *versus* long-course antibiotic treatment for community-acquired pneumonia: a literature review

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Abstract

Background: It is well known that antibiotic use is the main driver for the increasing problems with resistant bacteria. Consequently, some countries have recommended shortening the duration of antibiotic treatment of community-acquired pneumonia (CAP). The aim of this study was to investigate if the effectiveness of a short-course antibiotic is comparable to a longer course of antibiotics in adults with CAP and to assess if the duration of an antibiotic course influences the development of resistant bacteria.

Methods: A literature search was performed in PubMed and EMBASE. We included randomised, controlled trials (RCTs) comparing clinical success, microbiological efficacy, patient safety and antibiotic resistance in a short-course (5 days) *versus* a long-course antibiotic treatment (7+ days) for CAP.

Results: Six RCTs were included. Clinical success rates were 87-95% in patients treated with short-course antibiotics and 88-94% in patients treated with a longer course. Eradication of pathogenic bacteria was found to be 100% and 95-100% in patients treated with short-course and long-course antibiotics, respectively.

No significant differences in adverse events were reported. However, none of the trials reported on the impact on the development of resistant bacteria.

Conclusion: Only few trials were included in this review and more RCTs are highly needed to be able to provide solid evidence for optimal treatment durations for patients diagnosed with CAP. Importantly, fluoroquinolones were often the drug of choice, and trials testing beta-lactam antibiotics, which are the type of antibiotics most often used in many European countries, should be aimed for in near future.

Introduction

Antibiotics are one of the most commonly used drugs worldwide (1). It has long been acknowledged that consumption of any antibiotic generates unwanted adverse events, like antibiotic resistance. The higher the consumption of antibiotics, the greater the risk of selection of resistant bacteria (2). According to a recent report by O'Neill 2016, in the year 2050, the number of deaths due to infections caused by resistant bacteria will reach 10 million lives each year (3). Following this, modern medicine can be set back to a time where simple infections again will be lethal.

Around 90% of antibiotics are prescribed in primary care (4), thus making general practice a crucial area for interventions aimed at reducing unnecessary use of antibiotics.

In general practice, most lower respiratory tract infections (LRTI) are mild and require no antibiotic treatment. In fact, only about 13% of patients with the diagnosis of pneumonia in general practice have a radiologically verifiable pneumonia (5).

Furthermore, many patients are recommended to complete an antibiotic treatment even if their symptoms have resolved; the rationale behind these recommendations are not evidence-based, but mainly based on traditions (1, 6).

Use, misuse and overuse of antibiotics are the main drivers for the selection of resistance bacteria. Reduced prescribing rate and shorter duration of an antibiotic course can reduce exposure to antibiotics and hereby curbing antibiotic resistance.

The duration of antibiotic treatment of community-acquired pneumonia (CAP) has long been discussed in the scientific community due to lacking evidence of the current regimen, i.e. 7-10 days of treatment. Consequently, several studies have recently been conducted to investigate the effects of a shorter duration of antibiotic treatment.

The aim of this review was to investigate if the effectiveness of a short-course antibiotic is comparable to a longer course of antibiotics in adults with CAP, and to assess if the duration of an antibiotic course will influence the development of resistant bacteria.

Materials and Methods

Literature search

A literature search was performed to identify randomised, controlled trials comparing short- *versus* long-course antibiotic treatments for CAP. Trials published before 23 April 2018 in English were identified in PubMed and EMBASE. The search was based on the following terms: "community-acquired pneumonia", the MeSH term "community-acquired infections" with the following subheadings: "therapy" and "drug therapy" and a combination of the following words: antibiotic*, short/shorter-course, long/longer-course, duration and antibiotic duration. A complete search string is available from the authors on request.

Selection of articles

Only randomised, controlled trials were included. A trial was considered eligible for inclusion if it (i) included adults (18+ years) diagnosed with CAP, (ii) compared a short-course antibiotic treatment with a longer course, and (iii) if patients exclusively were treated at outpatient clinics.

Furthermore, the following exclusion criteria were applied: (i) studies testing individualised treatment, and (ii) studies including patients with comorbidity such as chronic lung disease or lung cancer.

Outcome measures

A short-course antibiotic treatment was defined as 5 days of treatment and a long-course antibiotic treatment was defined as 7+ days of treatment.

The following outcomes were reported:

1. Clinical success, defined as if clinical symptoms and signs associated with the pneumonia were resolved.
2. Microbiological efficacy, defined as decrease pre-treatment compared to post-treatment, in the amount of bacterial colonies or eradication of bacterial cultures.
3. Patient safety, defined as the reporting of adverse events, which were classified as either related, possibly related or unrelated, and/or mild, moderate or severe.
4. Development of resistant bacteria (any reporting on resistant bacteria).

Quality assessment

The quality of the included randomised, controlled trials was assessed by the Jadad criteria (7). The trials were evaluated in seven items, the first five items can obtain +1 point and the last 2 items can be given -1 point, which makes the highest score in a total of five the best assessment (Table 4). The points were awarded for randomisation, blinding, description of withdrawals and dropouts.

Results

Study characteristics

The searches in PubMed and EMBASE resulted in 276 and 19 potential studies, respectively. Most trials (N = 125) were excluded as they compared the effects of different types of antibiotics, 38 trials were excluded because they included children, and an additional 29 trials were excluded as they were not about CAP.

Six studies were included in this literature review. The selection process is described in detail in Fig. 1.

Four of the included trials randomised the population right from the start of the trial (9, 10, 11, 13), and two studies did not randomise the study population until after five days of treatment, and only if a treatment effect was observed (8, 12) (Table 1).

Table 2 presents an overview of all study results from the six included trials.

Type and dose of antibiotics

The included studies tested various antibiotics such as levofloxacin, gemifloxacin, amoxicillin and cefuroxime. Three trials used different doses of antibiotics in the short- and long-course treatment groups, respectively, with the highest dose of antibiotics used in the short-course treatment groups (9, 10, 13). In another two studies, the short-course treatment group and long-course treatment group received the same dose of antibiotics (11, 12). In the study by Uranga *et al.*, it was only stated that antibiotic treatments were according to local guidelines; consequently, it is unknown what type of antibiotic was used, and in which doses they were prescribed (8).

Clinical success

In the three studies using different dosage of antibiotics but same type of antibiotic, 750 mg levofloxacin short-course regimen (5 days) *versus* 500 mg levofloxacin (median 10 days), all had high clinical success rates and there was no statistically significant difference between the two groups. The clinical success rates were 90-94% in patients treated with short-course levofloxacin and 91-96% in patients treated with long-course levofloxacin (9, 10, 13).

In the three studies, where the intervention group and control group received the same dose of antibiotics, there were likewise a high clinical success rate with no statistically significant difference between the short-course and long-course treatment groups. The clinical success rates were 88-95% in patients treated with short-course antibiotics and 88-92% in patients treated with long-course antibiotics (11, 12).

In the study by Uranga *et al.* (2016), in which the local guidelines determined the dose of antibiotic, the clinical success rate at follow-up was 92.7% and 94.4%, respectively, in the short-course treatment group (5 days) and long-course treatment group (median 10 days) (p=0,54)(8).

Overall, a clinical success rate of 91-94% was observed when antibiotics were given for 7-14 days (long-course). Similarly, a clinical success rate of 86.9-95.0% was observed when antibiotic courses were prescribed for 5 days (short-course).

Microbiological efficacy

Table 3 provides an overview of pathogens identified in patients diagnosed with CAP in the six included trials. Three studies included the microbiological eradication as a secondary efficacy parameter (9, 10, 11). The microbiological efficacy was based on the results of cultures taken pre- and post-treatment. Zhao, T. (2016) and Zhao, X. (2014) found a bacterial eradication rate of 100% in both the short-course and long-course treatment groups (9, 10). File *et al.* (2007) examined the eradication rates of *Streptococcus pneumoniae* and identified a small non-significant difference in the eradication efficacy rate at follow-up, with 100% for those treated for 5 days (short-course) and 95% for those treated with antibiotics for 7+ days (long-course)(11), (Table 2).

Patient safety evaluation

All six studies reported on patient safety outcomes (Table 2).

In the studies by Uranga *et al.* (2016) and Dunbar *et al.* (2003), no significant differences in adverse events were observed between the groups by day 30 (8, 13). In one study, 55% of patients had experienced an adverse event in the 750-mg levofloxacin group (short-course), and 49% of patients had reported an adverse events in the 500-mg levofloxacin group (long-course)(10). These adverse events were considered drug-related but with no significant difference (10). One study showed that the incidence of adverse events was low and the proportion of discontinuations due to adverse events was 1.2% and 2% for the short-course and long-course treatment groups, respectively (11). In the study by El Moussaoui *et al.* (2006), 11% in the short-course treatment group compared with 21% in the long-course treatment group reported mild adverse events during or at the end of treatment periods (12) (Table 2).

Of the five studies reporting on adverse events, none of them demonstrated statistically significant differences in the number of adverse events, whether antibiotics were given for a shorter or longer period.

Antibiotic resistance

None of the included trials reported on the impact of the duration of an antibiotic course on the development of resistant bacteria (9, 10, 11, 12, 13).

Jadad score

The quality of the included trials varied and ranged from two to four in Jadad score - a detailed overview of the quality assessments is available in Table 4.

Three points were given to three of the studies (8, 9, 11), one trial obtained two points (10) and the rest obtained four points (12, 13). All of the included studies obtained points for being a randomised, controlled trial and for the description of withdrawal. None of the studies were deducted a point for inappropriate randomisation or blinding.

Discussion

Main findings

Adults treated for CAP had similar clinical cure rates when given a short-course of antibiotics (5 days) compared to those receiving a longer course (7+ days). Also, almost identical bacterial eradication rates were demonstrated regardless of treatment duration, and no difference in the reporting of adverse events was found. Importantly, there was an absence of evidence on the impact of treatment duration on the development of antibiotic resistance.

Strengths and limitations

This literature review has summarised the evidence from the relatively few trials reporting on short- *versus* long-course antibiotic treatment for CAP. The included trials differ in certain aspects (Table 1 and 5). The differences include various randomisation procedures, diverse study populations, dispersed geographical locations, different types of antibiotics used and various definitions of short-course and long-course treatment.

Only six randomised, controlled trials were included in this review and the risk of a type 2 error, i.e. rejecting that there is a difference between choosing a shorter treatment period compared to a longer treatment period is present. This possible difference in effectiveness between the treatment duration is important to identify due to the risk of severe complications associated with CAP. With this in mind, more trials testing optimal treatment durations are highly needed to be able to provide solid evidence for optimal treatment durations for patients diagnosed with CAP.

Several other limitations have to be kept in mind when interpreting the results of this literature review. Firstly, none of the included trials provided any information about the effect of the duration of the antibiotic courses on the development of resistant bacteria. Consequently, we were not able to report on this outcome, however, it seems plausible that by minimising the days of antibiotic treatment, the risk of antimicrobial resistance can be reduced.

Secondly, none of the included trials provided sufficient data to report on the comparative effectiveness of short- *versus* long-courses of antibiotics for rare outcomes associated with CAP, such as hospitalisation or deaths.

Furthermore, the various treatment durations were not assessed in accordance with the severity of the infections (mild, moderate, severe), or perhaps more importantly the aetiology of the pneumonia. For example, pneumonia caused by *Legionella pneumophila* is recommended antibiotic treatment for two to three weeks, compared with seven days for pneumonia caused by *Streptococcus pneumonia* (14).

Some of the included trials used different doses of antibiotic, with a higher dosage in the short-course duration group compared with the dosage in the long-course duration group. This decreases internal comparability in this review, and instead raises the

question whether it is the duration or total amount of antibiotics that matter to the success rate.

Fluoroquinolones were used as treatment regimens in five out of six of the included RCTs (Urange 2016, Zhao 2016, Zhao 2014, File 2007 and Dunbar 2003). Only one study used amoxicillin (El Moussaoui 2006). Consequently, the results from this literature review cannot be generalised to a Danish setting, nor to many other European countries in which fluoroquinolones are seldom used for treatment of patients with CAP.

In one study, patients were first treated with intravenous treatment, in contrast to a complete oral course (El Moussaoui 2006). This approach is not usual care in most general practices and consequently influences the generalisability of these findings.

The quality of the included trials was moderate with Jadad scores of two to four, primarily three. However, this score only indicates something about the methodological quality of the trials and nothing about generalisability or the quality of the results in the included studies. For example, most studies were conducted in middle- and high-income countries and with great variation in the study population. There were few data on comparative effectiveness of short and long courses of antibiotics in low-income countries, where baseline risks, immunization rates, complication rates and access to antibiotic treatment may differ substantially from middle- or high-income countries.

Comparison with other studies

In the fight against the increasing problems with resistant bacteria, the optimal length of antibiotic treatment for CAP is being massively investigated these years (15, 16, 17). A meta-analysis from 2007 found no significant differences between short-course (5 days) and long-course (7+ days) antibiotic regimens for the treatment of mild to moderate CAP with respect to clinical success, mortality, bacteriological success and adverse events (15). A more recent review from 2017 showed similar clinical cure rates when given shorter courses of antibiotics compared to those receiving longer courses. In this review, a shorter course of antibiotics was also associated with lower rates of adverse events than longer courses of antibiotic (16). This present literature review did not include children, however, a study by Agarwal G. *et al.* (2004) demonstrated equivalent efficacy of three days *versus* five days of antibiotic treatment of pneumonia in children (17).

Importantly, a newly published review from 2018 by López-Alcalde J. *et al*. did not identify any randomised, controlled trials studying a short course of antibiotic compared to a longer course, with the same type of antibiotic and with the same daily dosage, for CAP in adult outpatients (18).

Conclusion

Despite the above-mentioned differences in the designs of the included studies and the limitations of this literature review, all of the included trials demonstrated a similar clinical effect in patients treated with either a short or long antibiotic course. However, only six trials were included and more trials investigating the optimal antibiotic treatment duration of CAP are warranted. Preferably, these trials should compare treatments with the same

type of antibiotic, and same dose, and test antibiotics commonly used in most European countries (e.g. phenoxymethylpenicillin or amoxicillin). Also, these trials should involve both children and adults and importantly not only focus on efficacy outcomes, but also on adverse events including the development of resistant bacteria.

Appendix

Figure 1 – Study selection process

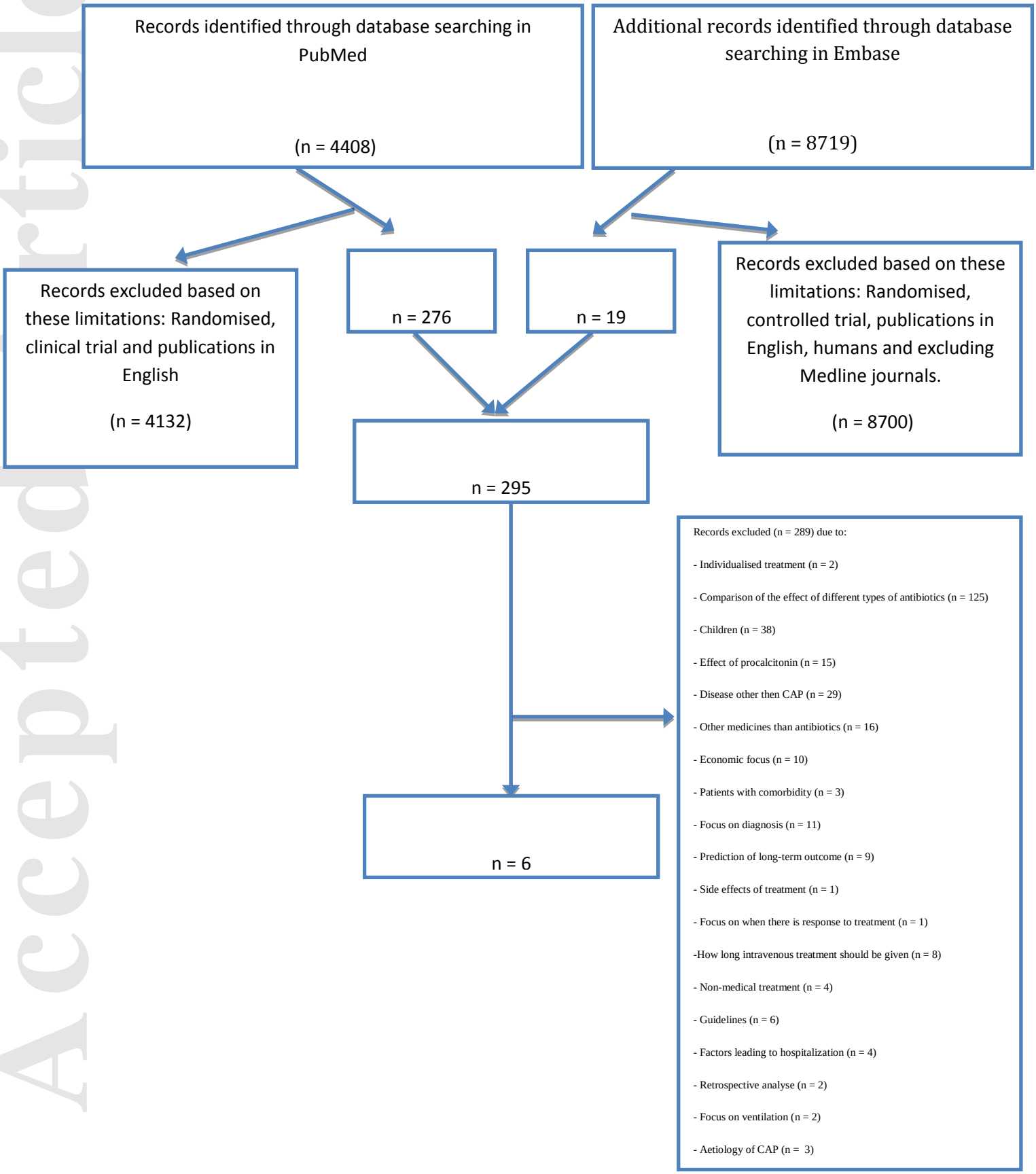

Table 1 – Study design of included studies

Study (year)	Country	Population	Method	Type of antibiotics	Duration of long treatment	Duration of short treatment
Uranga A *et al.* (2016) (8)	Spain	283 patients, 137 in control group and 146 in intervention group.	RCT, starts with oral treatment, if there were effect after 5 days, they were randomised for long or short course treatment.	According to local guidelines. 80% underwent treatment with quinolones. - Unknown if it is the same dose of drug in the two groups.	Physicians, determined duration of antibiotics in the control group. Median 10 days	5 days
Zhao T *et al.* (2016) (9)	China	427 patients, 219 in control group and 208 in intervention group.	RCT, starts by randomisering patients for a long or short course treatment.	Levofloxacin - 750 mg in the intervention group and 500 mg in the control group.	7-14 days. Median 10.35 days	5 days
Zhao X *et al.*	China	211 patients, 104 in control	RCT, starts by randomisering	Levofloxacin	7-14 days	5 days

(2014) (10)		group and 107 in intervention group.	patients for a long or short course treatment.	- 750 mg in the intervention group and 500 mg in the control group.		
File TM *et al.* (2007) (11)	9 countries: Bulgaria, Croatia, Czech Republic, Lithuania, Poland, Romania, Russia, Ukraine and the USA.	469 patients, 227 in control group and 242 in intervention group.	RCT, starts by randomisering patients for a long or short course treatment.	Gemifloxacin - Same dose of drug in the two groups	7 days	5 days
El Moussaoui R *et al.* (2006) (12)	Netherlands	96 patients, 49 in control group and 47 in intervention group.	RCT, starts with intravenous treatment end shift to oral, if there were effect of the treatment, patients were randomised to short or long course treatment.	Amoxicillin - Same dose of drug in the two groups	10 days	5 days
Dunbar LM *et*	United State of	390 patients, 192 in control	RCT, starts by randomisering	Levofloxacin	10 days	5 days

***al.* (2003) (13)**	America	group and 198 in intervention group.	patients for a long or short course treatment.	- 750 mg in the intervention group and 500 mg in the control group.		

Table 2 – Overview of study results

Study (year)	Clinical success – at follow-up				Bacterial eradication		Adverse events		Other results
	Intervention group	*Control group*	*P-value*	*CI-95%*	*Intervention group*	*Control group*	*Intervention group*	*Control group*	
Uranga A *et al.* (2016) (8)	92.7%	94.4%	0,54	-	-	-	17%	18% P = 0,24	The CAP symptom questionnaire scores on day 10: 18.1 and 17.6 in the control and intervention groups, respectively, *P*= .81.
Zhao T *et al.* (2016) (9)	93.75%	95.98%	0,35	0.269 – 1,537	100.0%	100.0%	15,35%	10,48% P < 0,05	The mean drug exposure was 3,641.4 mg in intervention group and 5,169.6 mg in control group. P<0.0001.
Zhao X *et al.* (2014) (10)	89,9%	91,9%	-	-13,9 – 12,3	100.0%	100.0%	22,3%	22,5% P > 0,05	-
File TM *et al.* (2007) (11)	95,0%	92,1%	0,2	-1,48 – 7,42	100%	95%	1,2%	2%	-
El Moussaoui R *et al.* (2006) (12)	90%	88%	-	-9 - 15	-	-	11%	21%	-
Dunbar LM *et al.* (2003) (13)	92,4%	91,1%	-	-7,0 – 4,4	-	-	57,8%	59,6%	By day 3 of therapy, 67.4% in intervention group reported subjective resolution of fever, compared with 54.6% in control group. *P* =.006.

Table 3 – Article overview of pathogens in included trials

Study (year)	Pathogen	Evaluable (n)	Eradicated
Uranga A *et al.* (2016) (8)	Unknown		
Zhao T *et al.* (2016) (9)	Unknown		
Zhao X *et al.* (2014) (10)	Gram-positive	34	34
	- S. pneumoniae	18	18
	- Streptococcus mitis	1	1
	- Group A and B hemolytic Streptococcus	1	1
	- S. aureus	14	14
	Gram-negative	58	58
	- H. influenzae	6	6
	- Haemophilus parainfluenzae	21	21
	- C. pneumoniae	20	20
	- E. cloacae	2	2
	- Enterobacter aerogenes	1	1
	- E. coli	1	1
	- Serratia marcescens	1	1
	- Proteus mirabilis	1	1
	- A. baumanniia	1	1
	- A. lwoffii	1	1
	- Pseudomonas aeruginosa	3	3
	Total	92	92
File TM *et al.* (2007) (11)	Gram-positive	108	103
	- S. pneumoniae	68	66
	- S. aureus	40	37

	Gram-negative - *H. influenzae* - *C. pneumoniae* - *Mycoplasma pneumoniae*	139 42 51 46	134 41 49 44
El Moussaoui R *et al.* (2006) (12)	Gram-positive - *S. pneumoniae* Gram-negative - *H. influenzae* - *Moraxella catharrhalis* - *Haemophilus parainfluenzae* - *Influenza A or B* - *C. pneumoniae* - *Mycoplasma pneumoniae*	Unknown how the number of bacteria is distributed, but overall there were 45 verified at the start of study	Unknown how the number of bacteria is distributed, but overall 41 were eradicated at the end of the study
Dunbar LM *et al.* (2003) (13)	Gram-positive - *S. pneumoniae* Gram-negative - *H. influenzae* - *Haemophilus parainfluenzae* - *C. pneumoniae* - *Legionella pneumophila* - *Mycoplasma pneumoniae*	42 42 180 27 22 38 14 79	38 38 171 25 21 36 14 75

Table 4 – Jadad score

Study (year)	1. Was the study described as randomised (this includes words such as randomly, random and randomisation)? (+1 Point)	2. Was the method used to generate the sequence of randomisation described and appropriate (table of random numbers, computer-generated)? (+1 Point)	3. Was the study described as double blind? (+1 Point)	4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy)? (+1 Point)	5. Was there a description of withdrawals and dropouts? (+1 Point)	6. Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number)	7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. Injection with no double dummy).	Total
Uranga A *et al.* (2016) (8)	1	1	0	0	1	0	0	3
Zhao T *et al.* (2016) (9)	1	1	0	0	1	0	0	3

Zhao X *et al.* (2014) (10)	1	0	0	0	1	0	0	2
File TM *et al.* (2007) (11)	1	0	1	0	1	0	0	3
El Moussaoi R *et al.* (2006) (12)	1	0	1	1	1	0	0	4
Dunbar LM *et al.* (2003) (13)	1	0	1	1	1	0	0	4

Table 5 – Article overview of relapses, withdrawals and limitations

Study (year)	Relapses	Patients withdrawals/ Mortality	Limitations
Uranga A *et al.* (2016) (8)	Readmission by day 30 was significantly more common in the control group than in the intervention group 9 vs. 2, *P* = .02.	Before randomisation, 227 patients did not meet the selection criteria. Thirteen patients were later excluded for protocol violation. In addition, 16 were unavailable for the late follow-up. For one of these patients no data was found, and it is not known if this is alive.	First, almost 80% of the patients received quinolones. Second, because of the open design after day 5, there could have been an effect on physicians' decisions concerning antibiotic duration in the control group. Third, patients with complications were excluded. Fourth, the study was conducted in 4 teaching hospitals in the Basque Country.
Zhao T *et al.* (2016) (9)	1 patient in 750 mg group and 3 patients in 500 mg group. P=0.6235.	7 patients were unable to be evaluated due to incomplete data and 2 did not meet the inclusion criteria. Another 21 patients did not meet the eligibility criteria or exclusion criteria. No death occurred in both groups.	First, patients were diagnosed with mild to moderate CAP. Second, bacterial culture positive rate was low, 8.14% in 750 mg group and 7.49% in 500 mg group. Third, the detection of atypical pathogens was not performed. Fourth, this was an open-label design. Fifth, relative stringent exclusion criteria were set. Sixth, there was a difference of the evaluation time points.
Zhao X *et al.* (2014) (10)	Unknown	30 patients were excluded due to violation of inclusion/ exclusion criteria.	First, late follow-up visit was missing. Second, the positivity of blood culture was too low to assess

			microbiologic response.
File TM *et al.* (2007) (11)	Unknown	14 patients, including the two randomisation failures, were withdrawn prematurely from the study and 10 patients completed therapy but withdrew from follow-up. Adverse events were the main reason for premature discontinuation. An additional 3 patients were excluded as a result of poor visits compliance.	A potential limitation of the study is that there was a trend towards sicker patients in the 7-day group.
El Moussaoui R *et al.* (2006) (12)	Unknown	Between enrolment and randomisation 19 patients withdrew their consent for participation, 41 did not meet the criteria for randomisation, and 5 were not randomised for other reasons. Two were subsequently excluded because of protocol violations.	First, there were more severe symptoms and a higher percentage of smokers in the 3-day treatment group. Second, only patients with mild to moderate- severe community acquired pneumonia who substantially improved after 3 days' amoxicillin treatment. Third, we excluded patients with a severe immunodeficiency. Fourth, our sample size was moderate.
Dunbar LM *et al.* (2003) (13)	4 patients, all of whom were in the 750-mg group, were classified as having relapses solely on the basis of clinical and radiographic criteria.	6 patients were withdrawal.	First, patients with a PSI score of >130 were excluded from the study. Second, there were a relatively large number of CAP cases attributed to *M. pneumoniae,* which is generally understood to have a less severe presentation.

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