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# Short- versus Long-Course Antibacterial Therapy for Community-Acquired Pneumonia

## A Meta-Analysis

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## Abstract

**Background:** The evidence for traditionally recommended 7- to 14-day duration of antibacterial therapy for community-acquired pneumonia (CAP) is not well established.

**Objectives:** We endeavoured to assess the effectiveness and safety of shorter than traditionally recommended antibacterial therapy for CAP.

**Methods:** We performed a meta-analysis of randomized controlled trials (RCTs) comparing short- (≤7 days) versus long- (≥2 days difference) course therapy for CAP with the same antibacterial regimens, in the same daily dosages.

**Results:** Five RCTs involving adults (including outpatients and inpatients who did not require intensive care) and two RCTs involving children (aged 2–59 months, residing in developing countries) were included. All RCTs were double-blind and assessed patients with CAP of mild to moderate severity. No differences were found between short- (adults 3–7 days; children 3 days) and long- (adults 7–10 days; children 5 days) course regimens (adults – amoxicillin, cefuroxime, ceftriaxone, telithromycin and gemifloxacin; children – amoxicillin) regarding clinical success at end-of-therapy (six RCTs; 5107 patients [1095 adults, 4012 children]; fixed-effect model [FEM]; odds ratio [OR] = 0.89; 95% CI 0.74, 1.07), clinical success at late follow-up, microbiological success, relapses, mortality (seven RCTs; 5438 patients; FEM; OR = 0.57; 95% CI 0.23, 1.43), adverse events (five RCTs; 3214 patients; FEM; OR = 0. 90; 95% CI 0.72, 1.13) or withdrawals as a result of adverse events. No differences were found in subset analyses of adults or children, and of patients treated with no more than 5-day short-course regimens versus at least 7-day long-course regimens.

**Conclusion:** No difference was found in the effectiveness and safety of short- versus long-course antimicrobial treatment of adult and paediatric patients with CAP of mild to moderate severity.

## Background

Community-acquired pneumonia (CAP) is a common clinical entity,[1,2] which is associated with considerable mortality.[3] However, the severity of the disease is variable.[4,5] Adverse outcomes are primarily observed in the subset of patients who require hospital admission, particularly in those who need to be treated in an intensive care unit. The great majority of patients with milder disease, who can be treated as outpatients (approximately 70% of the total number of cases),[6] have a low risk of a fatal outcome.[4,7] CAP is also associated with substantial healthcare costs.[6,8]

In an attempt to improve the efficiency of provided medical care, a strategy of early switch to oral therapy followed by early discharge has been evaluated in selected hospitalized patients with CAP, with favourable findings.[9,10] In this direction, another aspect of the treatment of CAP that could be reassessed is the total duration of antimicrobial therapy. The rationale for the use of traditional 7- to 14-day regimens is observed effectiveness of these regimens in routine clinical practice, rather than superiority over shorter-duration regimens, proven in appropriately designed clinical trials. The hypothesis that shorter-duration therapy for CAP may be as effective as traditional regimens of longer duration sounds appealing because short-course therapy could plausibly be associated with less toxicity, better patient compliance, fewer rates of bacterial drug resistance development, as well as decreased financial costs.

A recently published meta-analysis of randomized trials addressing the issue of the duration of therapy for CAP led to the conclusion that treatment of 7 days or less for mild to moderate disease can be as effective and safe as treatment of longer duration.[11] However, this finding was primarily based on the comparison of short-course regimens of azithromycin, versus long-course therapy with different antimicrobials. Since azithromycin has an extended serum half-life, and therapeutic concentrations of this drug remain in tissues for many days after the end of therapy,[12] administration of this agent for a short period of time is not translated into a short period of antimicrobial activity. Furthermore, differences in terms of antimicrobial potency among the compared antimicrobial agents may have confounded the findings of the meta-analysis. Similarly, a randomized trial, which was included in the aforementioned meta-analysis,[11] compared short-course, high-dose treatment with levofloxacin versus conventional treatment with this agent and found comparable effectiveness of the two regimens.[13] This was attributed to the increased potency, on the basis of pharmacodynamic principles, of the higher dose of levofloxacin compared with the lower dose of this drug.

Hence, the question of whether the duration of antimicrobial therapy for CAP could be shortened without compromising effectiveness remains largely unanswered. In this regard, we sought to perform a meta-analysis of randomized controlled trials (RCTs) comparing treatment for CAP with the same agents used in the same daily dosage but for different durations of treatment.

## Methods

### Data Sources

The literature search was performed in MEDLINE, using PubMed, (1 January 1966 to 1 November 2007) and the Cochrane Central Register of Clinical Trials databases. 'Pneumonia' and 'drug therapy' were combined with either of the following keywords: 'short', 'shorter', 'long', 'longer', 'course', 'duration', 'day' and 'days', excluding the keywords: 'pneumocystis', 'aspiration', 'aspirate', 'nosocomial', 'ventilator', 'ventilation' and 'ventilated'. The search was limited to clinical trials that were performed on humans. Additionally, all of the articles that were eligible for inclusion were manually searched for relevant references. Any disagreement between reviewers was resolved in meetings of all authors.

### Study Selection Criteria

A trial was considered eligible for inclusion in the meta-analysis if (i) it constituted an RCT (i.e. a trial involving at least one test treatment and one control treatment, selected by a random process, as well as concurrent enrolment and follow-up of the compared treatment groups); (ii) it included patients of all ages (excluding neonates) with a diagnosis of

CAP, of any severity (this diagnosis was established on the basis of at least two of three types of criteria, namely clinical, radiological and microbiological); (iii) it compared treatment with the same antibacterial regimens, in the same daily dosages, but with different total duration of administration; (iv) the duration of the short-course treatment arm was no more than 7 days; (v) the long-course treatment arm was at least 2 days longer in duration than the short-course; and (vi) it reported data regarding clinical success, microbiological success, mortality, relapses, adverse events and/or withdrawals as a result of adverse events. In cases where RCTs included patients with mixed types of infections, they were included if separate data for patients with CAP were reported or if patients with CAP accounted for more than 70% of the total study population. No exclusion of studies was done on the basis of patient comorbidities. Conference abstracts were not included. Articles in languages other than English, French, Spanish, German, Italian and Greek were not included.

### Quality Assessment

The quality of the included trials was assessed using the Jadad criteria. The maximum score that can be appointed to a trial is 5 points. One point is awarded for the presence of randomization, blinding and information regarding study withdrawals, respectively. The randomization procedure is merited +1 point if deemed appropriate, −1 point if inappropriate and 0 points if no data regarding the methodology of the randomization procedure are reported. The methodology of blinding is also evaluated and points are assigned, in the same manner as for the evaluation of randomization.[14,15] Trials rated with more than 2 points are considered to be of adequately good quality.

### Data Extraction

The extraction and tabulation of data from the qualifying RCTs included information on the type of study design, the characteristics of the included population, the regimens used in the compared treatment arms, the type of concomitantly administered therapy, the size of the intention-to treat (ITT) population, the size of the evaluable population, the time of the end-of-therapy and of the late follow-up evaluation, the clinical and microbiological treatment outcomes, as well as information regarding mortality, relapses, adverse events and withdrawals due to adverse events.

### Definitions

The primary effectiveness outcome was clinical success, which was defined as complete resolution (cure) or improvement of symptoms and signs of CAP, assessed at the end-of-therapy evaluation visit of each included RCT. If data for the combined outcome of cure or improvement were not reported, data for cure alone were included. Clinical success was evaluated on the per protocol (otherwise described as evaluable) population, which included patients meeting the criteria for evaluation for a specific outcome that was employed in each included RCT. The choice of per protocol population for the evaluation of outcomes was made because outcome differences between patients in short- and long-course regimens are more likely to be documented in this analysis.

The secondary effectiveness outcomes included (i) clinical success at the late follow-up evaluation visit of each included RCT; (ii) microbiological success, defined as the rate of patients with eradication of the pre-treatment isolated pathogens or with presumed eradication, judged in accordance with the clinical outcome in the case that post-treatment cultures were not performed; (iii) microbiological success at the late follow-up evaluation; (iv) mortality, defined as death of patients due to any cause occurring until the end of the follow-up period; and (v) relapses, which were defined as the reappearance of signs and symptoms in patients deemed as clinically cured or improved at the end-of-therapy evaluation.

The primary safety outcome was the total number of adverse events that occurred until the end of the follow-up period. If data regarding total number of adverse events were not reported, but instead data for adverse events deemed as drug-related were provided, the latter were included in the analysis. The secondary safety outcome was withdrawals due to adverse events, which included patients who were withdrawn from trials due to any adverse event.

Subset analyses were performed including studies involving either adult or paediatric populations. Additional subset analyses evaluated the primary outcomes of the meta-analysis in studies comparing short-course therapy of no more than 5 days to long-course therapy of at least 7 days.

### Statistical Analysis

The presence of statistical heterogeneity among the included trials was assessed by the chi-square ($\chi^2$) test and the $I^2$ test. For the $\chi^2$ test, a p-value lower than 0.1 was considered to denote the presence of statistically significant heterogeneity between the included trials.[16,17] Publication bias because of small sample size of trials was assessed with the funnel plot method by using the Egger test. Pooled odd ratios and 95% confidence intervals were calculated by the Mantel-Haenszel fixed-effect model,[18] in case statistically significant heterogeneity between the analysed trials was not observed. Otherwise, the DerSimonian-Laird random-effects model[19] was used. Statistical analyses were performed with 'RevMan Analyses v1.0 for Windows' statistical software (The Cochrane Collaboration, Copenhagen, Denmark).

## Results

### Study Selection Process

A flow diagram is presented in figure 1 depicting the detailed process of screening and selecting articles from MEDLINE, via PubMed, and the Cochrane Central Register of Controlled Trials to be included in the meta-analysis. We initially retrieved 381 and 287 potentially relevant articles in these two databases, respectively. Six RCTs were identified as eligible for inclusion in the meta-analysis among the articles retrieved from MEDLINE, while four eligible RCTs were identified among the articles retrieved from the Cochrane Central Register of Controlled Trials. All of the latter four RCTs were included in those identified through the PubMed search. In the six individual RCTs eligible for inclusion identified through this process, one more RCT, which was identified from manually searching bibliographies of relevant articles, was added. Thus, we finally selected seven RCTs[20-26] for inclusion in this meta-analysis.

### Characteristics of Selected Studies

Table I presents the characteristics of the RCTs that were included in this meta-analysis (patient population and setting, study treatments, concomitantly administered agents and timing of the evaluation visits). All of the included RCTs were double-blind.[20-26] Regarding the quality of the included trials, six of seven were assigned a Jadad score of at least 4.[21-26] The diagnosis of pneumonia was based on clinical, radiological and microbiological criteria in four trials,[20,21,23,24] clinical and radiological criteria in two trials[25,26] and on clinical and microbio-

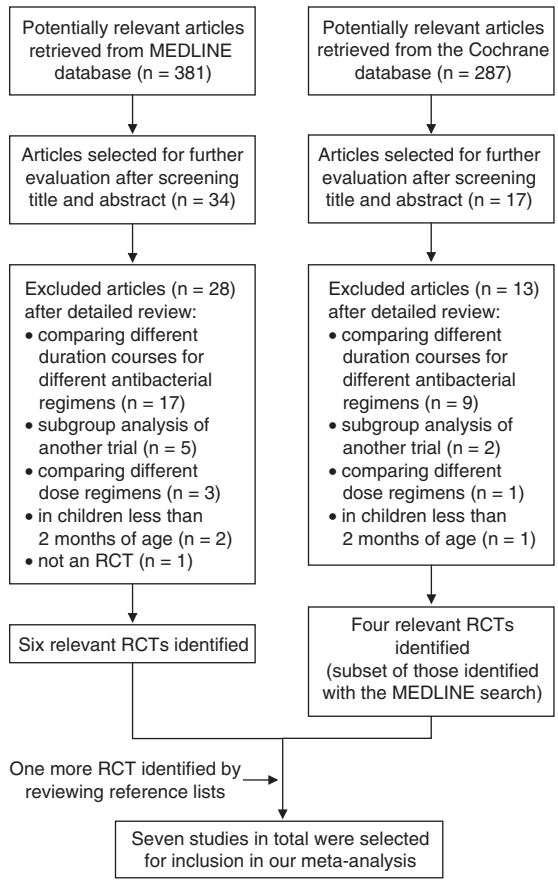


**Fig. 1.** Flow diagram of the detailed process for selection of articles for inclusion in the meta-analysis. **RCT** = randomized controlled trial.

**Table I.** Main characteristics of the randomized, controlled, multicentre, double-blind trials included in the meta-analysis

| Study (year) | Population (age group, type of pneumonia, diagnostic criteria) | SC regimen | LC regimen | Concomitant therapy | No. of pts in ITT population (SC/LC) | No. of pts in PP population (SC/LC) | Day(s) of test-of-cure visit/follow-up | Jadad score |
|---|---|---|---|---|---|---|---|---|
| File et al.[20] (2007) | Pts aged >18 y<br>CAP, excluding those requiring parenteral antimicrobial therapy<br>Outpatients<br>Clinical, radiological and microbiological (blood cultures, bronchial secretions, serology, urine antigen testing) criteria | Gemifloxacin 320 mg PO od for 5 d | Gemifloxacin 320 mg PO od for 7 d | NR | 510 (256/254) | 483 (247/236) | 7–9/24–30 | 3 |
| El Moussaoui et al.[21] (2006) | Pts aged >18 y<br>Mild to moderate-severe CAP (PSI score ≤110), excluding pts with suspected aspiration, atypical, staphylococcal or *Klebsiella* pneumonia, who had improved after 72 h of treatment,[a] not infected with a resistant pathogen<br>Inpatients<br>Clinical, radiological and microbiological (bronchial secretions, serology) criteria | Amoxicillin 1 g IV q6h for 3 d[a] | Amoxicillin 1 g IV q6h for 3 d[a] → amoxicillin 750 mg PO q8h for 5 d (8 d in total) | NR | 119 (56/63) | 114 (54/60) | 10/28 | 4 |
| Agarwal et al.[22] (2004) | Children aged 2–59 mo<br>Non-severe CAP<br>Outpatients<br>Clinical and microbiological (nasopharyngeal swabs) criteria | Amoxicillin 31–54 mg/kg/d PO in 3 divided doses for 3 d | Amoxicillin 31–54 mg/kg/d PO in 3 divided doses for 5 d | Symptomatic treatment for wheezing and fever | 2188 (1095/1093) | 2059 (1033/1026) | 6/12–14 | 4 |
| Tellier et al.[23] (2004) | Pts aged >18 y<br>CAP, excluding those requiring ICU admission, receiving parenteral antibacterials or having significant respiratory complications<br>Inpatients or outpatients<br>Clinical, radiological and microbiological (blood cultures, bronchial secretions, serology) criteria | Telithromycin 800 mg PO od for 5 d | Telithromycin 800 mg PO od for 7 d | NR | 378 (187/191) | 320 (161/159) | 17–21/31–36 | 4 |
| Leophonte et al.[24] (2002) | Pts aged >18 y<br>CAP, requiring at least 5 d of hospitalization and having at least one factor of severity, excluding those with decompensation of vital signs<br>Inpatients<br>Clinical, radiological and microbiological (blood cultures, bronchial secretions) criteria | Ceftriaxone 1 g IV od for 5 d | Ceftriaxone 1 g IV od for 10 d | None | 244 (125/119) | 186 (94/92) | 10/30–45 | 4 |

*Continued next page*

**Table I.** Contd

| Study (year) | Population (age group, type of pneumonia, diagnostic criteria) | SC regimen | LC regimen | Concomitant therapy | No. of pts in ITT population (SC/LC) | No. of pts in PP population (SC/LC) | Day(s) of test-of-cure visit/follow-up | Jadad score |
|---|---|---|---|---|---|---|---|---|
| MASCOT[25] (2002) | Children aged 2–59 mo<br>Non-severe CAP<br>Outpatients<br>Clinical and radiological criteria | Amoxicillin 15 mg/kg PO q8h for 3 d | Amoxicillin 15 mg/kg PO q8h for 5 d | Salbutamol (albuterol) and paracetamol (acetaminophen) on an as needed basis | 1953 (980/973) | 1953 (980/973) | 5/14 | 5 |
| Siegel et al.[26] (1999) | Pts aged >18 y<br>CAP, excluding those with empyema, septic shock or respiratory failure<br>Inpatients<br>Clinical and radiological criteria | Cefuroxime 750 mg q8h IV for 2 d → cefuroxime axetil 500 mg q12h PO for 5 d (7 d in total) | Cefuroxime 750 mg IV q8h for 2 d → cefuroxime axetil 500 mg PO q12h for 8 d (10 d in total) | NR | 52 | 46 (24/22) | NR/42–44 | 4 |

a Randomization was performed after 72 h of treatment with amoxicillin.

**CAP** = community-acquired pneumonia; **ICU** = intensive care unit; **ITT** = intention-to-treat; **IV** = intravenous; **LC** = long course; **NR** = not reported; **od** = once daily; **PO** = oral; **PP** = per protocol; **PSI** = Pneumonia Severity Index; **pts** = patients; **qxh** = every *x* hours; **SC** = short course; → indicates followed by.

logical criteria in one trial.[22] The latter RCT involved children who were additionally required not to have responded to 3 days of symptomatic therapy. In addition, five of seven trials[20,21,23,24,26] involved adult patients with CAP who were treated either as inpatients or as outpatients. None of the included RCTs evaluated patients who required admission in intensive care units. The remaining two trials were performed on children with non-severe CAP, aged 2–59 months, residing in developing countries.[22,25] Data regarding the use of any concomitantly administered therapy were reported in two trials.[22,25] The timing of the end-of-therapy and late follow-up evaluation visits varied appreciably (minimum day 6, maximum days 17–21 for the end-of-therapy evaluation; minimum days 12–14, maximum days 30–45 for the late follow-up evaluation; all values counting from the beginning of study treatments).

## Outcomes

In table II, we present the extracted data regarding the primary and secondary outcomes of this meta-analysis.

### *Clinical Success*

Data on the primary effectiveness outcome of clinical success at the end-of-therapy evaluation were provided in six of seven included RCTs.[20-25] There was no difference regarding clinical success at the end of therapy between short- and long-course regimens for the treatment of CAP (5107 patients; fixed-effect model [FEM]; odds ratio [OR] = 0.89; 95% CI 0.74,1.07) [figure 2]. In the secondary analysis regarding clinical success at the late follow-up evaluation,[20,21,24,26] there was no difference in clinical success at the follow-up visit between the short- and the long-course regimens (five RCTs, 2762 patients; FEM; OR = 0.98; 95% CI 0.80, 1.20) [figure 3]. In the subset analysis of studies including adult patients,[20,21,23,24] no difference was found in end-of-therapy clinical success between the short- and long-course regimens (four RCTs, 1095 patients; FEM; OR = 0.92; 95% CI 0.58, 1.47) [figure 2]. In the subset analysis of studies involving paediatric patients,[22,25] there was no difference in end-of-therapy clinical success between the short- and long-course regimens (two RCTs, 4012 patients; FEM; OR = 0.88; 95% CI 0.72, 1.08) [figure 2]. The

**Table II.** Data from the included randomized controlled trials regarding the primary and secondary outcomes of the meta-analysis

| Study (year) | Clinical success [n/N (%)] at EOT and *late FU* | | Microbiological success [n/N (%)] at EOT and *late FU* | | Relapses [n/N (%)] | | Mortality [n/N (%)] | | Pts with adverse events [n/N (%)] | | Pt withdrawals due to adverse events [n/N (%)] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SC | LC | SC | LC | SC | LC | SC | LC | SC | LC | SC | LC |
| File et al.[20] (2007) | 236/247 (95.5) *230/242 (95)* | 226/236 (95.8) *209/227 (92.1)* | 101/108 (93.5) *96/105 (91.4)* | 121/126 (96) *110/121 (90.9)* | NR | NR | 0/256 (0) | 1/254 (0.4) | 54/256 (21) | 53/254 (21) | 3/256 (1.2) | 5/254 (2) |
| El Moussaoui et al.[21] (2006) | 50/54 (92.6) *47/52 (90.4)* | 56/60 (93.3) *49/56 (87.5)* | 22/25 (88) *20/25 (80)* | 19/20 (95) *15/20* (75) | NR | NR | 0/56 (0) | 0/63 (0) | 6/56 (10.7) | 13/63 (20.6) | 0/56 (0) | 0/63 (0) |
| Agarwal et al.[22] (2004) | 980/1033 (94.9) *NR* | 983/1026 (95.8) *NR* | NR | NR | 58/1095 (5.3) | 48/1093 (4.4) | 0/1095 (0) | 0/1093 (0) | NR | NR | NR | NR |
| Tellier et al.[23] (2004) | 142/159 (89.3) *NR* | 143/161 (88.8) *NR* | 57/65 (87.7) *NR* | 52/65 (80) *NR* | NR | NR | 1/193 (0.5) | 2/195 (1.0) | 47/193 (24.4) | 41/195 (21) | 9/193 (4.7) | 6/195 (3.1) |
| Leophonte et al.[24] (2002) | 82/91 (90.1) *69/94 (73.4)* | 81/87 (93.1) *67/92 (72.8)* | NR | NR | NR | NR | 4/125 (3.2) | 7/119 (5.9) | 100/125 (80) | 98/119 (82.4) | 4/125 (3.2)[a] | 5/119 (4.2)[a] |
| MASCOT[25] (2002) | 803/980 (81.9) *791/980 (80.7)* | 811/973 (83.4) *798/973 (82)* | NR | NR | 12/980 (1.2) | 13/973 (1.3) | 0/980 (0) | 1/973 (0.1) | 43/980 (4.4) | 57/973 (5.9) | 0/980 (0) | 0/973 (0) |
| Siegel et al.[26] (1999) | NR *21/24 (87.5)* | NR *20/22 (90.9)* | NR | NR | 0/24 (0) | 0/22 (0) | 1/24 (4.2) | 0/22 (0) | NR | NR | 0/24 (0) | 0/22 (0) |

a Withdrawals due to adverse events or another disease.

**EOT** = end of therapy; **FU** = follow-up; **LC** = long course; **NR** = not reported; **pt** = patient; **SC** = short course.

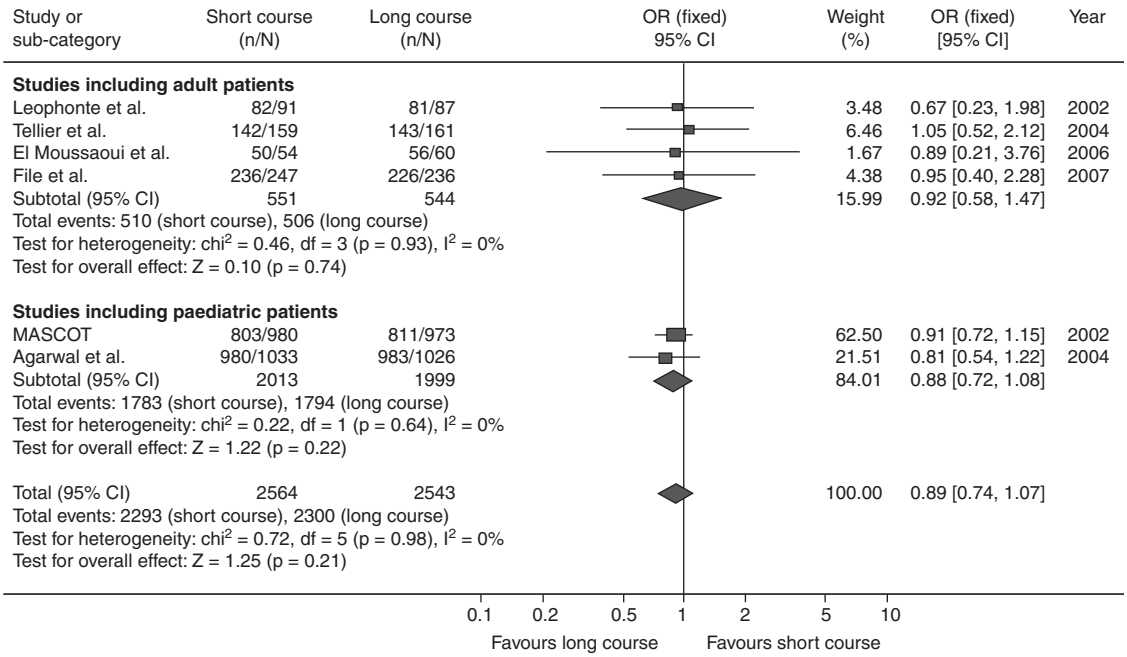


**Fig. 2.** Meta-analysis of clinical success at the end-of-therapy assessment of per protocol patients with community-acquired pneumonia treated with short- vs long-course antibacterial regimens. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled odds ratio (OR) plus 95% confidence interval.[20-25]

subset analysis that compared clinical success in patients treated with short-course regimens of no more than 5 days duration with patients treated with long-course regimens of at least 7 days duration, corresponded to the subset analysis of studies including adult patients mentioned here.[20,21,23,24] Additionally, a sensitivity analysis was performed excluding the study by El Moussaoui et al.,[21] because randomization was done on patients who had improved on day 3, so an accurate estimation of the clinical success of a 3-day versus longer regimen cannot be done. In this analysis, there was no difference in clinical success at the end of therapy between the short- and long-course regimens (five RCTs, 4993 patients; FEM; OR = 0.89; 95% CI 0.74, 1.07).

### *Microbiological Success*

Data regarding microbiological success at the end-of-therapy evaluation were provided in three of the seven included RCTs that involved adult patients.[20,21,23] There was no difference regarding microbiological success at the end of therapy between the short- and long-course regimens for the treatment of CAP (409 patients; FEM; OR = 1.03; 95% CI 0.52, 2.05). In the secondary analysis regarding microbiological success at the late follow-up evaluation,[20,21] there was no difference in microbiological success between the short- and long-course regimens (two RCTs, 271 patients; FEM; OR = 1.14; 95% CI 0.53, 2.47).

### *Relapses*

Data regarding relapses were provided in one adult[26] and in the two paediatric[22,25] RCTs included in the meta-analysis. There was no difference regarding the relapse rate between the short- and long-course regimens for the treatment of CAP (4187 patients; FEM; OR = 1.15; 95% CI 0.81, 1.63). In the subset analysis limited to paediatric patients, relapses did not differ between compared treatments (two RCTs, 4141 patients; OR = 1.15; 95% CI 0.81, 1.63).

### *Mortality*

Data regarding mortality were provided in all of the seven included RCTs.[20-26] There was no difference regarding mortality between the short- and long-course regimens for the treatment of CAP (5438 patients; FEM; OR = 0.57; 95% CI 0.23, 1.43) [figure 4]. In the subset analysis of studies including adult patients,[20,21,23,24,26] no difference was found in mortality between the short- and long-course regimens (five RCTs, 1188 patients; FEM; OR = 0.60; 95% CI 0.23, 1.58) [figure 4]. In the subset analysis of paediatric studies, no difference was found in mortality between compared treatments (two RCTs, 4141 patients; OR = 0.33; 95% CI 0.01, 8.13) [figure 4].

### *Adverse Events*

Data regarding adverse events were provided in five (four involving adults and one involving paediatric patients) of the seven included RCTs.[20,21,23-25] There was no difference regarding adverse events between the short- and long-course regimens for the treatment of CAP (3214 patients; FEM; OR = 0.90; 95% CI 0.72, 1.13) [figure 5]. In the subset analysis of studies including adult patients,[20,21,23,24] no difference was found in adverse events between the short- and long-course regimens (four RCTs, 1261 patients; FEM; OR = 0.98; 95% CI 0.75, 1.29) [figure 5]. This analysis corresponded to the subset analysis comparing adverse events in patients treated with short-course regimens of no more than 5 days duration with patients treated with long-course regimens of at least 7 days duration.

### *Withdrawals due to Adverse Events*

Data regarding the withdrawals due to adverse events were provided in six (all five adult studies and one paediatric study) of the seven included RCTs.[20,21,23-26] In total, withdrawals due to adverse events were noted in 16 of 1634 patients (1%) allocated to the short-course treatment arms and in 16 of 1626 patients (1%) allocated to the long-course treatment arms. There was no difference regarding withdrawals due to adverse events between the short- and the long-course regimens

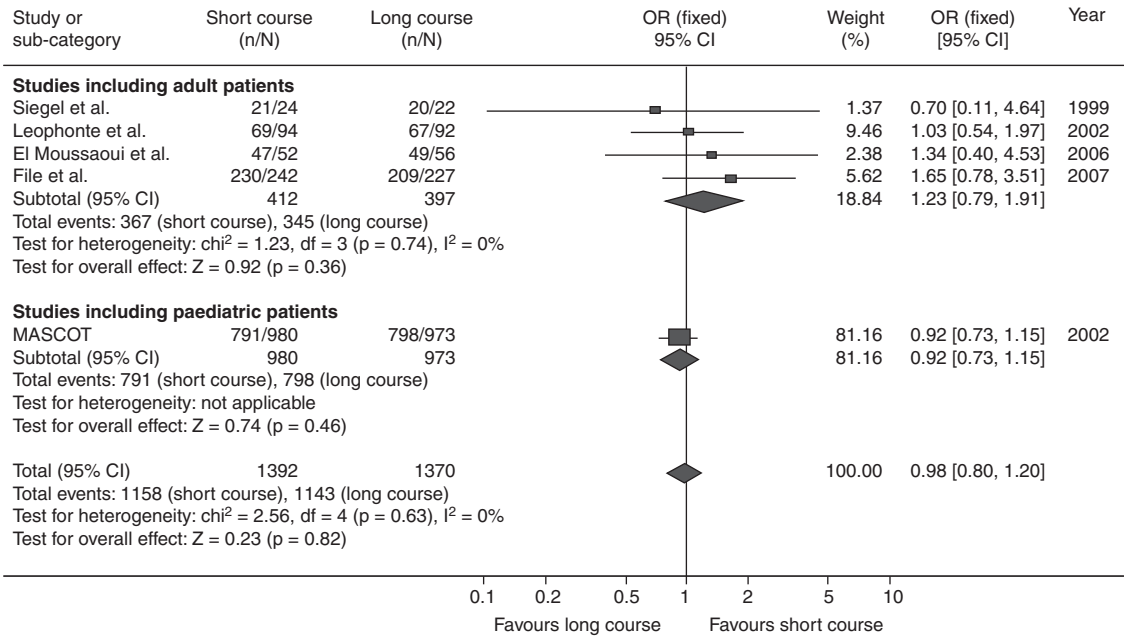


**Fig. 3.** Meta-analysis of clinical success at the late follow-up assessment of per protocol patients with community-acquired pneumonia treated with short- vs long-course antibacterial regimens. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled odds ratio (OR) plus 95% confidence interval.[20,21,23-26]

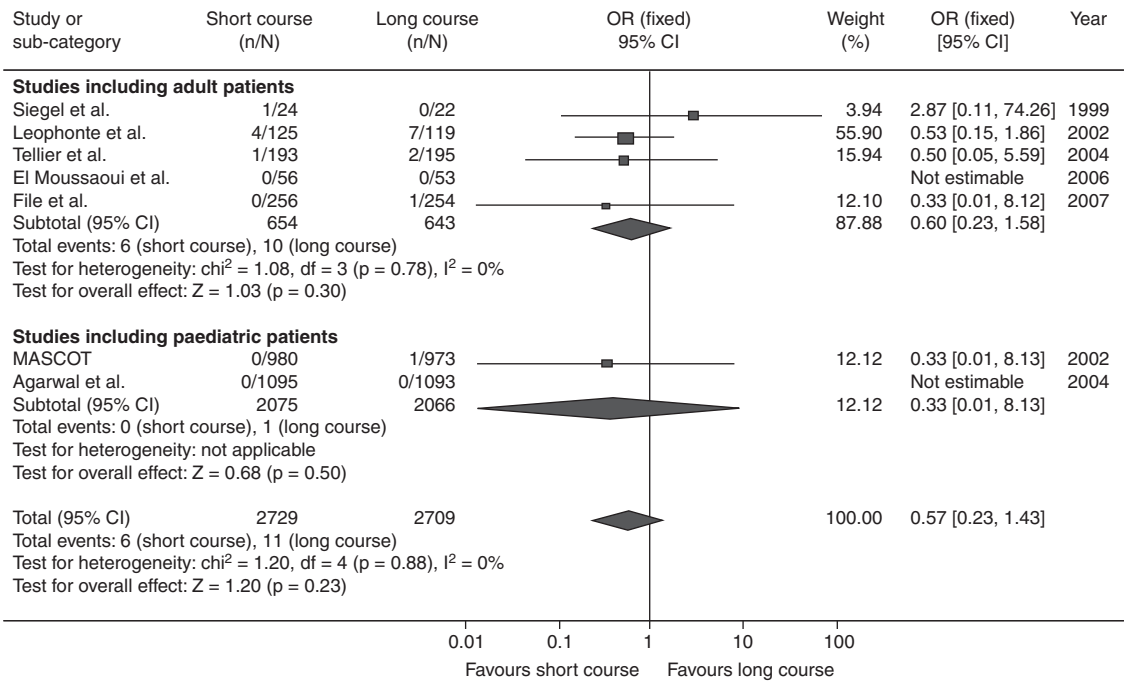


**Fig. 4.** Meta-analysis of mortality in patients with community-acquired pneumonia treated with short- vs long-course antibacterial regimens. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled odds ratio (OR) plus 95% confidence interval.[20-26]

for the treatment of CAP (3260 patients; FEM; OR = 0.99; 95% CI 0.49, 2.00).

## Discussion

The main finding of this meta-analysis is that short-course therapy for CAP was found to be as effective as treatment of traditionally longer duration for this entity. However, the analysis of mortality is based on too few deaths resulting in wide 95% confidence intervals that do not allow us to make any firm conclusions. In terms of safety, no difference was found between compared treatments. It should be mentioned that the population of the RCTs included in this meta-analysis was heterogeneous. This primarily refers to the inclusion of two large paediatric studies performed in developing countries, along with studies performed on adult patients in Western countries. In this regard, outcomes were evaluated in separate analyses for these two different subsets of patients. The findings of the meta-analysis proved consistent in both subpopulations.

Regarding the analysis in the adult population, it should be noted that all relevant RCTs excluded patients with various determinants of disease severity, mostly relating to unstable vital signs.[23,24,26] Yet, three of the five RCTs referring to adult patients evaluated exclusively hospitalized patients,[21,24,26] while an additional RCT evaluated both inpatients and outpatients.[23] Still, standardized scoring systems for the evaluation of the degree of severity of the disease were not used in the great majority of studies. Thus, it cannot be adequately assessed whether the hospitalized patients included in the these RCTs[21,23,24,26] had pneumonia of such severity to require hospitalization by current standards. Consequently, the extrapolation of the findings of this meta-analysis in non-ambulatory patients with moderate to severe disease should be done with caution.

The effectiveness of short-course therapy for CAP, observed in this meta-analysis, is supported by additional evidence. First, there are increasingly more data derived from studies in other types of respiratory tract infections where antimicrobial therapy can be shortened without compromising effectiveness.[27-29] Additionally, an observational study concluded that, in the great majority of patients with ventilator-associated pneumonia, the infection can be cleared or be substantially contained after 3 days of antimicrobial treatment. The prognosis of this group of patients was favourable.[30] Another study, in a tropical area, effectively treated patients with CAP up to the time that they remained afebrile for 24 hours. The average duration of treatment was 2.54 days and no patient had adverse outcomes.[31]

Current US guidelines recommend that treatment for CAP can be discontinued after a minimum of 5 days in patients who remain afebrile for 48–72 hours, provided that no more than one sign of pneumonia-associated clinical instability is present.[32] In patients with CAP, even those who are hospitalized, the median time to resolution of fever and the median time to clinical stability have been shown to be 3[33,34] and 4 days,[35] respectively; therefore, it can be inferred that, on the basis of current recommendations, approximately half of the patients with CAP should be treated for a total duration of 5–6 days.[36] It should be noted that some of the pneumonia-associated symptoms that do not relate to clinical instability, such as cough or fatigue, can persist for a relatively longer period of time without serious clinical implications.[34,37] Thus, they should preferably not be used to guide decisions regarding the duration of therapy.

A potential consideration regarding the duration of antimicrobial therapy in CAP is that inappropriately short regimens may lead to relapse of the disease after initial improvement. In patients with ventilator-associated pneumonia, short-course treatment was associated with a 15% higher relapse rate of specific pathogens, namely non-fermentative Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; however, this did not affect the mortality of patients infected with the respective pathogens.[28] On the contrary,

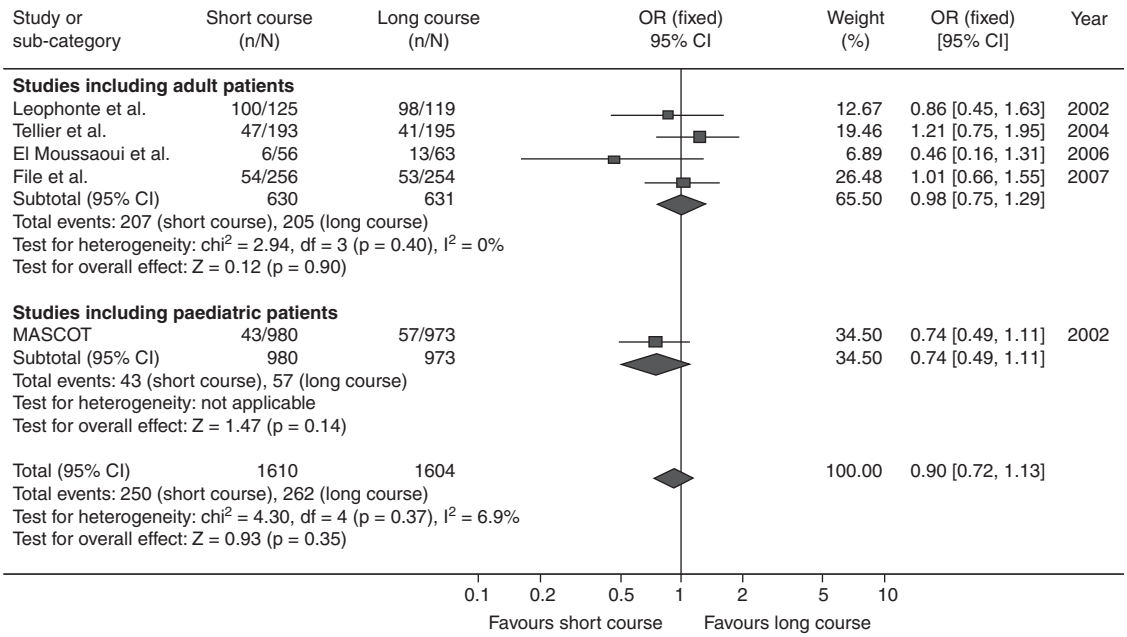


**Fig. 5.** Meta-analysis of adverse events reported for patients with community-acquired pneumonia treated with short- vs long-course antibacterial regimens. Vertical line indicates 'no difference' between compared treatments; horizontal lines indicate 95% confidence intervals; squares indicate point-estimates; size of the squares indicates weight of the study in the meta-analysis; diamond shape indicates pooled odds ratio (OR) plus 95% confidence interval.[20,21,24,25]

the present meta-analysis for CAP showed that treatment success evaluated at the time of late follow-up, thus presumably incorporating the majority of relapses, did not differ among compared treatment arms.

Although not assessed in this meta-analysis, because of a lack of relevant data, a longer course of antimicrobial therapy may be associated with a higher rate of secondary infections caused by resistant pathogens, due to the selective pressure of antibacterials, as has been shown in patients with ventilator-associated pneumonia.[28] Additionally, an increased risk for emergence of resistant strains related to longer courses of therapy may derive from declining patient adherence to the assigned regimen after the first days of therapy and symptom resolution.[38-41] Specifically, decreased compliance can lead to longer exposure of pathogens to low drug concentrations, which, in turn, promotes the emergence of drug resistance.[41,42]

With regard to paediatric CAP, it should be noted that the incidence of this entity in the community peaks in children between the ages of 2 months and 5 years, which was the population on which the two included paediatric RCTs focused.[1] Particularly for developing countries, acute lower respiratory tract infections is the primary cause of mortality observed among children under 5 years of age.[42] Issues relating to treatment cost, adherence to therapy and emergence of resistance, which are linked to the type and cost of potentially effective antibacterials, are essential for the choice of antibacterial therapy. In fact, in one of the two included studies, in which relevant outcomes were measured, the longer course of therapy was related to decreased compliance to therapy and increased resistance rates of *Streptococcus pneumoniae* to cotrimoxazole (trimethoprim/sulfamethoxazole).[22]

The 5-day amoxicillin regimen used as the comparator arm in the paediatric studies performed in developing countries, may be regarded insufficient for maximal therapeutic benefits to be achieved. However, a 5-day duration of therapy corresponds to the recommendations of the WHO for non-severe CAP in children.[43] In developed countries, data about the optimal treatment of CAP in children are scarce. Few professional societies have issued relevant guidelines. Among these, the British Thoracic Society recommends treatment duration of 7–10 days for agents without an extended half-life.[44] It is noteworthy that the major bacterial aetiological agents of CAP in the particular group of children aged between a few months and 5 years, are the same (namely *S. pneumoniae* and *Haemophilus influenzae*) in both developing and developed countries.[22,45,46] In this regard, the finding of this meta-analysis that shorter duration regimens may be equally effective to longer duration ones could be considered in decision-making regarding the treatment of paediatric CAP in developed countries. However, an issue of concern is that the overall rate of clinical failure in the 5-day treatment control arms of both included paediatric studies was relatively high. Yet, this could be disregarded because it was mainly attributed to the inclusion of many cases of viral pneumonia, particularly due to respiratory syncytial virus.[47]

The main limitation of this meta-analysis is the relatively small number of studies that have been performed on the issue addressed. Moreover, the duration of pathogen-specific therapy, as well as the duration of therapy with combination regimens, which are frequently used in clinical practice, were not evaluated in the included RCTs. Although the findings of this meta-analysis regarding the comparable effectiveness of short-course monotherapy regimens with regard to long-course ones could plausibly be extrapolated to combination regimens as well, further research on the latter issue is recommended. On the other hand, the strengths of this meta-analysis are that all of the included trials had a double-blind design and almost all had a high methodological quality. Additionally, in practically all of the analyses performed, no statistical heterogeneity was noted between studies.

## Conclusion

The findings of this meta-analysis indicate that the treatment of CAP could effectively be shortened compared with traditionally used regimens for most adult patients, including those with disease of milder severity who do not require hospitalization, as well as a subset of those with more severe disease that necessitate in-hospital therapy, but who are in a rather stable clinical condition. Also, the findings of this meta-analysis regarding the two included paediatric studies[22,25] imply that the duration of treat-

ment of CAP could be shortened to a 3-day regimen for children aged between 2 and 59 months with non-severe disease, without appreciably compromising clinical effectiveness. Since the findings of this meta-analysis require further evaluation in appropriately designed studies, before definite recommendations can be made, we suggest that a shorter duration of antimicrobial therapy be particularly considered for patients who rapidly respond to initially administered antimicrobial regimens. However, future studies should also involve groups of patients who are sicker, where severity is measured using appropriate scores such as CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age ≥65 years)[5] or the Pneumonia Severity Index.[4] Besides, regulatory agencies should demand that sicker pneumonia populations are included in clinical trials in order to approve new indications for shorter antibacterial courses versus a traditionally longer fixed course.

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