BMJ Open

Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis

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ABSTRACT

Objectives To find the optimal treatment duration with antibiotics for community-acquired pneumonia (CAP) in adults.

Design Systematic review and duration-effect meta-analysis.

Data sources MEDLINE, Embase and CENTRAL through 25 August 2021.

Eligibility criteria All randomised controlled trials comparing the same antibiotics used at the same daily dosage but for different durations for CAP in adults. Both outpatients and inpatients were included but not those admitted to intensive care units. We imposed no date, language or publication status restriction.

Data extraction and synthesis Data extraction by two independent reviewers. We conducted a random-effects, one-stage duration-effect meta-analysis with restricted cubic splines. We tested the non-inferiority with the prespecified non-inferiority margin of 10% examined against 10 days . The primary outcome was clinical improvement on day 15 (range 7–45 days). Secondary outcomes: all-cause mortality, serious adverse events and clinical improvement on day 30 (15–60 days).

Results We included nine trials (2399 patients with a mean (SD) age of 61.2 (22.1); 39% women). The duration-effect curve was monotonic with longer duration leading to a lower probability of improvement, and shorter treatment duration (3–9 days) was likely to be non-inferior to 10-day treatment. Harmful outcome curves indicated no association. The weighted average percentage of the primary outcome in the 10-day treatment arms was 68%. Using that average, the absolute clinical improvement rates of the following durations were: 3-day treatment 75% (95% CI: 68% to 81%), 5-day treatment 72% (95% CI: 66% to 78%) and 7-day treatment 69% (95% CI: 61% to 76%).

Conclusions Shorter treatment duration (3–5 days) probably offers the optimal balance between efficacy and treatment burden for treating CAP in adults if they achieved clinical stability. However, the small number of included studies and the overall moderate-to-high risk of bias may compromise the certainty of the results. Further research on the shorter duration range is required.

PROSPERO registration number CRD 42021273357.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We conducted a comprehensive and up-to-date systematic literature review.

⇒ The duration-effect meta-analysis treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution than the conventional pairwise meta-analysis that dichotomised duration arbitrarily.

⇒ The small number of trials included limited the precision of some study results.

⇒ Most of the trials had a moderate-to-high overall risk of bias.

⇒ About 80% of the patients had Pneumonia Severity Index class III or less and thus the results may not be generalisable to severely ill patients.

BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally, especially among the elderly.[1] In the USA, it is the second most common cause of hospitalisation and the top infectious cause of death.[2 3] The initial treatment for CAP is empirical, with guidelines recommending starting several antibiotics depending on patients' severity and risk factors for certain pathogens.[4–6]

The optimal duration of antimicrobial therapy remains unclear and controversial. The American and British guidelines recommend a minimum of 5 days of treatment before therapy discontinuation for patients achieving clinical stability.[4 5] The European guideline states that the duration of treatment should not exceed 8 days in responding patients.[6] In clinical practice, however, antibiotics for pneumonia are often prescribed for 10 to 14 days.[7 8] This may mean that many patients are receiving more antibiotics than necessary, with a consequent increase in costs and a higher probability of antimicrobial resistance.[9] Finding the optimal duration of

antibiotics can facilitate reducing antimicrobial use efficiently. Several meta-analyses have been reported on this topic.[10–12] A major limitation of the method used in the previous pairwise meta-analyses is the arbitrary categorisation of duration when the original studies compared different duration, ranging from 3 to 10 days. A pairwise meta-analysis published in 2008,[10] for example, categorised a 7-day treatment arm in one trial as short-course and the same in other two trials as long-course.[13–15] Another pairwise meta-analysis in 2018 excluded a trial comparing 7-day against 10-day treatment because they defined long-course as 7 days or longer.[11] The duration range of short-course therapy defined by a systematic review of systematic reviews and guidelines with pairwise meta-analyses in 2019 was wide (3–7 days) and the duration-effect relationship within that range remains unclear.[12] We overcame the limitation of arbitrary dichotomisation of duration by using a novel method called dose-effect meta-analysis.[16] It has been used, for example, to examine the effects of potassium intake or sodium reduction on blood pressure.[17 18] Unlike conventional categorisation-based meta-analyses,[19] dose-effect meta-analysis can reveal more fine-grained optimal dose.[20] By treating duration as dose, we aimed to apply this method to obtain a more specific optimal treatment duration.

METHODS

We summarised the currently available evidence to find the optimal treatment duration of antibiotics for CAP in adults. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses.[21 21] The protocol has been prospectively registered in PROSPERO and can be found in the appendix (online supplemental eAppendix 1).

Data sources
Criteria for considering studies for this review
Types of studies

To examine the duration-effect relationship, we included all trials that compared two or more different durations of the same antibiotic treatment for CAP.

Types of participants

Patients were eligible if they were 18 years or older of both genders with a diagnosis of CAP as defined by the original authors. We included both outpatients and inpatients. We excluded patients who were admitted to the intensive care unit. To focus on individuals at low-to-medium risk, we excluded trials with 20% or more patients meeting one or more of the following criteria: having immunodeficiency; having been treated with another antibiotic within a month.

Types of interventions

We included trials examining any antibiotics, administered orally or intravenously. We evaluated antibiotics as a class because clinical guidelines recommend treatment duration irrespective of the antibiotic used,[4–6] and because recent meta-analyses of antibiotics for CAP have not shown efficacy differences among antibiotics.[22 23] Oral and intravenous antibiotics were merged because they have been shown equally effective in many infectious conditions within the same time frame.[24–26] We included trials comparing the same agents used at the same daily dosage but for different durations. We used the predefined duration for fixed-duration arms. If some studies did not prespecified the duration (eg, left it to clinicians' judgement[27]), we used the median duration actually prescribed.

Primary outcome and secondary outcomes

The primary outcome of interest in this study was the clinical improvement as defined by the original authors at a time point as close to 15 days (range 7–45 days) as possible in each included study.[28] Secondary outcomes of interest were: all-cause mortality on day 15 (range 7–45 days), serious adverse events as defined by the original study on day 15 (range 7–45 days) and clinical improvement as defined by the original study on day 30 (range 15–60). We used the number of randomised patients as the denominator for the intention-to-treat (ITT) data set. When only clinical failure was reported, clinical improvement was calculated by subtracting clinical failure from the total number randomised. We used ITT for the primary analysis and the per-protocol (PP) data set for a sensitivity analysis.[29 30] We used the odds ratio (OR) of each outcome to synthesise data.[31 32]

Search methods for identification of studies
Electronic searches

We systematically searched the following electronic bibliographic databases from inception through 25 August 2021: MEDLINE, Embase and CENTRAL. We used search terms for CAP in conjunction with the names of individual antibiotics as well as the names of antibiotic classes. Detailed search formulas are presented in the appendix (online supplemental eAppendix 2). We imposed no date, language or publication status restriction.

Reference lists

We checked the reference lists of all the included studies and review articles for additional references.

Data collection and analysis
Selection of studies

Two review authors independently screened and selected the included studies (YF and one of AO, EO, SF or YL). Two review authors extracted data independently from the included studies (YF and one of AO, EO, SF or YL). We used the Cochrane risk of bias tool V.2[33] to assess and summarise the risk of bias. Disagreements were resolved through discussion.

Statistical analysis

To perform our analyses, we used the *dosresmeta* package (V.2.0.1) and *meta* package (V.5.0–1) for *R* (V.4.1.0. R foundation, Wien, Austria).[34–36]

Assessment of heterogeneity

We investigated the heterogeneity between studies by the variance partition coefficient (VPC).[16] VPC represents the percentage of variation attributed to heterogeneity rather than sampling error and can be interpreted similarly to the I^2.

Duration-effect meta-analysis

In the duration-effect meta-analysis, we assumed that the relative efficacy of a certain treatment duration ($duration_i$) against another ($duration_j$) can be expressed in the log-OR ($\log OR_{ij}$) and that it is a function of both durations ($\log OR_{ij} = f(duration_i; duration_j)$). We fitted restricted cubic splines with three knots to the data set obtained by the systematic review because this model has shown sufficient flexibility to capture different shapes.[37] Given the clinical and methodological heterogeneity likely present in the included studies, we used the random effects model. We used three knots, equally spaced across the duration range (25%, 50% and 75%). Typically, in dose-effect meta-analyses, the reference dose is assigned to the zero or the minimal dose to make interpretation easier.[37] As this duration-effect meta-analysis aimed to test the non-inferiority of the shorter treatment duration, we decided to use the maximum duration as the reference to make interpretation easier. Also, the reference we set (10-day treatment) can be regarded as the current practice.[7 8 27] We tested the non-inferiority with the non-inferiority margin of 10%, as previously proposed,[28] and the superiority of the shorter duration examined against 10-day treatment using the ITT data set.

Sensitivity analyses

To ascertain the robustness of the primary analyses, we conducted the following sensitivity analyses. To test the stability of the shape of the spline curves, we used different locations of knots (10%, 50% and 90%). To test the influence of trials included, we conducted sensitivity analyses excluding trials with an overall high risk of bias and excluding trials with outpatients. To test the robustness of the analytical method, we used the PP data set. To test the influence of antibiotics examined, we conducted sensitivity analyses restricting eligible antibiotics only to those recommended by clinical guidelines for empirical treatment of CAP.[4 5] In addition to the predefined sensitivity analyses, we conducted exploratory sensitivity analyses including only trials that randomised before the initial antibiotic treatment to test the influence of randomisation timing. We further conducted sensitivity analyses excluding trials with substantial deviation from the day 15 measurement time and analyses imputing missing data as improved outcomes.

Amendments

We report amendments with the date and the rationale in the appendix (online supplemental eAppendix 3).

RESULTS

We identified 1994 records via database and 1 record via searching websites, which revealed that some different records refer to the same clinical trial. We assessed 38 full-text records for eligibility and included eleven eligible studies (figure 1). Of these, eight were published,[13–15 27 38–41] one was unpublished[42] and two studies were still ongoing,[43 44] resulting in nine trials for the primary outcome analysis. The lists of included and excluded studies are provided in the appendix (online supplemental eAppendies 4 and 5). The nine studies with 2399 participants in total included 18 eligible arms. Treatment duration ranged from 3 to 10 days. The study year ranged between 1999 and 2021. Table 1 presents the characteristics of the included studies (more details can be found in online supplemental eAppendix 4).

The included studies were all parallel-group and individually randomised. Seven out of nine were reported as non-inferiority trials. In total, 1199 participants were randomly assigned to the shorter duration arm and 1200 to the longer duration arm. The mean age was 61.2 years (SD 22.1); 831 (39%) of 2140 reported were women. Six were conducted in a single European country, one in the USA and the two were cross-continental. CAP was defined as newly confirmed clinical symptoms (eg, dyspnoea, cough, purulent sputum or crackles), and radiological findings. Antibiotic treatment was discontinued when the patient was clinically stable, and the predetermined treatment period was completed. Clinical stability was often defined as without fever (temperature ≤37.8°C) for 48 hours, heart rate below 100 beats per min, a respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mm Hg or higher and normal mental status.[45] Clinical improvement was often described as 'clinical cure' or 'clinical success' and was often defined as the resolution of fever and improvement of symptoms related to pneumonia without further antibiotics. More detailed definitions of clinical improvement in each included study are listed in the appendix (online supplemental eAppendix 6). The percentage of Pneumonia Severity Index class IV or V was on average 19% (362 of 1896 reported; ranging from 2% to 41%). Seven studies focused on inpatients, whereas one study focused on outpatients and one included both. Antibiotics used included β-lactams (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, ceftazidime, ceftriaxone, cefuroxime, piperacillin/tazobactam), macrolides (azithromycin, clarithromycin), quinolones (ciprofloxacin, gemifloxacin, levofloxacin, telithromycin), amikacin, doxycycline and meropenem. Pharmaceutical companies funded four studies.[13–15 38] Four studies had a high overall risk of bias, four some concerns
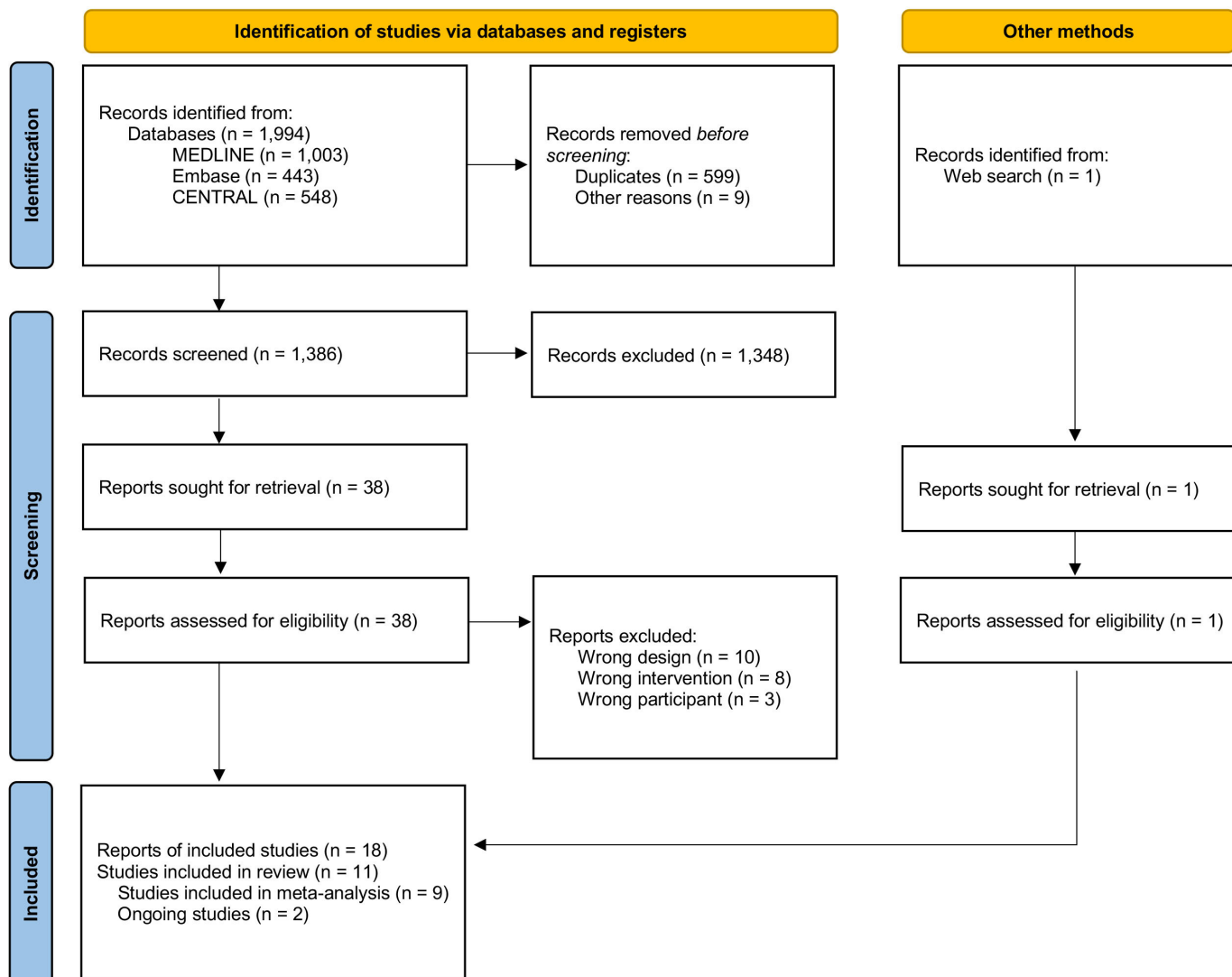
Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram.

and only one had a low overall risk of bias (online supplemental eAppendix 7).

Assessment of heterogeneity and publication bias

We assessed the heterogeneity in the efficacy outcome across the duration range (nine studies). VPC values were constantly below 10% which suggests low levels of heterogeneity. Visual inspection of the funnel plot suggested no significant publication bias. However, these assessments need to be carefully interpreted due to the small number of included studies (online supplemental eAppendies 8 and 9).

Duration-effect meta-analysis

We present the duration-effect curves in figures 2 and 3, and the tabulation of results in table 2. The x-axis of the figures represents the treatment duration in days. The y-axis represents the OR of the outcome on a logarithmic scale, just as in the forest plot of conventional pairwise meta-analysis using binary outcomes. The thin dotted horizontal line in the clinical improvement figures and the all-cause mortality figure corresponds

to the non-inferiority margin translated into OR. (The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%. The non-inferiority margin was therefore 58% and the corresponding OR was 0.65. For all-cause mortality, the numbers were 3%, 13% and OR 4.8, respectively. For clinical improvement on day 30, the numbers were 77%, 67% and OR 0.61, respectively. We did not show the non-inferiority margin in the figures for severe adverse events, because the position paper did not provide any margin for this outcome.[28]) The thick solid line represents the duration-effect curve and the thick dotted lines represent its 95% CI. The 95% CI band becomes narrower when the duration range was examined by many trials or when it gets closer to the reference point. For the beneficial outcomes (clinical improvement), OR >1 means more effective. For the harmful outcomes (all-cause mortality and serious adverse events), OR <1 means safer.

The duration-effect curve is monotonic with a longer duration leading to a lower probability of improvement. The lower 95% CI curve was constantly above the prespecified

Table 1 Characteristics of included studies

Study	Age, mean (SD), years	Female, %	PSI IV+V, %	Setting	Duration, day, median	Antibiotics	No. of participants	No. of clinical improvement on day 15
Siegel et al[13]	61.1 (15.1)	NA	NA	Inpatient	7	CXM	25	21
					10		27	20
Léophonte et al[38]	64.0 (18.7)	25	NA	Inpatient	5	CRO	125	93
					10		119	85
Tellier et al[14]	45.8 (18–87*)	42	7	Both	5	TEL	193	154
					7		195	157
El Moussaoui et al[39]	57.2† (23.9†)	40	12	Inpatient	3	AMX	57	50
					8		64	56
File et al[15]	45.4 (16.8)	42	3	Outpatient	5	GMI	256	240
					7		256	234
Strålin et al[42]	NA (NA)	NA	NA	Inpatient	5	β-lactam	103	79
					10		104	81
Uranga et al[27]	65.4 (18.3)	37	39	Inpatient	5	Various	162	90
					10		150	71
Aliberti et al[40]	60.6† (24.8†)	40	24	Inpatient	6	Various	125	111
					8		135	125
Dinh et al[41]	73.2† (21.0†)	41	39	Inpatient	3	β-lactum+placebo	152	117
					8	β-lactum+AMC	151	102

*Range.
†Calculated using median and IQR.
AMC, amoxicillin-clavulanic acid; AMX, amoxicillin; CRO, ceftriaxone; CXM, cefuroxime; GMI, gemifloxacin; PSI, Pneumonia Severity Index; SAE, serious adverse events; TEL, telithromycin.
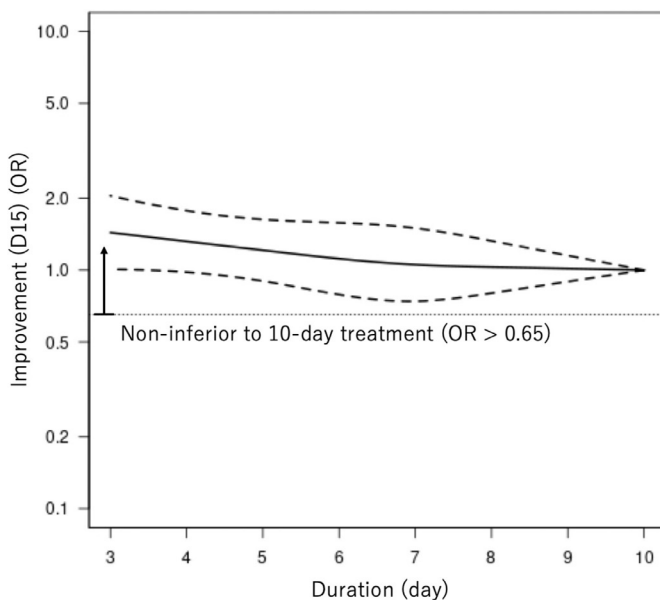
Figure 2 Duration-effect relationship of antibiotics for community-acquired pneumonia in adults. Clinical improvement on day 15. D15, day 15. The dotted lines represent 95% CIs. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 68% (OR 0.65). ORs greater than the non-inferiority threshold signifies that the treatment is non-inferior to the 10-day treatment.

non-inferiority margin, meaning that a shorter treatment duration (3–9 days) was likely to be non-inferior to the standard treatment duration (10 days). It was slightly above the OR=1 around 3-day treatment, suggesting 3-day treatment may be superior to 10-day treatment. Harmful outcome curves (all-cause mortality and severe adverse events) were almost flat and 95% CI curves did not cross the OR=1, indicating no association. Although the CI curves were wide for all-cause mortality, shorter treatment duration (3–9 days) was likely to be non-inferior to 10-day treatment. Clinical improvement on day 30 showed a similar trend with the primary outcome with the lower 95% CI curve constantly above the prespecified non-inferiority margin. We made a league table (online supplemental eAppendix 10), which showed that shorter treatment duration was likely to be non-inferior to longer treatment duration, regardless of the reference duration.

ORs need to be translated into absolute event rates so that the results can be interpreted from the clinical point of view. The weighted average percentage of clinical improvement rate on day 15 in the 10-day treatment arms was 68%, based on a single proportion meta-analysis of the included studies. Using this average, we computed the absolute clinical improvement rates at the following durations as follows: 3-day treatment 75% (95% CI: 68% to 81%), 5-day treatment 72% (95% CI: 66% to 78%) and 7-day treatment 69% (95% CI: 61% to 76%) (table 2).
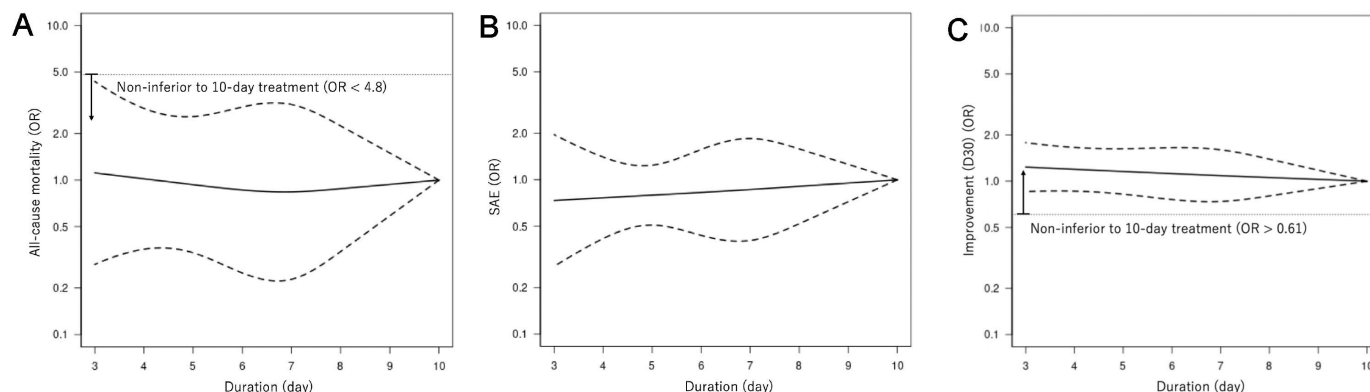
Figure 3 Duration-effect relationships of antibiotics for community-acquired pneumonia in adults. (A) All-cause mortality. (B) Severe adverse events. (C) Clinical improvement on day 30. D30, day 30. The dotted lines represent 95% CIs. The thin horizontal dotted line represents the non-inferiority margin, corresponding with 10% absolute risk difference given the control event rate of 3% (OR 4.8) in all-cause mortality and 77% (OR 0.61) in clinical improvement on day 30. SAE, serious adverse event.

Sensitivity analyses

Sensitivity analyses were in line with the primary analyses. Sensitivity analyses using different locations of knots confirmed the stability of the shape of the spline curves (online supplemental eAppendix11, figure S1). Sensitivity analyses excluding trials with an overall high risk of bias were also in agreement with the primary analyses (online supplemental eAppendix11, figure S2.1). Sensitivity analyses excluding trials with outpatients also confirmed the main findings, suggesting the results are generalisable to inpatients, except for those admitted to the intensive care unit (online supplemental eAppendix11, figure S2.2). Sensitivity analyses using the PP data set and those including only trials that used antibiotics recommended for empirical treatment of CAP by clinical guidelines also confirmed the results (online supplemental eAppendix11, figures S3 and S4). Exploratory sensitivity analyses showed that non-inferiority of the shorter duration was more likely to be the case in studies that randomised patients who had reached clinical stability early (online supplemental eAppendix11, figure S5.1 and 5.2). Furthermore, post hoc sensitivity analyses which excluded trials with substantial deviation from the day 15 measurement time (online supplemental eAppendix11, figure S5.3) and those which imputed missing data as clinically improved (online supplemental eAppendix11, figure S5.4) also aligned with the primary analyses.

DISCUSSION

To our knowledge, this is the first systematic review and duration-effect meta-analysis of antibiotics treatment for CAP in adults. The results showed that shorter treatment duration (3–9 days) was likely to be non-inferior to the standard treatment duration (10 days) for CAP in adults if they achieved clinical stability. There may be no significant difference in all-cause mortality or serious adverse events. Shorter treatment duration (3–5 days) probably achieves the optimal balance between efficacy and treatment burden. Multiple sensitivity analyses confirmed the primary findings.

This is in line with the previous pairwise meta-analyses that showed shorter duration was non-inferior to longer duration.[10–12] We updated the systematic review and found four trials that were not included in the previous studies. This allowed us to focus on trials that used the same antibiotics with the same daily dosage. The previous studies

Table 2 Primary and secondary outcomes for 3, 5, 7 and 10-day treatment

Outcome		Treatment duration (days)						
		3		5		7		10
Clinical improvement on day 15	OR	1.44	(1.01–2.05)	1.21	(0.90–1.63)	1.05	(0.74–1.50)	1.00
	Rate	75%	(68–81%)	72%	(66–78%)	69%	(61–76%)	68%
All-cause mortality	OR	1.11	(0.28–4.35)	0.93	(0.34–2.58)	0.84	(0.23–3.09)	1.00
	Rate	3%	(1–11%)	3%	(1–7%)	2%	(1–8%)	3%
Serious adverse events	OR	0.73	(0.27–1.96)	0.80	(0.51–1.24)	0.86	(0.40–1.85)	1.00
	Rate	15%	(6–31%)	16%	(11–22%)	17%	(9–30%)	19%
Clinical improvement on day 30	OR	1.24	(0.86–1.78)	1.16	(0.82–1.63)	1.09	(0.74–1.60)	1.00
	Rate	81%	(74–86%)	80%	(74–85%)	79%	(73–84%)	77%

included trials using different antibiotics or different daily dosages, so the results may not have reflected the differences in treatment durations alone. Moreover, they subcategorised the treatment durations and may have thus lost some statistical power to detect meaningful differences among durations. We overcame this limitation by examining the duration of antibiotic treatment range in days as a continuous variable and found that 3 to 9-day treatment is likely to be non-inferior to 10-day treatment. Our results are in line with the guidelines for CAP recommending antibiotics to be prescribed for a duration shorter (5–8 days) than current clinical standard practice (10 days).[4–6] Our results suggest that an even shorter duration (3–5 days) may be considered, which is in line with the trials that found 3-day treatment was non-inferior to 8-day treatment.[39 41] Possibility of 3-day treatment being superior to 10-day treatment should be carefully interpreted, as none of the included trials, previous meta-analyses[11 12] or the pairwise meta-analysis of the included trials (online supplemental eAppendix 12, post hoc analysis) showed the superiority of shorter treatment duration. This could be explained by the fact that most of the combinations of treatment durations examined (7 days vs 10 days, 5 days vs 10 days, 5 days vs 7 days, 3 days vs 8 days) suggested better efficacy of shorter durations, if not statistically significant alone (online supplemental eAppendix 12, post hoc analysis). The duration-effect meta-analysis combined these findings, leading to the possible superiority of the shortest duration examined (3 days) over the longest duration examined (10 days). Further research focusing on the shorter duration range is warranted to confirm this finding.

Limitations

Our study has several limitations. First, most of the included studies presented a moderate-to-high overall risk of bias, which compromises the validity of this meta-analysis. Second, the number of studies was small, leaving CIs for secondary outcomes wide. Third, original studies excluded patients with complications of CAP and therefore the results of this study may not be generalisable to those patients. Fourth, baseline severity of the included studies varied. We included both the outpatients and inpatients, which may have concealed important heterogeneity in the study results. However, sensitivity analyses excluding trials with outpatients generally confirmed the primary analyses (online supplemental eAppendix 11) and the overall statistical heterogeneity was low. Fifth, we did not include patients admitted to the intensive care units and the results of this study may not be generalisable to those patients. Sixth, the actual measurement day for the primary outcome in each included study varied (7–44 days) and this may have introduced between-study heterogeneity. However, post hoc sensitivity analyses excluding trials with large deviation from the day 15 measurement time were in line with the primary analyses.

Strengths

First, we did a comprehensive systematic review and found four studies that were not included in the previous systematic reviews. Second, we treated duration as a continuous variable, which allowed us to estimate the duration-effect relationship with greater resolution of change points. Third, we examined the impacts of treatment duration not only for clinical improvement but also for all-cause mortality and severe adverse events and made sure that a shorter treatment duration would not translate into more harmful events. Finally, the very nature of shortened duration treatment offers a unique opportunity for interpretation. Shorter treatment duration has been examined by non-inferiority trials. The underlying assumption has been that there was a trade-off between a loss in the efficacy of standard treatment duration and other benefits of shortened treatment duration,[46 47] such as less time, less cost and probably a diminished rate of antimicrobial resistance. This study suggests that there may be even no trade-off for antibiotic treatments of 3–5 days. The shorter treatment duration reduces the burden on patients, the healthcare system and the risk of antimicrobial resistance and might even offer better clinical outcomes at the same time.

CONCLUSIONS

Short treatment duration (3–9 days) was likely to be non-inferior to the standard treatment duration (10 days) for adults with CAP if they achieved clinical stability. Shorter range (3–5 days) probably results in an optimal balance between efficacy and treatment burden. However, the small number of included studies and the overall moderate-to-high risk of bias may compromise the certainty of the results. Further research focusing on the shorter duration range is required.

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