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Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis

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ABSTRACT: The comparative effectiveness and safety of macrolides, quinolones and amoxicillin/clavulanate (A/C) for the treatment of patients with acute bacterial exacerbation of chronic bronchitis (ABECB) was evaluated in the present study.

PubMed, Current Contents and the Cochrane Central Register of Controlled Trials were searched to identify relevant randomised controlled trials (RCTs).

In total, 19 RCTs (20 comparisons) were included in the present analysis. There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, A/C and quinolones or A/C and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared with quinolones (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.31–0.69). Fewer quinolone-recipients experienced a recurrence of ABECB after resolution of the initial episode compared with macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of A/C was associated with more adverse effects (mainly diarrhoea) than quinolones (OR 1.36, 95% CI 1.01–1.85).

Macrolides, quinolones and amoxicillin/clavulanate may be considered equivalent for the treatment of patients with an acute bacterial exacerbation of chronic bronchitis in terms of short-term effectiveness. Quinolones are associated with better microbiological success and fewer recurrences of acute bacterial exacerbation of chronic bronchitis than macrolides, while amoxicillin/clavulanate is associated with more adverse effects than both comparators.

KEYWORDS: Chronic obstructive pulmonary disease, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*

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STATEMENT OF INTEREST
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Chronic bronchitis (CB), a disease of continuously increasing prevalence [1] that is associated with considerable morbidity, mortality and cost, is characterised by intermittent exacerbations manifesting with at least one of the following symptoms: increased dyspnoea; sputum production; and sputum purulence [2]. There is evidence that flares of CB contribute to a progressive loss of lung function [3], have a major impact on quality of life [4] and account for a significant proportion of the cost of caring for these patients [5]. In addition, exacerbations of CB requiring hospitalisation are associated with an in-patient mortality of 3–4% [6], while 50% of hospitalised patients who recover are readmitted at least once in the ensuing 6 months [7, 8]. Thus, appropriate treatment of CB exacerbations should be compulsory.

At least 50% of CB exacerbations are not bacterial in origin and, therefore, administration of antimicrobial agents must be avoided. Only for the remaining half of CB exacerbations, which are presumably caused by bacteria, does use of antibiotics seem to be of value [9]. Indeed, two meta-analyses of randomised controlled trials (RCTs) performed in patients with acute CB exacerbations and comparing antibiotic with placebo, agreed that in CB exacerbations with increased cough and sputum purulence, antibiotics, regardless of choice, are beneficial [10, 11].

Although the beneficial role of antimicrobial agents for the management of patients with acute bacterial exacerbations of CB (ABECB) is supported by adequate evidence, controversy remains as to whether the choice of antibiotic has any impact on the outcomes of such patients [12]. Recent guidelines recommend the use of amoxicillin, trimethoprim (TMP)/sulfamethoxazole (SMX) and doxycycline for the treatment of patients with ABECB [13, 14]. However, the

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recommended first-line agents now have limited *in vitro* activity against a considerable proportion of pathogens frequently implicated in ABECB (*i.e. Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*) due to the emergence of antimicrobial resistance in these bacteria. Moreover, a retrospective analysis of patients with ABECB showed that the administration of a broader spectrum antimicrobial agent (azithromycin, quinolone or amoxicillin/clavulanate (A/C)) was associated with fewer clinical failures compared with the use of first-line agents (mainly amoxicillin, TMP/SMX, and doxycycline) [15].

Macrolides, quinolones and A/C have been used extensively for the management of patients with ABECB. The present study sought to further clarify the role of broader spectrum antimicrobial agents for the treatment of patients with ABECB by performing a meta-analysis of RCTs that compared macrolides with quinolones, A/C with quinolones or A/C with macrolides in this population.

METHODS

Data sources

A systematic literature search was conducted of PubMed (until May 2006), Current Contents and the Cochrane Central Register of Controlled Trials to identify relevant RCTs. The search strategy was as follows: ''chronic obstructive pulmonary disease'' OR ''chronic bronchitis'', AND ''amoxicillin/clavulanic'' OR ''macrolides'' OR ''clarithromycin'' OR ''azithromycin'' OR ''quinolones'' OR ''levofloxacin'' OR ''moxifloxacin'' OR ''gemifloxacin''. Searches were limited to RCTs only. In addition, references of the initially identified articles were hand-searched and reviewed, including relevant review papers. Abstracts presented in scientific conferences were not searched for.

Study selection

Two investigators (I.P. Korbila and I.I. Siempos) independently performed the literature search and examined the relevant retrieved articles for further evaluation of data on effectiveness and toxicity. To be included in the analysis, a study had to be an RCT, study the role of macrolides in comparison with quinolones or the role of A/C in comparison with macrolides or quinolones for the treatment of patients with ABECB and report data on effectiveness, toxicity and/or mortality, in the groups of patients receiving the compared therapeutic regimens. No restriction in time of publication was set. Only RCTs written in English, French, German or Italian were included in the analysis. Trials with both blind and unblind design were included in the current analysis. RCTs conducted in both hospitalised patients and outpatients were included in the meta-analysis. Exclusion criteria included trials that compared macrolides, quinolones or A/C with an antibiotic other than one from these classes of antimicrobial agents, or compared with placebo for the treatment of ABECB patients. RCTs in which the same antibiotic or antibiotics of the same antimicrobial class were in both study arms were excluded. RCTs in which the study drug has not been commercially available or is no longer used for the treatment of patients with ABECB were also excluded. Finally, RCTs that compared a ketolide (such as telithromycin) with a quinolone or A/C for the treatment of patients with ABECB were also omitted.

Data extraction

Two reviewers (I.P. Korbila and I.I. Siempos) independently extracted and recorded data on a predefined checklist. Discrepancies were resolved by consensus or referral to a third reviewer (M.E. Falagas). Extracted data included the following: 1) year of publication; 2) patient population; 3) number of patients (enrolled, intention-to-treat (ITT) and clinically evaluable (CE)); 4) use of systemic corticosteroids before ABECB; 5) antimicrobial agents and doses administered; 6) clinical and microbiological outcomes; 7) mortality; and 8) toxicity outcomes. In addition, the two reviewers independently evaluated the methodological quality of each RCT by assessing the following components: 1) randomisation; 2) generation of random numbers; 3) details of double-blinding procedure; 4) information on withdrawals; and 5) concealment of allocation. One point was awarded for the specification of each criterion; the maximum score for a study was five. High-quality RCTs were considered as those that scored $\geqslant 3$ points (low-quality RCTs were those that scored $\leqslant 2$ points) according to a modified Jadad score [16].

Definition of CB and ABECB

The criterion used for the diagnosis of CB in all RCTs included in the meta-analysis was a medical history of cough and expectoration on most days during at least three consecutive months in each of two or more consecutive years. Moreover, the ABECB had to be classified according to symptoms described by ANTHONISEN *et al.* [2] as follows. Type I who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea. Type II who met two of the above three criteria. Type III who met only one of the above three criteria.

Analysed outcomes

Primary outcome measures for the present meta-analysis were considered as treatment success (cure defined as resolution of all symptoms and signs of the bacterial exacerbation with a return to baseline condition, or improvement defined as subsidence of the ABECB but with an incomplete return to baseline condition) in ITT and CE patients, need for hospitalisation during the study period in ITT patients, all-cause mortality in ITT patients and adverse effects (in ITT patients) were probably or possibly related to study antibiotics. The effectiveness of the therapeutic regimen was evaluated at the test-of-cure visit, performed 6–21 days after the onset of the ABECB. Patients considered as CE in the individual RCTs who had an indeterminate clinical outcome at the test-of-cure visit were deemed unevaluable for the treatment success analysis. All-cause mortality was analysed based on the reported data for mortality during the study period (*e.g.* during the treatment and follow-up period) in the ITT population. Secondary outcome measures were considered as the number of patients without recurrence of ABECB after treatment of the initial ABECB episode with macrolides, quinolones or A/C over a period of $\geqslant 26$ weeks, adverse effects (any adverse effect, diarrhoea and the number of patients withdrawn from the RCTs due to drug-related adverse effects), treatment success in the microbiologically evaluable (ME) patients, and pathogen eradication (documented or presumed) of *H. influenzae, M. catarrhalis* and *S. pneumoniae*.

Data analysis and statistical methods

The heterogeneity between RCTs was assessed using the I-squared statistic [17]. Publication (sample size) bias was assessed by the funnel plot method using Egger's test [18]. Pooled odds ratios (ORs) and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated using the DERSIMONIAN-LAIRD [19] random effects models.

RESULTS

Selected RCTs

The process of identifying eligible studies is presented in figure 1. Search criteria identified 157 potentially relevant RCTs; one additional RCT that was not captured in the search of the electronic databases was found through the review of the references of the relevant articles. Of these 158 articles, 107 articles were excluded from this meta-analysis for the reasons presented in figure 1. In addition, 28 RCTs were not included in the analysis as the administered quinolone (*i.e.* ciprofloxacin, sparfloxacin, trovafloxacin, ofloxacin, gatifloxacin and grepafloxacin) is not used for the treatment of ABECB or it was withdrawn from the market due to serious adverse effects. Another RCT was excluded because the comparison regarded telithromycin with A/C [20]. Finally, from two RCTs [21, 22] that compared moxifloxacin with clarithromycin, cefuroxime/axetil and amoxicillin, specific data regarding the clinical outcomes of the clarithromycin recipients could not be extracted. Similarly, in one RCT [23] in which azithromycin was compared with A/C for the treatment of patients with various acute lower tract respiratory infections (including ABECB), specific data on clinical outcomes of patients with ABECB could not be extracted. Thus, 19 RCTs that compared macrolides with quinolones (n=8) [24–31] and A/C with quinolones (n=4) [24, 32–34] or macrolides (n=8) [35–42] were included in the meta-analysis. In one RCT [24] the quinolone levofloxacin was compared with both a macrolide (azithromycin) and A/C.

Table 1 summarises the characteristics of the 19 RCTs, representing 7,405 patients included in the meta-analysis. The mean quality score of the analysed trials was 3.2 (range 1–5), which was considered good. The quality of 13 RCTs [24–26, 28–31, 34–38, 40] was high ($\geqslant$3), while the quality of the remaining 6 RCTs [27, 32, 33, 39, 41, 42] was low.

All patients enrolled in the RCTs of the meta-analysis were $\geqslant$18 yrs old, not hospitalised during enrolment (except for one RCT [41] in which both in-patients and outpatients were enrolled) and could be treated on an in-patient or outpatient basis. There was a medical history of CB or CB/chronic obstructive pulmonary disease (COPD) in 16 [24–28, 31–34, 36–42] and two [29, 30] RCTs, respectively; in one RCT [26] patients with COPD other than CB were excluded, while in another RCT [35] only patients with COPD (baseline forced expiratory volume in one second (FEV_1) <70% predicted) were included. Patients presented with ABECB characterised as Anthonisen type I, II or III in two RCTs [29, 30] (in these two RCTs a macrolide was compared with a quinolone), or Anthonisen type I or II in 10 RCTs [24–27, 31, 33, 36, 38, 40, 41]. In contrast, in the remaining RCTs [28, 32, 34, 35, 37, 39, 42] only patients with an Anthonisen type I [28, 34, 35, 37, 39] or type II [32, 42] ABECB were enrolled.

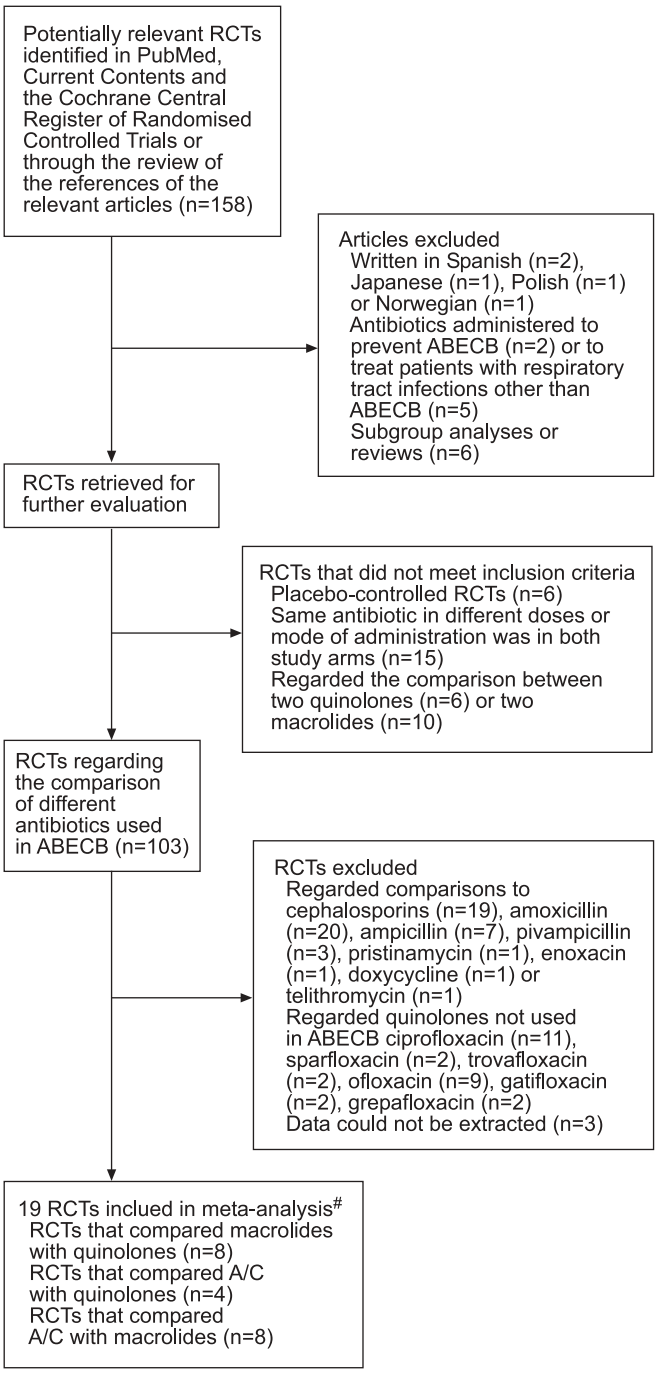

FIGURE 1. Flow diagram of reviewed articles. RCTs: randomised controlled trials; ABECB: acute bacterial exacerbation of chronic bronchitis; A/C: amoxicillin/clavulanate. #: In one RCT the quinolone levofloxacin was compared with both a macrolide (azithromycin) and A/C.

In nine RCTs, data regarding the use of systemic corticosteroids before the occurrence of ABECB [26, 27, 30, 33, 37–40, 42] were not provided, while in four RCTs the use of systemic corticosteroids at a dose of $\geqslant$10 mg of prednisone [25, 41] or at any dose [34, 36] was an exclusion criterion. In the six RCTs [24, 28, 29, 31, 32, 35] in which relevant data were provided, there was no statistically significant difference regarding the use of systemic corticosteroids at baseline between the compared groups. However, administration of systemic

TABLE 1 Main characteristics of randomised controlled trials (RCTs) included in the meta-analysis

First author [Ref.]	Publication yr	Study design	Population#	Regimen 1¶	Regimen 2	Additional antibiotics allowed	Systemic corticosteroid before ABECB	Enrolled patients n	ITT patients n	Study quality score+
Macrolides *versus* quinolones										
MARTINEZ [24]	2005	MC, DB, RCT	Aged ⩾18 yrs with CB and type I or II ABECB	Azithromycin 500 mg q24 h day 1 and 250 mg q24 h days 2–5	Levofloxacin 750 mg q24 h for 3 days	None	15/151 (10) *versus* 16/143 (11)	394	202 *versus* 192	4
LODE [25]	2004	MC, DB, RCT	Aged >35 yrs with CB and type I or II ABECB	Clarithromycin 250 mg q12 h for 10 days	Levofloxacin 500 mg q24 h for 7 days	None	NA§	511	254 *versus* 250	4
AMSDEN [26]	2003	MC, DB, RCT	Aged 35–75 yrs with CB and type I or II ABECB/	Azithromycin 500 mg q24 h day 1 and 250 mg q24 h days 2–5	Levofloxacin 500 mg q24 h for 7 days	None	NA	235	118 *versus* 117	3
WEISS [27]	2002	MC, RCT	Aged ⩾18 yrs with CB and type I or II ABECB	Clarithromycin 500 mg q12 h for 10 days	Levofloxacin 500 mg q24 h for 10 days	None	NA	191	97 *versus* 94	1
WILSON [28]	2002	MC, DB, RCT	Aged >40 yrs with CB and type I ABECB	Clarithromycin 500 mg q12 h for 7 days	Gemifloxacin 320 mg q24 h for 5 days	None	76/358 (21) *versus* 74/351 (21)§	712	358 *versus* 351	3
CHODOSH [29]	2000	MC, DB, RCT	Aged ⩾18 yrs with CB or COPD with type I,II or III ABECB	Clarithromycin 500 mg q12 h for 10 days	Moxifloxacin 400 mg q24 h for 5 or 10 days	None	74/312 (24) *versus* 134/614 (22)	936	312 *versus* 614	5
DEABATE [30]	2000	MC, DB, RCT	Aged ⩾18 yrs with CB or COPD with type I, II or III ABECB	Azithromycin 500 mg q24 h day 1 then 250 mg q24 h for 4 days	Moxifloxacin 400 mg q24 h for 5 days	None	NA	567	284 *versus* 283	5
WILSON [31]	1999	MC, DB, RCT	Aged ⩾18 yrs with CB and type I or II ABECB	Clarithromycin 500 mg q12 h for 7 days	Moxifloxacin 400 mg q24 h for 5 days	None	128/327 (39) *versus* 160/322 (50)##	750	371 *versus* 374	4
A/C *versus* quinolones										
MARTINEZ [24]	2005	MC, RCT	Aged⩾18 yrs with CB and type I or II ABECB	A/C 875/125 mg q12 h for 10 days	Levofloxacin 750 mg q24 h for 5 days	None	17/126 (14) *versus* 20/120 (17)	369	182 *versus* 187	2
STARAKIS [32]	2004	RCT	Aged ⩾18 yrs with CB and type II ABECB	A/C 500/125 mg q8 h for 7 days	Moxifloxacin 400 mg q24 h for 5 days	None	32/74 (43) *versus* 38/79 (48)	162	79 *versus* 83	2
SCHABERG [33]	2001	MC, RCT	Aged ⩾18 ys with CB and type I or II ABECB	A/C 500/125 mg q12 h for 7 days	Moxifloxacin 400 mg q24 h for 5 days	None	NA	577	283 *versus* 292	1
FILE [34]	2000	MC, DB, RCT	Aged ⩾40 yrs with CB and type I ABECB	A/C 500/125 mg q8 h for 7 days	Gemifloxacin 320 mg q24 h for 5 days	None	0/296 (0) *versus* 0/304 (0)¶¶	600	296 *versus* 304	4
A/C *versus* macrolides										
ANZUETO [35]	2001	MC, IB, RCT	Aged ⩾40 yrs with COPD (FEV_1 ⩽70% pred) and type I ABECB	A/C 875/125 mg q12 h for 10 days	Clarithromycin 1000 mg q24 h for 7 days	None	Treatment groups with comparable steroid use++	287	143 *versus* 140	4
MARTINOT [36]	2001	MC, IB, RCT	Aged ⩾35 yrs with CB and type I or II ABECB	A/C 500/125 mg q8 h for 7 days	Clarithromycin 500 mg q24 h for 7 days	None	0/123 (0) *versus* 0/127 (0)¶¶	250	123 *versus* 127	4

TABLE 1 (*Continued.*)

First author [Ref.]	Publication yr	Study design	Population[#]	Regimen 1[¶]	Regimen 2	Additional antibiotics allowed	Systemic corticosteroid before ABECB	Enrolled patients n	ITT patients n	Study quality score[+]
HOEFELMAN [37]	1997	MC, DB, RCT	Aged ⩾18 yrs with CB and type I ABECB	A/C 500/125 mg q8 h for 10 days	Azithromycin 500 mg q24 h for 3 days	None	NA	123	61 *versus* 62	4
VAN ROYEN [38]	1997	MC, RCT	Aged ⩾18 yrs with CB and type I or II ABECB	A/C 500/125 mg q8 h for 7 or 10 days	Dirithromycin 500 mg q24 h for 5 days	None	NA	334	165 *versus* 169	3
BIEBUYCK [39]	1996	MC, RCT	Aged ⩾18 yrs with CB and type I ABECB	A/C 500/125 mg q8 h for 5 or 10 days	Azithromycin 250 mg q12 h for 3 days	None	NA	139	45 *versus* 94	2
GRIS [40]	1996	MC, DB, RCT	Aged ⩾18 yrs with CB and type I or II ABECB	A/C 500/125 mg q8 h for 10 days	Azithromycin 500 mg q24 h for 3 days	None	NA	61	28 *versus* 33	4
BEGHI [41]	1995	MC, RCT	Aged ⩾18 yrs with CB and type I or II ABECB[§§]	A/C 875/125 mg q12 h for 8 days	Azithromycin 500 mg q24 h for 3 days	None	Allowed, ⩽25 mg·day^{-1}[++]	142	73 *versus* 69	2
DAUTZENBERG [42]	1992	MC, RCT	Aged ⩾18 yrs with CB and type II ABECB	A/C 500/125 mg q8 h for 14 days	Roxithromycin 150 mg q12 h for 14 days	None	NA	65	33 *versus* 32	1

Data are presented as n (patients affected)/total number of patients in the study (%), unless otherwise stated. ABECB: acute bacterial exacerbation of chronic bronchitis (CB); ITT: intention-to-treat; A/C: amoxicillin/clavulanate; MC: multicentre; DB: double-blind; NA: not applicable; COPD: chronic obstructive pulmonary disease; IB: investigator blinded; FEV1: forced expiratory volume in one second; % pred; % predicted. [#]: ABECB classified according to ANTHONISEN *et al.* [2]; [¶]: all antibiotics were administered *per os*; [+]: according to a modified Jadad score; [§]: use of systemic corticosteroids at a dose of >10 mg prednisone or the equivalent was an exclusion criterion; [f]: patients with COPD other than CB were excluded from this RCT; [##]: refers to clinically evaluable patients who received inhaled, oral or *i.v.* corticosteroids; [¶¶]: use of systemic corticosteroids at any dose was an exclusion criterion; [++]: according to the authors; [§§]: both hospitalised patients and outpatients were included. In the RCT by MARTINEZ *et al.* [24] the quinolone levofloxacin was compared with both a macrolide (azithromycin) and A/C.

corticosteroids during ABECB was permitted in four trials [26, 33, 35, 37]; in two of these [33, 35], the treatment groups were comparable with respect to the use of corticosteroids during exacerbation, while in the other two RCTs [26, 37] the authors reported that corticosteroids were permitted without giving more details. Out of 19 RCTs included in this meta-analysis, 13 [24, 28–32, 34, 36, 38–42] did not provide relevant data regarding use of corticosteroids during ABECB, while in the remaining two RCTs [25, 27] administration of systemic corticosteroids during ABECB was not permitted.

Administration of study drugs

The administration of study antibiotics prior to enrolment, as well as the administration of additional antimicrobial agents during the trial, was not allowed in any of the RCTs included in the meta-analysis. The dosages of the administered drugs as well as the duration of administration are shown in table 1. All antibiotics were given *per os*. In eight RCTs [24–31], macrolides were compared with quinolones; specifically clarithromycin was compared with levofloxacin [25, 27], gemifloxacin [28] or moxifloxacin [29, 31], while azithromycin was compared with levofloxacin [24, 26] and moxifloxacin [30]. A/C was compared with quinolones in four RCTs [24, 32–34] and with macrolides in eight RCTs [35–42]. In detail, the quinolone compared with A/C was levofloxacin[24], moxifloxacin[32, 33] or gemifloxacin [34], while the macrolide compared with A/C was clarithromycin [35, 36], azithromycin [37, 39–41], dirithromycin [38] or roxithromycin [42].

Treatment success in ITT and CE patients

Table 2 presents the primary outcomes studied in the present meta-analysis. Data regarding treatment success of the administered antimicrobial regimens for the ITT and CE patients was reported in 10 [28–31, 33, 35, 36, 39, 41, 42] and 17 [24, 26–38, 40–42] RCTs, respectively. In another RCT [25] insufficient data were provided regarding the number of patients cured, among those treated with macrolides or quinolones; thus, this RCT was excluded from the analysis of treatment success. There was no difference in treatment success between patients with ABECB treated with macrolides and those treated with quinolones (2,822 ITT patients, OR 1.01 (95% CI 0.81–1.27), I^2 0 (95% CI 0–0.85), data from four trials [28–31]; 2,606 CE patients, OR 0.94 (0.73–1.21), I^2 0 (0–0.71), data from seven trials [24, 26–31]) or between A/C and quinolone recipients (only one trial [33] provided data on treatment success in ITT patients; 1,441 CE patients, OR 0.86 (0.55–1.34), I^2 0.28 (0–0.73) data from four trials [24, 32–34]) or between A/C and macrolide recipients (869 ITT patients, OR 1.09 (0.41–2.95), I^2 0.79 (0.52–0.91), data from five trials [35–36, 39, 41–42]; 1,082 CE patients, OR 1.70 (0.72–4.03), I^2 0.67 (0.25–0.85), from seven trials [35–38, 40–42]).The ORs for the treatment success of compared antibiotics for the CE patients in the individual randomised controlled trials, as well as the pooled ORs, are presented in figure 2a–c.

Need for hospitalisation

Out of the 19 RCTs included in the analysis, only seven [24, 27–29, 31, 32, 35] provided data regarding the need for hospitalisation of ABECB patients. The follow-up of patients regarding the need for hospitalisation was limited during the study period in five RCTs [27, 29, 31, 32, 35], while in the

TABLE 2 Outcome data from the selected randomised controlled trials for the meta-analysis (macrolides *versus* quinolones, amoxicillin/clavulanate (A/C) *versus* quinolones and A/C *versus* macrolides)

First author [Ref.]	Treatment success, n/N (%)				Adverse effects, n/N (%)			
	ITT at TOCV	CE at TOCV	Hospitalisation	Patients without recurrence	Total	Patients withdrawn	Diarrhoea	All-cause mortality
Macrolides *versus* quinolones								
MARTINEZ [24]	NA	136/151 (90) *versus* 133/143 (93)	2/151 (1) *versus* 0/143 (0) [#]	NA	16/199 (8) *versus* 12/190 (6)	1/199 (0.5) *versus* 4/190 (2)	10/199 (5) *versus* 3/190 (2)	0/199 (0) *versus* 0/190 (0)
LODE [25]	(80) *versus* (83)	(85) *versus* (86)	NA	122/254 (48) *versus* 109/250 (44)[¶]	25/258 (10) *versus* 24/252 (10)	12/258 (5) *versus* 14/252 (6)	NA	NA
AMSDEN [26]	NA	86/105 (82) *versus* 83/97 (86)[+]	NA	NA	21/118 (18) *versus* 23/117 (20)	NA	10/118 (9) *versus* 5/117 (4)	NA
WEISS [27]	NA	80/91 (88) *versus* 76/87 (87)	0/91 (0) *versus* 3/87 (3)	NA	NA	NA	NA	NA
WILSON [28]	280/358 (78) *versus* 279/351 (79)	190/224 (85) *versus* 183/214 (86)[+]	14/224 (6) *versus* 5/214 (2)[§]	100/171 (58) *versus* 120/169 (71)[ƒ]	90/358 (25) *versus* 66/351 (19)	15/358 (4) *versus* 9/351 (3)	25/358 (7) *versus* 18/351 (5)	NA
CHODOSH [29]	268/286 (94) *versus* 540/569 (95)	121/127 (95) *versus* 263/279 (94)	16/312 (5) *versus* 21/614 (3)	NA	103/312 (33) *versus* 172/614 (28)	NA	15/312 (5) *versus* 33/614 (5)	1/312 (0.3) *versus* 1/614 (0.2)
DEABATE [30]	239/261 (92) *versus* 228/252 (90)	208/227 (92) *versus* 192/212 (91)	NA	NA	49/284 (17) *versus* 61/283 (22)	0/284 (0) *versus* 5/283 (2)	19/284 (75) *versus* 13/283 (5)	1/284 (0.4) *versus* 0/283 (0)
WILSON [31]	308/371 (83) *versus* 302/374 (81)	289/327 (88) *versus* 287/322 (89)	23/371 (6) *versus* 25/374 (7)	NA	82/371 (22) *versus* 80/374 (21)	14/371 (4) *versus* 23/374 (6)	15/371 (4) *versus* 11/374 (3)	2/371 (0.5) *versus* 1/374 (0.3)
Pooled OR (95% CI)	1.01 (0.81–1.27)	0.94 (0.73-1.21)	1.37 (0.75–2.50)		1.11 (0.94–1.32)	0.75 (0.39–1.41)	1.37 (0.99–1.87)	1.96 (0.45–8.51)
A/C *versus* quinolones								
MARTINEZ [24]	NA	103/126 (82) *versus* 95/120 (79)	3/126 (2) *versus* 0/120 (0)	NA	16/179 (9) *versus* 16/183 (9)	1/179 (0.5) *versus* 5/183(3)	5/179 (3) *versus* 4/183 (2)	0/179 (0) *versus* 0/183 (0)
STARAKIS [32]	NA	66/74 (89) *versus* 70/79 (89)	1/79 (1) *versus* 0/83 (0)	NA	11/79 (14) *versus* 8/83 (10)	NA	4/79 (5) *versus* 1/83 (1)	NA
SCHABERG [33]	241/283 (85) *versus* 270/292 (93)	230/251 (92) *versus* 251/261 (96)	NA	NA	55/283 (19) *versus* 52/292 (18)	NA	21/283 (7) *versus* 9/292 (3)	NA
FILE [34]	NA	248/266 (93) *versus* 247/264 (94)	NA	NA	57/296 (19) *versus* 34/304 (11)	NA	31/296 (11) *versus* 7/304 (2)	0/296 (0) *versus* 3/304 (1)
Pooled OR (95% CI)	NA	0.86 (0.55-1.34)	NA	NA	1.36 (1.01-1.85)	NA	3.02 (1.75-5.21)	NA
A/C *versus* macrolides								
ANZUETO [35]	116/143 (81) *versus* 117/140 (84)	116/133 (87) *versus* 117/137 (85)	3/145 (2) *versus* 5/142 (4)	NA	35/145 (24) *versus* 28/142 (20)	8/145 (6) *versus* 2/142 (1)	18/145 (12) *versus* 12/142 (8)	NA
MARTINOT [36]	108/119 (90.7) *versus* 113/124 (91)	96/106 (91) *versus* 105/113 (93)	NA	NA	27/123 (22) *versus* 17/127 (13)	NA	12/123 (10) *versus* 3/127 (2)	NA
HOEPELMAN [37]	NA	54/58 (89) *versus* 59/62 (95)	NA	NA	NA	NA	NA	NA
VAN ROYEN [38]	NA	148/149 (99) *versus* 153/162 (94)	NA	NA	NA	NA	NA	NA
BIEBUYCK [39]	33/44 (75) *versus* 84/93 (90)	NA	NA	NA	NA	NA	NA	NA
GRIS [40]	NA	24/26 (92) *versus* 24/28 (86)	NA	NA	NA	NA	NA	NA
BEGHI [41]	71/73 (97) *versus* 46/68 (68)	71/73 (97) *versus* 46/68 (68)	NA	NA	NA	NA	NA	NA
DAUTZENBERG [42]	28/33 (85) *versus* 29/32 (91)	28/33 (85) *versus* 29/32 (91)	NA	NA	NA	NA	NA	NA
Pooled OR (95% CI)	1.09 (0.41–2.95)	1.70 (0.72-4.03)	NA	NA	NA	NA	NA	NA

n: Number of patients affected; N: total number of patients in the study; ITT: intention-to-treat; TOCV: test-of-cure visit; CE: clinically evaluable; OR: odds ratio; CI: confidence interval; NA: not available/applicable. [#]: 9-months assessment; [¶]: 12-month period after therapy; [+]: in these two RCTs treatment success in CE patients was evaluated at 24 days from the onset of ABECB; [§]: 26-week period after therapy; [ƒ]: 26-week assessment. In the trial by MARTINEZ *et al.* [24] the quinolone levofloxacin was compared with both a macrolide (azithromycin) and A/C.

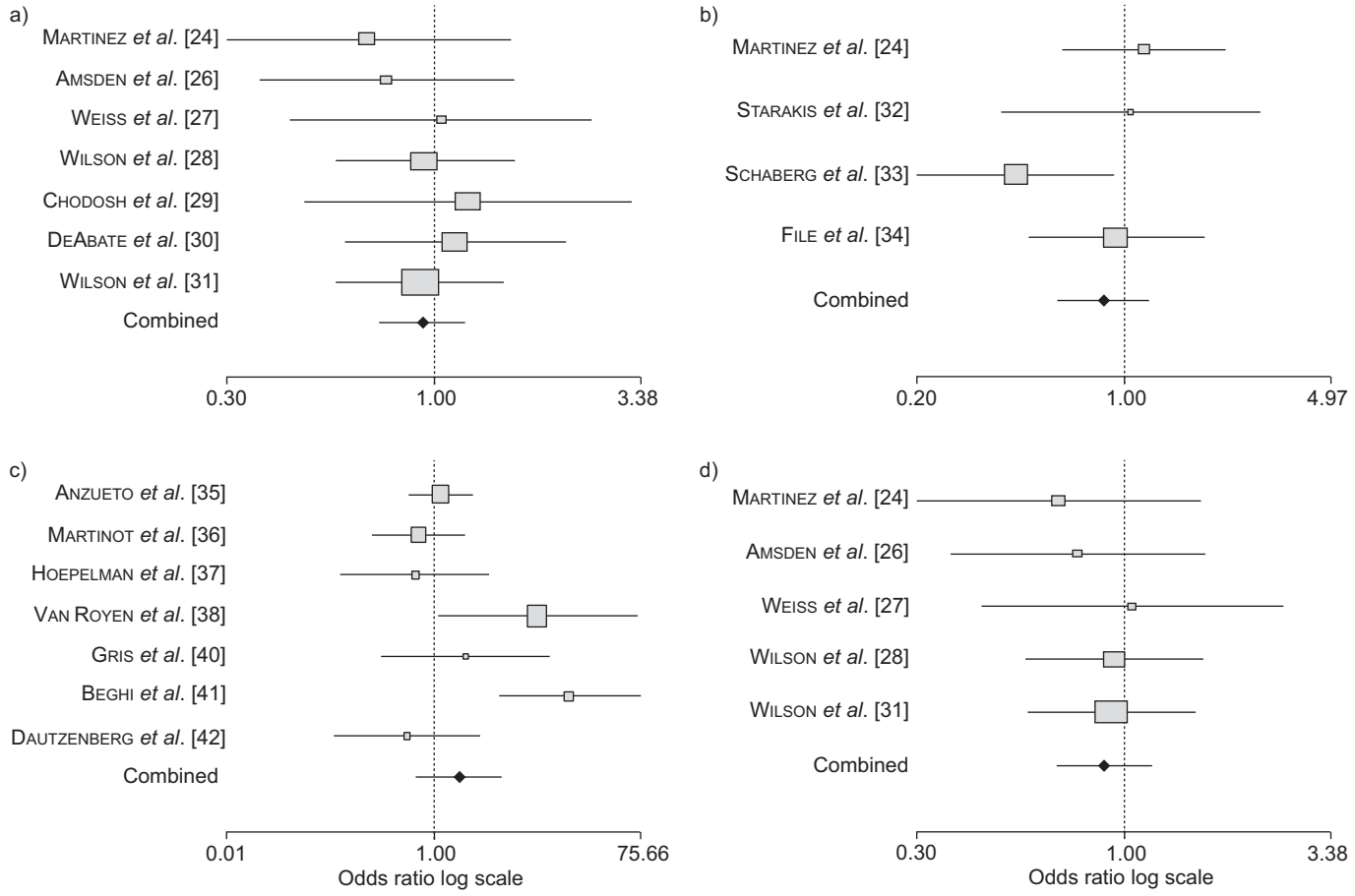

FIGURE 2. Treatment success in clinically evaluable patients with acute bacterial exacerbations of chronic bronchitis (ABECB) in randomised controlled trials (RCTs). a) Macrolides *versus* quinolones (odds ratio 0.94 (95% confidence interval 0.73–1.21)), 0.30–1.00 favours quinolones and 1.00–3.38 favours macrolides. b) Amoxicillin/clavulanate (A/C) *versus* quinolones (0.86 (0.55–1.34)), 0.20–1.00 favours quinolones and 1.00–4.97 favours A/C. c) A/C *versus* macrolides (1.70 (0.72–4.03)), 0.01–1.00 favours macrolides and 1.00–75.66 favours A/C. d) Macrolides *versus* quinolones in RCTs that only enrolled patients with Anthonisen type I or II ABECB (0.89 (0.67–1.18)), 0.30–1.00 favours quinolones and 1.00–3.38 favours macrolides. ·····: no difference between the two regimens. ■: odds ratio with the size of each square denoting the proportion of information given by each trial; ♦: pooled odds ratio for all RCTs; —: 95% confidence interval.

remaining two trials [24, 28] follow-up was extended until 26 weeks [28] or 9 months [24]. In the 12 other RCTs [25, 26, 30, 33, 34, 36–42] the relevant data were not reported. There was no difference in patients treated with macrolides compared with patients treated with quinolones regarding this outcome (2,581 ITT patients, OR 1.37 (0.75–2.50), I^2 0.39 (0–0.78), data from five trials [24, 27–29, 31]).

Unfortunately, data regarding need for hospitalisation were only available in two [24, 32] RCTs comparing A/C with quinolones, and in one RCT [35] comparing A/C with macrolides (data shown in table 2).

Recurrence of ABECB after resolution of the initial episode

Data regarding patients with recurrence(s) of ABECB after resolution of the initial episode was available in only two [25, 28] out of the 19 RCTs included in the meta-analysis. In both trials macrolides were compared with quinolones. In one RCT [25] a total of 48% (122 out of 254) of macrolide-treated patients and 44% (109 out of 250) of quinolone-treated patients exhibited no recurrence during the 12-month period after therapy (p=0.967 calculated using Chi-squared). Whereas, in another RCT [28] included in the meta-analysis, more patients treated with macrolide experienced a recurrence of ABECB after resolution of the initial episode compared with quinolone recipients during a 26-week period after therapy (100 out of 171 (58%) *versus* 120 out of 169 (71%), p=0.016).

Mortality

All-cause mortality during the study period (based on the reported data) was available in five RCTs [24, 29–31, 34]. There was no difference in mortality between macrolide-treated patients with ABECB and those treated with quinolones (ITT: 2,627 patients, OR=1.96 (95% CI 0.45–8.51), I^2=0 (95% CI 0–0.85), data from four trials [24, 29–31]). However, data on mortality were provided in only two RCTs [24, 34] comparing A/C with quinolones (data shown in table 2).

Treatment success in ME patients

Table 3 presents the microbiological outcomes of 14 [24–26, 28–37, 41] out of the 19 RCTs included in the meta-analysis that provided data relevant to the treatment success in ME patients. Regarding this outcome, macrolides performed worse than

TABLE 3 Microbiological outcomes from the selected randomised controlled trials in the meta-analysis (macrolides *versus* quinolones, amoxicillin/clavulanate (A/C) *versus* quinolones, and A/C *versus* macrolides)

First author [Ref.]	Treatment success microbiological evaluation	Pathogen eradication, n/N (%)		
		Haemophilus influenzae	*Moraxella catarrhalis*	*Streptococcus pneumoniae*
Macrolides *versus* quinolones				
MARTINEZ [24]	72/87 (83) *versus* 75/80 (94)	21/24 (88) *versus* 26/27 (96)	18/20 (90) *versus* 14/14 (100)	10/11 (91) *versus* 11/12 (92)
LODE [25]	55/66 (83) *versus* 62/64 (97)	NA	NA	NA
ANSSEN [26]	22/23 (96) *versus* 17/20 (85)	14/15 (93) *versus* 5/6 (83)	7/7 (100) *versus* 9/10 (90)	1/1 (100) *versus* 2/2 (100)
WEISS [27]	NA	NA	NA	NA
WILSON [28]	44/54 (81) *versus* 44/47 (94)	NA	NA	NA
CHODOSH [29]	115/127 (91) *versus* 265/280 (95)	33/40 (83) *versus* 69/69 (100)	24/24 (100) *versus* 57/58 (98)	21/23 (91) *versus* 36/36 (100)
DE ABATE [30]	108/115 (94) *versus* 111/116 (96)	33/36 (92) *versus* 34/34 (100)	20/20 (100) *versus* 29/29 (100)	19/19 (100) *versus* 17/17 (100)
WILSON [31]	71/114 (62) *versus* 89/115 (77)	23/43 (53) *versus* 40/44 (91)	23/24 (96) *versus* 14/16 (88)	35/36 (97) *versus* 32/38 (84)
Pooled OR (95% CI)	0.47 (0.31–0.69)	0.18 (0.06–0.55)	1.28 (0.32–5.19)	1.19 (0.27–5.24)
A/C *versus* quinolones				
MARTINEZ [24]	71/89 (80) *versus* 70/86 (81)	20/20 (100) *versus* 25/30 (83)	16/19 (84) *versus* 10/12 (83)	10/13 (77) *versus* 16/18 (88)
STARAKIS [32]	18/20 (89) *versus* 20/22 (91)	NA	NA	NA
SCHABERG [33]	60/67 (90) *versus* 64/73 (88)	NA	NA	NA
FILE [34]	35/44 (80) *versus* 40/44 (91)	NA	NA	NA
Pooled OR (95% CI)	0.84 (0.49–1.42)			
A/C *versus macrolides*				
ANZUETO [35]	55/62 (89) *versus* 54/59 (92)	18/19 (95) *versus* 17/20 (85)	12/14 (86) *versus* 18/20 (90)	11/14 (79) *versus* 11/15 (73)
MARTINOT [36]	41/55 (74) *versus* 55/69 (80)	8/15 (53) *versus* 15/29 (52)	3/4 (75) *versus* 5/6 (83)	9/12 (75) *versus* 12/16 (75)
HOEPELMAN [37]	26/59 (44) *versus* 26/60 (43)	16/20 (80) *versus* 15/21 (71)	11/11 (100) *versus* 11/11 (100)	6/6 (100) *versus* 9/9 (100)
VAN ROYEN [38]	NA	NA	NA	NA
BIEBUYCK [39]	NA	NA	NA	NA
GINS [40]	NA	NA	NA	NA
BEGHI [41]	70/71 (99) *versus* 45/67 (67)	15/15 (100) *versus* 13/26 (50)	9/9 (100) *versus* 5/5 (100)	34/34 (100) *versus* 19/27 (70)
DAUTZENBERG [42]	NA	NA	NA	NA
Pooled OR (95% CI)	1.49 (0.51–4.39)	2.21 (0.72–6.72)	0.78 (0.18–3.45)	1.96 (0.49–7.89)

n: Number of patients affected; N: total number of patients in the study; OR: odds ratio; CI: confidence interval; NA: not available/applicable.

quinolones (1,308 ME patients, OR 0.47 (0.31–0.69), I^2 0.06 (0–0.73), data from seven trials [24–26, 28–31]), while there was no difference between A/C and quinolones (445 ME patients, OR 0.84 (0.49–1.42), I^2 0 (0–0.85), data from four trials [24, 32–34]) or between A/C and macrolides (571 ME patients, OR 1.49 (0.51–4.39), I^2 0.75 (0.32–0.91), data from four trials [35–37, 41]).

Of the RCTs included in the analysis, nine reported data on pathogens isolated at baseline and eradicated at the test-of-cure visit [24, 26, 29–31, 35–37, 41]. Treatment of ABECB patients with macrolides was associated with lower eradication rates of *H. influenzae* compared with treatment with quinolones (338 isolates, OR 0.18 (0.06–0.55), I^2 0.24 (0–0.69), data from five RCTs [24, 26, 29–31]). However, there was no difference between the compared groups on eradication rates of *M. catarrhalis* (222 isolates, OR 1.28 (0.32–5.19), I^2 0 (0–0.79), data from five RCTs [24, 26, 29–31]) or of *S. pneumoniae* (195 isolates, OR 1.19 (0.27–5.24), I^2 0.14 (0–0.82), data from five RCTs [24, 26, 29–31]). Only one RCT [24] comparing A/C with quinolone reported data on these outcomes (data shown in table 3). In addition, treatment of patients with ABECB with A/C was not associated with better eradication rates of *H. influenzae* (165 isolates, OR 2.21 (0.72–6.72), I^2 0.35 (0–0.77), data from four RCTs [35–37, 41]), or of *M. catarrhalis* (91 isolates, OR 0.78 (0.18–3.45), I^2 0 (0–0.85), data from four RCTs [35–37, 41]), or of *S. pneumoniae* (149 isolates, OR 1.96 (0.49–7.89), I^2 0.32 (0–0.76), data from four RCTs [35–37, 41]) in comparison with treatment with macrolides.

Adverse effects

Data regarding adverse effects possibly related to the study drugs in ITT patients were reported for 12 RCTs [24–26, 28–36]. In the remaining seven RCTs [27, 37–42] the total (not only the drug-related) adverse effects [27, 38, 41] or the adverse effects of patients with any lower respiratory tract infection (not only ABECB) [37, 39, 40, 42] were reported. Therefore, these seven trials were excluded from the analysis of adverse effects. Administration of macrolides in ABECB patients was not associated with more adverse effects, in comparison with the administration of quinolones (4,081 ITT patients, OR 1.11 (0.94–1.32), I^2 0.13 (0–0.75), data from seven trials [24–26, 28–31]). This was also the case for participants withdrawn from the RCTs (2,920 ITT patients, OR 0.75 (0.39–1.41), I^2 0.43 (0–0.79), data from five RCTs [24, 25, 28, 30, 31]), but not for the development of diarrhoea (3,571 ITT patients, OR 1.37 (0.99–1.87), I^2 0 (0–0.75), data from six RCTs [24, 26, 28–31]).

In contrast, administration of A/C in ABECB patients was associated with more adverse effects, in general, in comparison with the administration of quinolones (1,699 ITT patients, OR 1.36 (1.01–1.85), I^2 0.14 (0–0.87), data from four trials [24, 32–34]. More A/C recipients experienced diarrhoea compared with quinolones recipients (1,699 ITT patients, OR 3.02 (1.75–5.21), I^2 0.07 (0–0.86), data from four trials [24, 32–34]). Only two trials [35, 36] comparing A/C with macrolides reported data for adverse effects in general and for diarrhoea; in both trials administration of A/C was associated with a higher probability of development of adverse effects in general and diarrhoea (data shown in table 2). Data regarding the number of patients who were withdrawn from the RCTs due to drug-related adverse effects were available in only one trial [24] comparing A/C with quinolone (one out of 179 (0.5%) *versus* five out of 183 (3%),

p=0.1), and in one trial [35] comparing A/C with macrolide (eight out of 145 (6%) *versus* two out of 142 (1%), p=0.06). Of note, the majority of adverse effects in patients of both study arms were mild-to-moderate in severity.

Sensitivity analyses

Treatment success in CE patients was analysed in various subsets of patients, based on the design of the current meta-analysis. Specifically, the subsets analysed were as follows. 1) Trials that only enrolled patients with an Anthonisen type I or II ABECB (macrolides *versus* quinolones: 1,761 patients, OR 0.89 (0.67–1.18), I^2 0 (0–0.79), data from five trials [24, 26–28, 31]; fig. 2d). 2) Trials in which the evaluation of the treatment success was performed up to 3 weeks from the onset of the ABECB (macrolides *versus* quinolones: 1,966 patients, OR 0.97 (0.71–1.33), I^2 0 (0–0.79), data from five trials [24, 27, 29–31]). 3) Trials in which use of systemic steroids before ABECB was comparable between the study arms of the individual RCTs (macrolides *versus* quinolones: 1,787 patients, OR 0.92 (0.68–1.26), I^2 0 (0–0.85), data from four trials [24, 28, 29, 31]; A/C *versus* quinolones: two trials [24, 32], 17 out of 126 (14%) *versus* 20 out of 120 (17%), p=0.49, in one trial [24] and 32 out of 74 (43%) *versus* 38/79 (48%), p=0.55, in the other trial [32]). 4) Trials in which >50% of the enrolled patients had a baseline FEV1 ⩽75% predicted (macrolides *versus* quinolones: 1,381 patients, OR 0.89 (0.64–1.24), I^2 0 (0–0.89), data from three trials [24, 28, 31]).

DISCUSSION

The results of the current meta-analysis suggest that there was no difference in treatment success between ABECB patients treated with macrolides and those treated with quinolones, nor was there any difference between A/C and quinolone recipients or between A/C and macrolide recipients. This was the case for the analyses of both ITT and CE patients.

This finding seems to support the suggestion that, overall, there is no clinical superiority of any one class of antimicrobial agents over another (among those compared) for the treatment of patients with ABECB and, thus, the choice of antibiotic has no influence on their outcome [10]. It could be also postulated that this lack of difference between the antimicrobial classes may simply reflect the lack of effectiveness of antimicrobials for the management of patients with ABECB.

The results of the present meta-analysis should be interpreted in the context of the design of the RCTs included. In fact, most of these RCTs were antibiotic comparison trials designed to show noninferiority between agents for drug registration and approval purposes; thus, they may not have enough power to show clinical superiority of any one antibiotic over another. In addition, a significant proportion of the RCTs included in the meta-analysis allowed the enrolment of patients with an Anthonisen type III ABECB (*i.e.* mild ABECB) [29, 30] as well as the enrolment of patients without impaired lung function (*i.e.* without a decrease in FEV1). It may be expected that less significant differences in the effectiveness would be found between different antibiotics for the subset of patients with mild ABECB, who should not receive antibiotic therapy at all according to the recently published guidelines on this issue [14, 43, 44]. Thus, the study design and the inclusion criteria of the individual RCTs included in the meta-analysis may be responsible for failing to reveal the potential superiority of one class of antimicrobial agents over another [45].

Several investigators advocate the administration of quinolones in certain subgroups of patients with ABECB [46]. Specifically, the first such subgroup includes patients of older age (>65 yrs), FEV1<50% at baseline (in these patients *P. aeruginosa* may also be the cause of ABECB) [47], more than three exacerbations of CB in the previous year, or with comorbid illness (especially cardiac disease); such patients are considered to be at increased risk for poor outcome [22]. Patients requiring admission to an intensive care unit due to the severity of their ABECB and patients at high risk for infection with an antibiotic-resistant pathogen are also included in the subgroups of ABECB patients in whom quinolones should be considered for the initial treatment. Unfortunately, the available data from the RCTs included in the meta-analysis were not enough to allow a stratification of the results of treatment success according to risk factors for poor outcome.

The findings of the present study must be viewed in the context of potential limitations. The major limitation of the meta-analysis is that results on treatment success in CE and ME patients were not stratified according to risk factors for poor outcome or for infection with an antibiotic-resistant pathogen. The available data from the RCTs included in the meta-analysis were not sufficient to evaluate the suggestion by experts that quinolones should be considered for the initial treatment of the subgroups of ABECB patients with the aforementioned risk factors. However, a sensitivity analysis was performed by only including the RCTs [24, 28, 31] in which the majority of the enrolled patients had an impaired FEV1 at baseline; quinolones were not found to be associated with better effectiveness in this subset of patients either.

Another limitation of the analysis is that the findings may not be fully applicable in areas where there is advanced problem of antimicrobial resistance among pathogens causing ABECB. It should be emphasised that antimicrobial resistance is a moving target and only data from local surveillance studies on this major clinical and public health problem provide information that helps the clinician in decision making regarding the choice of the appropriate antibiotic for a given patient with ABECB.

Also, the characteristics of the individual RCTs included in the present study contribute to others limitations of the meta-analysis. First, two [29, 30] out of the 19 RCTs included in the analysis also enrolled patients with a type III Anthonisen ABECB (not only patients with a type I or II Anthonisen ABECB). These type III patients do not need antibiotic therapy according to the recommendations of the international guidelines [14, 43, 44]. However, a subgroup analysis was performed after the exclusion of RCTs that included patients with a type III Anthonisen ABECB. Secondly, in two [26, 28] out of 19 RCTs the clinical end-points were determined ⩾3 weeks after the onset of treatment. ANTHONISEN *et al.* [2], in a large placebo-controlled trial, revealed that in 55% of patients with ABECB, spontaneous resolution of the infection happens at 3 weeks after the onset of the infection. This spontaneous resolution, which is due to the immune-inflammatory response to infection, could mitigate differences between compared antimicrobial agents. However, a subgroup analysis was performed by only including trials in

which the evaluation of the treatment success was performed ⩽3 weeks from the onset of the ABECB. Thirdly, 14 [24, 28–32, 34, 36, 38–42] out of 19 RCTs did not provide data on concurrent interventions for the management of ABECB, such as administration of systemic steroids, which could confound the results [48]. Fourthly, the majority of the RCTs included in this meta-analysis (18 out of 19 [24, 26, 27, 29–42]) were not designed to follow-up enrolled patients beyond 4–6 weeks; thus, the time to next exacerbation, which is an very important outcome, was not adequately assessed.

In addition, studies written in languages other than English, French, German and Italian were omitted, abstracts presented at scientific conferences were not sought and aspects related to cost-effectiveness issues of the compared antibiotics were not evaluated. Moreover, comparisons of individual antibiotics (except A/C), were not performed in the current study because there was not enough available data to perform such analyses. Instead, the comparative effectiveness of broad-spectrum antibiotics belonging to classes of antimicrobial agents commonly used for the treatment of patients with ABECB were examined, namely macrolides and quinolones.

Finally, one should bear in mind, when appreciating results on effectiveness and adverse effects, that the RCTs not only used different agents of the same antimicrobial class but also different dosages of the same antibiotic (as depicted in table 1). In addition, the extremely wide CIs of several of the results, namely those referring to treatment success between A/C and macrolide recipients as well as those pertaining to eradication rates, probably suggest that there is still insufficient evidence on these issues.

In conclusion, despite the above-mentioned limitations, the findings of the current meta-analysis suggest that there is no difference between macrolides, quinolones and amoxicillin/clavulanate for the treatment of patients with acute bacterial exacerbation of chronic bronchitis regarding effectiveness. However, there is enough evidence to suggest that quinolones are associated with better microbiological success than macrolides and very limited evidence that quinolones are associated with better long-term outcomes than comparators. As the available evidence is not enough to stratify outcomes according to the risk factors for poor outcome or for infection with an antibiotic-resistant pathogen, the present authors suggest that further research should be performed in the field of acute bacterial exacerbation of chronic bronchitis by focusing on this subgroup of patients (*i.e.* those with risk factors for poor outcome or for infection with an antibiotic-resistant pathogen).

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