

Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis

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Objectives: The aim of this study was to evaluate the comparative effectiveness and safety of short (5 days) and long (7 or 10 days) duration antimicrobial treatment of patients with acute exacerbations of chronic bronchitis (AECB).

Methods: We performed a meta-analysis of randomized controlled trials (RCTs) comparing regimens of the same antibiotic (same dosage and same route of administration) administered for a different time period. We searched PubMed, the Cochrane Central Register of Controlled Trials and reference lists from publications, with no language restrictions.

Results: Of the 1031 reports retrieved initially, seven RCTs, enrolling 3083 patients with AECB, met our inclusion criteria. The antimicrobials studied in these seven RCTs were quinolones, cefixime and clarithromycin. There was no difference between the short- and long-duration therapies with regard to treatment success in intention-to-treat [relative risk (RR) = 0.99, 95% confidence interval (CI) 0.95–1.03], clinically evaluable (RR = 0.99, 95% CI 0.96–1.02) or microbiologically evaluable (RR = 0.98, 95% CI 0.93–1.02) patients. Short-duration treatment, when compared with long, was associated with fewer adverse events (RR = 0.84, 95% CI 0.72–0.97).

Conclusions: Short-duration treatment seems to be as effective as and safer than long-duration antimicrobial treatment of patients with AECB. Additional research is required to clarify the long-term outcomes (namely the exacerbation-free interval after the resolution of an initial episode) of the compared regimens.

Keywords: chronic obstructive pulmonary disease, *Streptococcus pneumoniae*, quinolones, macrolides, β -lactams

Introduction

Acute exacerbations of chronic bronchitis (AECB) have been blamed for worsening health-related quality of life,^{1,2} accelerating lung-function decline^{3,4} and increasing the costs^{5,6} associated with treatment of patients. Moreover, among individuals with AECB requiring hospital admission, almost one-third die within 6 months.⁷ By acknowledging these poor outcomes of patients with AECB, clinicians expend considerable effort to effectively manage the flares of chronic bronchitis.⁸

Given that almost half of AECB is caused by bacteria,⁹ administration of antibacterial agents, although highly debatable once, is currently regarded as a considerable part of the management of patients with AECB, in whom a bacterial aetiology of the exacerbation is suspected.^{10,11} Indeed, a plethora of relevant guidelines generally agree that patients with at least two of the following symptoms—worsening dyspnoea, increase in sputum volume and sputum purulence—should receive antimicrobial therapy; therefore, recommendations for appropriate antibacterial use have been provided.^{10,12–17} In addition, two recent meta-analyses of randomized

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controlled trials (RCTs) from our research group focused on the optimal antimicrobial regimen for patients with AECB; they revealed that advanced antibiotics are more effective than the old ones (amoxicillin, ampicillin and doxycycline),¹⁸ while there is no difference between several classes of advanced antibiotics (amoxicillin/clavulanate, respiratory quinolones and macrolides) for this purpose.¹⁹

Although the optimal regimen of antimicrobial therapy for patients with AECB has been well examined, it seems that this is not the case for optimal duration of therapy. Indeed, in a position paper on the management of AECB by the American College of Physicians, American Society of Internal Medicine and the American College of Chest Physicians, the authors noted that 'there is little evidence regarding the appropriate duration of antibiotic administration' and that 'typical administration periods range from 3 to 14 days in the relevant trials'.¹⁷ Interestingly enough, the majority of guidelines on the topic do not specify the optimal duration,^{10,13,14,16} while the European guidelines for the management of adult, lower respiratory tract infections stated that 'antibiotic treatment in patients with exacerbations of chronic obstructive pulmonary disease should be maintained at an average of 7–10 days'.¹²

Shortening the duration of antimicrobial therapy has been advocated as a potentially effective measure for decreasing the emergence of antimicrobial resistance and minimizing the costs associated with various respiratory tract infections.^{20,21} Thus, we endeavoured to investigate whether short-duration (5 days) antimicrobial treatment is as effective as and safer than long-duration (at least 7 days) treatment for the management of patients with AECB, by performing a meta-analysis of RCTs comparing regimens of the same antimicrobial agent (same dosage and same route of administration) administered for different lengths of time.

Methods

Data sources

We performed this meta-analysis by following the QUOROM statement.²² Publications archived up to October 2007 from PubMed and the Cochrane Central Register of Controlled Trials were searched for potentially eligible reports by using the terms: (chronic bronchitis *OR* chronic obstructive pulmonary disease *OR* COPD) *AND* (antibiotics *OR* antimicrobials *OR* treatment) *AND* (short *OR* long *OR* course *OR* days *OR* day *OR* duration). We repeated our search by using the terms 'chronic obstructive respiratory disease', 'chronic airways limitation' and 'emphysema'. The Cochrane query was limited to RCTs. We also searched the references of the initially located RCTs, and omitted abstracts presented at scientific conferences.

Study selection

Two investigators (S. G. A. and I. I. S.) independently carried out a literature search and evaluated the eligibility of the reports retrieved. A study was considered eligible if it was an RCT that compared the effectiveness and safety of the same antimicrobial agent administered in the same dosage and via the same route, but for a different (short versus long) duration for the treatment of patients with AECB. No restrictions on language or year of publication were set. In previously conducted meta-analyses of RCTs comparing several antimicrobial classes for the treatment of AECB,^{18,19} we excluded

reports studying quinolones that were withdrawn due to safety concerns. However, for the present meta-analysis, where the same antimicrobial agent should be in both study arms, there was no reason to omit this information. We decided *a priori* to perform a subgroup analysis by excluding the RCTs that evaluated withdrawn quinolones.

Data extraction

Two investigators (S. G. A. and I. I. S.) independently extracted the following data from each study: year of publication, characteristics of patient population (including severity of underlying disease), number of patients, antimicrobial agents administered, treatment success, adverse effects, mortality and microbiological outcomes. The methodological quality of the trials included in the meta-analysis was assessed according to a modified Jadad score, which evaluates: randomization (0–1 points), double-blinding (0–1 points), account of dropouts/withdrawals (0–1 points), description of both randomization and the blinding process (points: –1 if inappropriate, 0 if inadequate data and 1 if appropriate).²³ A Jadad score more than 2 was considered to denote good methodological quality of an RCT.

Definitions

Chronic bronchitis. Chronic bronchitis is defined as cough and production of sputum on most days for a period of at least 3 consecutive months during a minimum of 2 successive years.²⁴

AECB. AECB is the presence of increased dyspnoea, increased amount of sputum and purulence of sputum according to the Anthonisen classification. AECB was characterized as type I, II or III by the presence of three, two or one of the above symptoms, respectively.²⁵

Outcomes of the present meta-analysis. Treatment success [defined as total (cure) or partial (improvement) resolution of initial symptoms such that no additional or alternative antimicrobial treatment was required] in both intention-to-treat (ITT; i.e. all patients who received at least one dose of the study drug) and clinically evaluable (CE; i.e. the subgroup of ITT patients who completed the study protocol) patients, and drug-related adverse events in ITT patients were regarded as the primary outcomes for this study. Treatment success was assessed at 6–21 days after initiation of antimicrobial treatment in order to avoid confounding due to spontaneous resolution of infection that occurs in half of the patients with AECB 21 days after the onset of infection;²⁵ this spontaneous resolution could mitigate differences between compared antimicrobial agents. On the other hand, all-cause mortality in ITT patients during the study period, long-term outcomes of patients (namely exacerbation-free interval or frequency of exacerbations after the resolution of an initial exacerbation), withdrawals from the study, incidence of diarrhoea, treatment success in microbiologically evaluable (ME; i.e. the subgroup of CE patients who had bacteriologically proven infection) patients (defined as the absence of pre-treatment isolated bacteria in sputum cultures) and pathogen eradication (documented or presumed) of the bacteria most frequently implicated in AECB isolates (namely *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*)²⁶ were considered as secondary outcomes. When determining microbiological outcomes, we elected to assess them at the longest post-treatment time point reported in each eligible trial, in an attempt to capture possible relapses.

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Statistical analysis

Review Manager (RevMan version 4.2.8; Copenhagen: Nordic Cochrane Center, Cochrane Collaboration, 2003) was used for statistical analysis. Heterogeneity among comparisons was assessed by the I^2 statistic. The Mantel–Haenszel fixed effect model was used in order to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs) for all outcomes, when there was no statistically significant heterogeneity among the studies; otherwise, the DerSimonian–Laird random effects model was employed.

Results

Selected RCTs

Out of the 1031 RCTs that were located through searches in PubMed and the Cochrane Central Register of Controlled Trials, we excluded 1024 trials for the reasons detailed in Figure 1 (flow diagram of the selection process). Thus, seven RCTs fulfilled the inclusion criteria for the present meta-analysis.^{27–33}

In Table 1, we list the characteristics of the seven trials included in this analysis.^{27–33} These trials enrolled an average of 440 patients (range: 217–614), were multicentre and published after 1998. The majority^{27–31,33} had a Jadad score >2. Table S1 with the individual components of the Jadad scale for each of the selected RCTs^{27–33} is available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

All patients included in the eligible RCTs^{27–33} were outpatients and had a history of chronic bronchitis^{27–29,32} or chronic bronchitis/COPD.^{30,31,33} Data on severity of underlying COPD were available only for two trials,^{31,33} according to the authors of one trial,³¹ the majority of the patients in the compared groups were classified as

having medium-stage disease, while in another trial³³ the mean forced expiratory volume in the first second of the patients in the compared groups (short and long) was 48% and 47% of predicted, respectively. The eligible trials enrolled patients experiencing an AECB classified as Anthonisen type I, II, III,^{28–30} or type I, II,^{31–33} or type I.²⁷

Patients with AECB requiring hospitalization were excluded from three^{29,30,33} of the seven^{27–33} selected studies, and patients requiring parenteral antibiotics were not included in another trial.³¹ As pertains to the concomitant administration of systemic corticosteroids during AECB, five^{27–29,31,33} of the trials included did not provide relevant data; in one trial,³⁰ patients in the compared groups did not differ with regard to this, and the report of the remaining trial,³² only mentioned that ‘concomitant use of systemic steroids was permitted’.

Drugs administered

In all^{27–33} RCTs included in this meta-analysis, short-duration antimicrobial treatment lasted 5 days, while long-duration antimicrobial treatment lasted 7 or 10 days (specific data are presented in Table 1). The studied antimicrobial agents were: β -lactams (cefixime²⁷), quinolones (namely, moxifloxacin,³⁰ levofloxacin,³¹ grepafloxacin^{28,29} and gatifloxacin³²) and macrolides (clarithromycin³³) (Table 1).

Treatment success in ITT and CE patients

Data regarding treatment success in ITT population were available for four^{27,30,31,33} out of the seven^{27–33} studies included in this meta-analysis, as shown in Table 2. No difference was observed

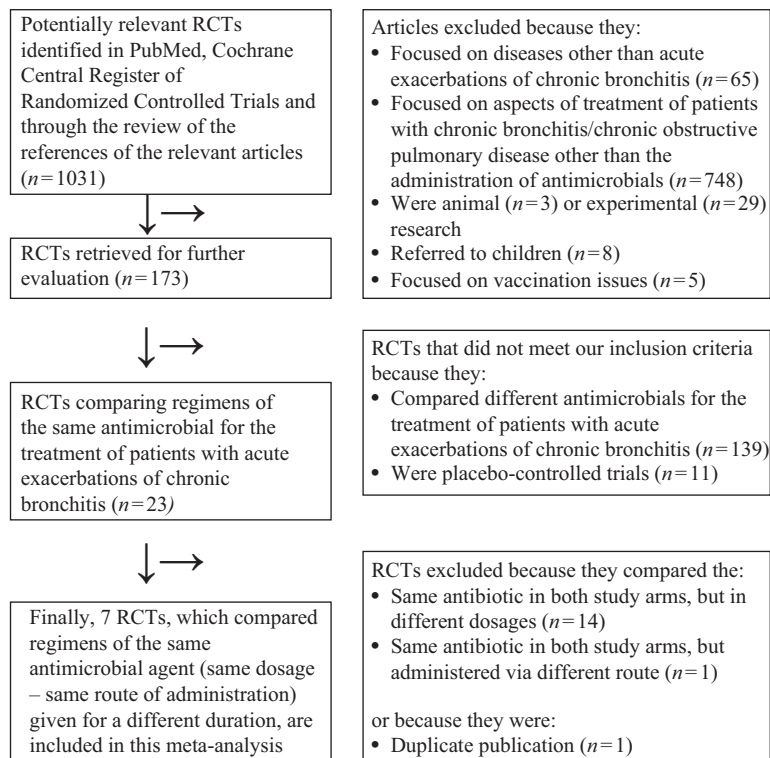


Figure 1. Flow diagram of the reviewed articles. RCTs, randomized controlled trials.

Table 1. Main characteristics of RCTs included in the meta-analysis (short versus long duration of antimicrobial administration)

First author ^{ref}	Year of publication/ country	Study design	Population	Mean age of patients (years, mean \pm SD)	Regimen 1	Regimen 2	Additional antibiotics allowed	Number of intention-to-treat patients	Study quality score ^a
Lorenz ²⁷	1998/ Germany	MC, DB, RCT	outpatients with chronic bronchitis and an Anthonisen type I AECB	56 \pm 14.3 vs 54 \pm 12.3	cefixime 400 mg every 24 h for 5 days	cefixime 400 mg every 24 h for 10 days	NA	217	4
DeAbate ²⁸	1999/USA	MC, DB, RCT	outpatients \geq 18 years with chronic bronchitis and an Anthonisen type I, II or III AECB	51 \pm 1 vs 51 \pm 1	grepafloxacin 400 mg every 24 h for 5 days	grepafloxacin 400 mg every 24 h for 10 days	none	388	4
Langan ²⁹	1999/Europe, Canada	MC, DB, RCT	outpatients \geq 18 years with chronic bronchitis and an Anthonisen type I, II or III AECB	57 vs 56	grepafloxacin 400 mg every 24 h for 5 days	grepafloxacin 400 mg every 24 h for 10 days	none	541	4
Chodosh ³⁰	2000/USA	MC, DB, RCT	outpatients aged \geq 18 years with chronic bronchitis or COPD and an Anthonisen type I, II or III AECB	57 \pm 15 vs 56 \pm 16	moxifloxacin 400 mg every 24 h for 5 days	moxifloxacin 400 mg q24 h for 10 days	none	614	5
Masterton ³¹	2001/Europe, Latin America	MC, DB, RCT	outpatients aged \geq 18 years with chronic bronchitis or COPD and an Anthonisen type I or II AECB	61 \pm 14 vs 60 \pm 13	levofloxacin 500 mg every 24 h for 5 days	levofloxacin 500 mg every 24 h for 7 days	none	530	3
Gotfried ³²	2001/USA	MC, DB, RCT	outpatients \geq 18 years with chronic bronchitis and an Anthonisen type I or II AECB ^b	48 \pm 15 vs 49 \pm 15	gatifloxacin 400 mg every 24 h for 5 days	gatifloxacin 400 mg every 24 h for 7 days	none	349	2
Gotfried ³³	2005/North America	MC, DB, RCT	outpatients aged \geq 40 years with chronic bronchitis or COPD and an Anthonisen type I or II AECB	62 \pm 12 vs 62 \pm 12	clarithromycin ER 1000 mg every 24 h for 5 days	clarithromycin IR 500 mg every 12 h for 7 days	none	444	4

MC, multicentre; DB, double-blind; RCT, randomized controlled trial; AECB, acute exacerbations of chronic bronchitis; COPD, chronic obstructive pulmonary disease; ER, extended-release; IR, immediate-release; vs, versus.

All antibiotics were administered per os.

^aAccording to a modified Jadad score.

^bIn this trial, one patient of the short-duration arm experienced an Anthonisen type III AECB.

Table 2. Outcome data from the selected RCTs for the meta-analysis (short versus long duration of antimicrobial administration)

First author ^{ref}	Treatment success, n/N (%)			Drug-related adverse effects, n/N (%)			All-cause mortality, n/N (%)
	intention-to-treat patients	clinically evaluable patients	total	withdrawn patients from RCTs	diarrhoea		
Lorenz ²⁷	95/108 (88)	77/85 (91)	15/110 (14)	12/110 (11)	NA	NA	NA
DeAbate ²⁸	NA	128/155 (83)	56/195 (29)	2/195 (1)	6/195 (3)	6/193 (3)	NA
Langan ²⁹	NA	142/156 (91)	NA	5/273 (2)	3/273 (1)	5/268 (2)	1/273 (0.4)
Chodosh ³⁰	274/288 (95)	127/135 (94)	81/312 (26)	NA	15/312 (5)	18/302 (6)	1/312 (0.3)
Masterton ³¹	222/268 (83)	197/238 (83)	52/268 (19)	NA	13/268 (5)	7/262 (3)	0/268 (0)
Gotfried ³²	NA	135/151 (89)	no clinically meaningful difference ^a	NA	12/174 (7)	11/175 (6)	0/174 (0)
Gotfried ³³	158/218 (72)	157/187 (84)	31/240 (13)	6/240 (3)	NA	4/245 (2)	NA

NA, not available/applicable; vs, versus.
 Treatment success was evaluated 6–21 days after the initiation of antimicrobial treatment.
^aAccording to the authors of this trial.

between ITT patients with AECB receiving the same antimicrobial for short versus long periods (1760 patients: RR = 0.99, 95% CI 0.95–1.03). The RRs for all outcomes of this meta-analysis were calculated by using a fixed effect model, because no heterogeneity was detected among comparisons.

Information dealing with treatment success in CE population was available for all seven RCTs.^{27–33} There was no difference between short- and long-duration regimens for the treatment of CE patients with AECB (2242 patients: RR = 0.99, 95% CI 0.96–1.02). The RRs for the treatment success of the compared antibiotics for the CE patients in the individual RCTs, as well as the pooled RR, are presented in Figure 2. This finding (i.e. the equivalence of comparators for treatment success) did not substantially change after the exclusion of three^{28,29,32} trials studying quinolones (grepafloxacin and gatifloxacin), which were withdrawn due to safety issues (1319 CE patients: RR = 0.99, 95% CI 0.95–1.03; data from four trials^{27,30,31,33}), the exclusion of one³³ trial studying different formulations of clarithromycin (namely extended- and immediate-release) (1851 CE patients: RR = 0.99, 95% CI 0.96–1.03; data from six trials^{27–32}) or the exclusion of one³² trial with Jadad score equal to 2 (1937 CE patients: RR = 0.99, 95% CI 0.96–1.02; data from six trials^{27–31,33}).

Similarly, in a subgroup analysis including trials that enrolled only patients with Anthonisen type I or II AECB, no difference was revealed between patients who received short-versus long-duration antibiotic therapy regarding treatment success (1345 CE patients: RR = 1.00, 95% CI 0.95–1.04; data from four trials^{27,31–33}). This was also the case for the subgroup analyses of RCTs having a long duration of 10 days (1064 CE patients: RR = 0.99, 95% CI 0.95–1.03; data from four trials^{27–30}) or 7 days (1178 CE patients: RR = 0.99, 95% CI 0.95–1.04; data from three trials^{31–33}).

Adverse events

Out of the seven^{27–33} eligible trials, five^{27,28,30,31,33} reported data on drug-related adverse events of ITT patients, while the authors of another eligible trial³² mentioned only that there was ‘no clinically meaningful difference’ between comparators regarding this outcome. Patients with AECB who received short- compared with long-duration antimicrobial therapy experienced fewer adverse events (2238 patients: RR = 0.84, 95% CI 0.72–0.97) (Figure 3).

Data regarding the number of ITT patients who withdrew from the included RCTs due to drug-related adverse events or who experienced diarrhoea were provided by four^{27–29,33} and five^{28–32} RCTs, respectively. No difference was found between the compared groups with regard to the number of patients withdrawn due to toxicity (1635 patients: RR = 0.93, 95% CI 0.55–1.57) and the number of patients with drug-related diarrhoea (2422 patients: RR = 1.02, 95% CI 0.69–1.51).

All-cause mortality

Data on all-cause mortality were available for four^{29–32} RCTs included in this meta-analysis. We observed no difference regarding mortality between short- and long-duration antimicrobial regimens for the treatment of ITT patients with AECB (2034 patients: RR = 0.73, 95% CI 0.16–3.27).

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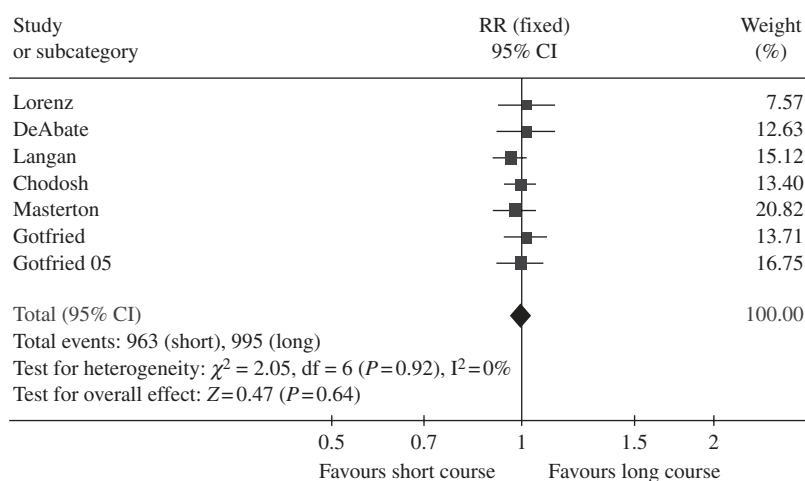


Figure 2. Treatment success in clinically evaluable patients with AECB in RCTs comparing short- versus long-duration antimicrobial treatment. Vertical line denotes the 'no difference' point between the two regimens. Square denotes the relative risk; the size of each square denotes the proportion of information given by each trial. Diamond denotes the pooled relative risk for all RCTs. Horizontal lines denotes the 95% CI.

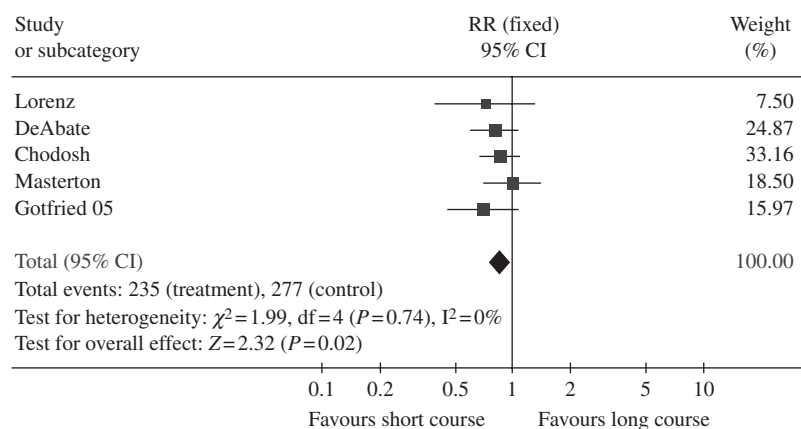


Figure 3. Drug-related adverse events in patients with AECB in RCTs comparing short- versus long-duration antimicrobial treatment. Vertical line denotes the 'no difference' point between the two regimens. Square denotes the relative risk; the size of each square denotes the proportion of information given by each trial. Diamond denotes the pooled relative risk for all RCTs. Horizontal lines denotes the 95% CI.

Long-term outcomes

None of the RCTs²⁷⁻³³ included in the meta-analysis provided data on long-term outcomes of patients with AECB, namely exacerbation-free interval or frequency of exacerbations after the resolution of an initial exacerbation.

Microbiological outcomes

Microbiological outcomes extracted from the individual trials are presented in Table 3. Information dealing with treatment success in ME patients was provided by all trials included in the analysis.²⁷⁻³³ The follow-up period for the evaluation of microbiological outcomes was extended up to 38 days after the initiation of antimicrobial treatment in the eligible trials. No difference was revealed between short and long duration regarding treatment success in ME patients with AECB (1372 ME patients: RR = 0.98, 95% CI 0.93-1.02).

In addition, based on the data provided by five^{28-31,33} of the seven²⁷⁻³³ eligible trials, there was no difference between the

compared groups regarding the eradication of *H. influenzae* (379 isolates: RR = 1.00, 95% CI 0.91-1.09), *M. catarrhalis* (193 isolates: RR = 0.94, 95% CI 0.83-1.06) and *S. pneumoniae* (148 isolates: RR = 1.01, 95% CI 0.86-1.19).

Discussion

By accumulating data from 3083 individuals, the findings of the present meta-analysis suggest that short-duration antimicrobial treatment as opposed to long-duration treatment of patients with AECB is not associated with lower treatment success in ITT, CE or ME patients. This finding persisted in the various subgroup analyses that we carried out, which further strengthens our finding. In addition, patients with AECB receiving antibiotics for 5 days experienced fewer adverse events than those receiving them for 7 or 10 days.

The findings of the present meta-analysis may help in the completion of the relevant guidelines that were recently released

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Table 3. Microbiological outcomes from the selected RCTs for the meta-analysis (short versus long duration of antimicrobial administration)

First author ^{ref}	Treatment success (microbiological evaluation)	Pathogen eradication, n/N (%)		
		<i>H. influenzae</i>	<i>M. catarrhalis</i>	<i>S. pneumoniae</i>
Lorenz ²⁷	25/35 (71) vs 14/17 (82)	NA	NA	NA
DeAbate ²⁸	104/138 (75) vs 94/123 (76)	31/35 (89) vs 35/47 (74)	11/12 (92) vs 9/11 (82)	11/14 (79) vs 5/7 (71)
Langan ²⁹	58/89 (65) vs 58/86 (67)	27/40 (68) vs 34/43 (79)	7/12 (58) vs 9/15 (60)	8/14 (57) vs 4/9 (44)
Chodosh ³⁰	130/149 (87) vs 144/159 (91)	33/37 (89) vs 31/32 (97)	29/34 (85) vs 26/27 (96)	16/16 (100) vs 20/21 (95)
Masterton ³¹	85/112 (76) vs 80/101 (79)	30/34 (88) vs 26/33 (79)	13/18 (72) vs 19/20 (95)	9/12 (75) vs 13/16 (81)
Gotfried ³²	85/87 (98) vs 75/80 (94) ^a	NA	NA	NA
Gotfried ³³	82/94 (87) vs 91/102 (89)	35/40 (88) vs 35/38 (92)	24/26 (92) vs 15/18 (83)	15/19 (79) vs 17/20 (85)

NA, not available/applicable.

Treatment success was evaluated up to 38 days after the initiation of antimicrobial treatment.

^aIn this trial, patients in whom a resistant pathogen was isolated were excluded.

by the European Respiratory Society in collaboration with the European Society for Clinical Microbiology and Infectious Diseases.¹² They recommended the administration of antimicrobials in such patients at an average of 7–10 days;¹² a period that may be excessive on the basis of our findings. Finally, our contribution underlines the need for the various organizational guidelines to establish recommendations regarding the optimal duration of antibiotic therapy of patients with AECB; this is the rule for other lower respiratory tract infections, such as pneumonia.

The results of the present study appear to be in line with those of other investigations that have explored the effectiveness of short-duration antimicrobial treatment for patients with lower respiratory tract infections other than AECB. For instance, short course chemotherapy for the management of patients with latent tuberculosis has been supported by a recent meta-analysis.³⁴ Additionally, in ventilator-associated pneumonia, it was revealed that patients who received 8 (short-course) versus 15 days (long-course) appropriate antibiotic treatment did not differ with regard to clinical effectiveness in terms of mortality.³⁵ Finally, in a recently published meta-analysis of RCTs comparing different durations of antimicrobial therapy for patients with community-acquired pneumonia, it was inferred that a short-course is comparable to long-course regarding effectiveness.³⁶ Our meta-analysis is methodologically even more rigorous than the above meta-analysis,³⁶ because we included only RCTs that compared the same antimicrobial agent, administered at the same dose via the same route in both study arms.

The fact that the majority of eligible RCTs did not enrol patients with AECB requiring hospitalization and/or parenteral antibiotics should be taken into consideration.^{29–31,33} First, due to the paucity of relevant data in the meta-analysis of the RCTs that were included, we could not examine the optimal duration of antimicrobial treatment of patients with AECB who needed hospital admission. Second, the results of our study are valid only for patients with mild or moderate AECB. Unfortunately, the majority of reports included in this analysis did not provide specific data on clinical outcomes of patients with various degrees of severity of AECB.^{27–30,32,33} However, in the RCT by Masterton *et al.*,³¹ which compared 5 and 7 day regimens of levofloxacin for the treatment of AECB, a subgroup analysis of

patients with severe exacerbation was reported. Clinical success in ITT patients with severe AECB receiving short- or long-duration levofloxacin treatment was 88% and 78%, respectively.³¹ Thus, although a more conservative interpretation of our findings suggests that they are applicable only to patients with mild or moderate AECB, one could argue that they might also be potentially extrapolated to patients with severe AECB, on the basis of the above limited evidence.

We acknowledge that the present meta-analysis has limitations, as has any meta-analysis in the field of antimicrobial treatment of AECB, entailed by the study design of the individual RCTs included in it. Indeed, eligible comparative trials were powered to demonstrate equivalence rather than reveal superiority of one regimen over another. Second, in three^{28–30} out of the seven^{27–33} eligible trials, patients with Anthonisen III AECB were enrolled; such patients should not have received antimicrobials at all based on the current guidelines.^{10,12–17} To address this issue, we performed a subgroup analysis by excluding these reports;^{28–30} no difference was revealed between patients with Anthonisen I/II AECB receiving short- or long-duration treatment.

Third, we should note that in the majority of the eligible RCTs,^{27–32} spirometry was not performed at study entry to confirm diagnosis of COPD, and patients older than 18 years could be enrolled; development of chronic bronchitis in subjects younger than 35 years is extremely rare. Fourth, no data were available from eligible studies regarding long-term outcomes, such as exacerbation-free interval or frequency of exacerbations (recurrences) after the resolution of an initial episode of AECB. The importance of such outcomes has been recognized in the field of AECB¹¹ and it is further emphasized by the evidence that short-duration antimicrobial treatment as opposed to long-duration treatment for patients with lower respiratory tract infections may lead more commonly to relapse, at least in the setting of nosocomial *Pseudomonas aeruginosa* pneumonia.³⁵

Fifth, although our meta-analysis included RCTs comparing different classes of antimicrobials (namely β -lactams, respiratory quinolones and macrolides), which are widely used for the treatment of patients with AECB, we should note that its results rely mainly on evidence derived from trials involving quinolones, which generally are not considered as first-choice antibiotics for

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this purpose. This might be taken into consideration in the generalizability of the results of this meta-analysis. Finally, one may question our decision not to exclude the trial³³ that compared extended- versus immediate-release clarithromycin with the rationale that they are different formulations. However, extended-release clarithromycin was manufactured in order to improve patient compliance (through once-daily instead of twice-daily administration) and tolerability (through prolongation of its absorption from the gastrointestinal tract) of clarithromycin; not to lengthen its half-life at respiratory sites of infection.³⁷ Thus, inclusion of the RCT studying clarithromycin seems not to confound the results of the meta-analysis; besides, in a subgroup analysis that we performed by excluding this RCT,³³ no difference was revealed between the compared groups in terms of treatment success.

In conclusion, despite its limitations, we believe that the findings of the present study are of clinical value. Short-duration antimicrobial treatment of patients with AECB was found to be as effective as and safer than long-duration antimicrobial treatment. These results are valid at least in patients with AECB who do not require hospitalization. Further research is warranted to clarify the long-term outcomes of patients with AECB receiving short-duration antimicrobial treatment.

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None.

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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